

NOS. 23-726 and 23-727

IN THE
Supreme Court of the United States

MIKE MOYLE, SPEAKER OF THE IDAHO HOUSE OF
REPRESENTATIVES, ET AL.

Petitioners,

v.

UNITED STATES OF AMERICA,

STATE OF IDAHO,

Petitioner,

v.

UNITED STATES OF AMERICA,

JOINT APPENDIX
(Volume 1 of 3)

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**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

COMPLAINT

The United States of America, by and through its undersigned counsel, brings this civil action for declaratory and injunctive relief, and alleges as follows:

PRELIMINARY STATEMENT

1. Under federal law, hospitals that receive federal Medicare funds are required to provide necessary stabilizing treatment to patients who arrive at their emergency departments while experiencing a medical emergency. Under the Emergency Medical Treatment and Labor Act (EMTALA), 42 U.S.C. § 1395dd, if a person with an “emergency medical condition” seeks treatment at an emergency department at a hospital that accepts Medicare funds, the hospital must provide medical treatment necessary to stabilize that condition before transferring or discharging the patient. Crucially, “emergency medical conditions” under the statute include not just conditions that present risks to life but also those that place a patient’s “health” in “serious jeopardy” or risk “serious impairment to

bodily functions” or “serious dysfunction of any bodily organ or part.”

2. In some circumstances, medical care that a state may characterize as an “abortion” is necessary emergency stabilizing care that hospitals are required to provide under EMTALA. Such circumstances may include, but are not limited to, ectopic pregnancy, severe preeclampsia, or a pregnancy complication threatening septic infection or hemorrhage.

3. The State of Idaho, however, has passed a near-absolute ban on abortion. Once the Idaho law takes effect on August 25, 2022, Idaho Code § 18-622 will make it a felony to perform an abortion in all but extremely narrow circumstances. The Idaho law would make it a criminal offense for doctors to comply with EMTALA’s requirement to provide stabilizing treatment, even where a doctor determines that abortion is the medical treatment necessary to prevent a patient from suffering severe health risks or even death.

4. Under the Idaho law, once effective, any state or local prosecutor can subject a physician to indictment, arrest, and prosecution merely by showing that an abortion has been performed, without regard to the circumstances. The law then puts the burden on the physician to prove an “affirmative defense” at trial. Idaho Code § 18-622(3) (2022). Nothing protects a physician from arrest or criminal prosecution under Idaho’s law, and a physician who provides an abortion in Idaho can avoid criminal liability only by establishing that “the abortion was necessary to prevent the death of the pregnant woman” or that, before performing the

abortion, the pregnant patient (or, in some circumstances, their parent or guardian) reported an “act of rape or incest” against the patient to a specified agency and provided a copy of the report to the physician. *Id.* Beyond care necessary to prevent death, the law provides no defense whatsoever when the health of the pregnant patient is at stake. And, even in dire situations that might qualify for the Idaho law’s limited “necessary to prevent the death of the pregnant woman” affirmative defense, some providers could withhold care based on a well-founded fear of criminal prosecution.

5. Idaho’s abortion law will therefore prevent doctors from performing abortions even when a doctor determines that abortion is the medically necessary treatment to prevent severe risk to the patient’s health and even in cases where denial of care will likely result in death for the pregnant patient. To the extent Idaho’s law prohibits doctors from providing medically necessary treatment, including abortions, that EMTALA requires as emergency medical care, Idaho’s new abortion law directly conflicts with EMTALA. *See* 42 U.S.C. § 1395dd(f) (EMTALA preempts State laws “to the extent that the requirement directly conflicts with a requirement of this section”). To the extent Idaho’s law renders compliance with EMTALA impossible or stands as an obstacle to the accomplishment of federal statutes and objectives, EMTALA preempts the Idaho law under the Supremacy Clause of the United States Constitution.

6. In this action, the United States seeks a declaratory judgment that Idaho’s law is invalid under the Supremacy Clause and is preempted by

federal law to the extent that it conflicts with EMTALA. The United States also seeks an order preliminarily and permanently enjoining Idaho's restrictive abortion law to the extent it conflicts with EMTALA.

JURISDICTION AND VENUE

7. This Court has jurisdiction over this action under 28 U.S.C. §§ 1331 and 1345.

8. Venue is proper in this judicial district under 28 U.S.C. § 1391(b) because Defendant resides within this judicial district and because a substantial part of the acts or omissions giving rise to this action arose from events occurring within this judicial district.

9. Pursuant to D. Idaho Civ. R. 3.1, venue is proper in the Southern Division because Defendant legally resides in Ada County, Idaho, and because that is where the claim for relief arose.

PARTIES

10. Plaintiff is the United States of America.

11. Defendant, the State of Idaho, is a State of the United States. The State of Idaho includes all of its officers, employees, and agents.

SUPREMACY OF FEDERAL LAW

I. The Supremacy Clause and Preemption

12. The Supremacy Clause of the U.S. Constitution mandates that “[t]his Constitution, and the Laws of the United States which shall be made in Pursuance thereof . . . shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any

State to the Contrary notwithstanding.” U.S. Const. art. VI, cl. 2.

13. “[S]tates have no power . . . to retard, impede, burden, or in any manner control the operations of the Constitutional laws enacted by [C]ongress to carry into effect the powers vested in the national government.” *M’Culloch v. Maryland*, 17 U.S. (4 Wheat.) 316, 317 (1819). “There is no doubt Congress may withdraw specified powers from the States by enacting a statute containing an express preemption provision,” and a State law is invalid if it conflicts with such a provision. *Arizona v. United States*, 567 U.S. 387, 399 (2012). Likewise, a State law is invalid if compliance with the state and federal law is impossible or if the state law “stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.” *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).

II. The Emergency Medical Treatment and Labor Act (EMTALA)

14. Medicare, enacted in 1965 as Title XVIII of the Social Security Act, 42 U.S.C. § 1395 *et seq.*, is a federally funded program, administered by the Secretary of the Department of Health and Human Services (HHS), that pays health care providers or insurers for health care services under certain circumstances.

15. Medical providers’ participation in Medicare is voluntary. When providers agree to participate in Medicare, they submit provider agreements to the Secretary of HHS. *See* 42 U.S.C. § 1395cc. Hospitals submitting such agreements agree that they will “adopt and enforce a policy to ensure compliance with

the requirements of [EMTALA] and to meet the requirements of [EMTALA].” *Id.* § 1395cc(a)(1)(I)(i).

16. Under EMTALA, hospitals participating in Medicare are generally required to provide stabilizing health care to all patients who arrive at an emergency department suffering from an emergency medical condition. *See* 42 U.S.C. § 1395dd.

17. Specifically, EMTALA requires these hospitals to “screen” patients who request treatment at the hospital’s emergency department and provide “necessary stabilizing treatment,” including an appropriate transfer to another facility that is able to provide stabilizing care not available at the originating hospital, for any “emergency medical condition” the hospital identifies. 42 U.S.C. § 1395dd.

18. The screening requirement necessitates that hospitals act “to determine whether or not an emergency medical condition” exists. *Id.* § 1395dd(a); *see also* 42 C.F.R. § 489.24(a) (noting that EMTALA requires “an appropriate medical screening examination within the capability of the hospital’s emergency department”).

19. Congress defined an “emergency medical condition” in EMTALA 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 ...

(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(e)(1).

20. If the hospital determines an individual has an emergency medical condition, “the hospital must provide either” (1) “further medical examination and such treatment as may be required to stabilize the medical condition,” or (2) “transfer of the individual to another medical facility in accordance with” certain requirements. *Id.* § 1395dd(b)(1); *see also* 42 C.F.R. § 489.24(a)(1)(i)-(ii). The hospital may also “admit[] th[e] individual as an inpatient in good faith in order to stabilize the emergency medical condition.” 42 C.F.R. § 489.24(d)(2)(i).

21. 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)(A). The term “transfer” is

defined to include “discharge” of a patient. *Id.* § 1395dd(e)(4).

22. A hospital may not transfer (including by discharging) an individual with an emergency medical condition who has not been stabilized, unless, *inter alia*, the individual requests a transfer or a physician certifies that the benefits of a transfer to another medical facility outweigh the increased risks to the patient. *Id.* § 1395dd(c).

23. In short, when an emergency medical condition exists, EMTALA requires participating hospitals to provide “stabilizing” treatment, as determined by the particular hospital’s facilities and the treating physician’s professional medical judgment.

24. As relevant here, there are some pregnancy-related emergency medical conditions—including, but not limited to, ectopic pregnancy, severe preeclampsia, or a pregnancy complication threatening septic infections or hemorrhage—for which a physician could determine that the necessary stabilizing treatment is care that could be deemed an “abortion” under Idaho law.¹ In that scenario, EMTALA requires the hospital to provide that stabilizing treatment. *See* Dep’t of Health and Human Servs., *Reinforcement of EMTALA Obligations*

¹ Termination of an ectopic pregnancy—which can never lead to a live birth and poses inherent danger to pregnant patients—is not considered an abortion by medical experts. However, the termination of an ectopic pregnancy appears to fall within Idaho’s broad definition of abortion. *See* Idaho Code § 18-604(1).

specific to Patients who are Pregnant or are Experiencing Pregnancy Loss, CENTERS FOR MEDICARE & MEDICAID SERVICES (July 11, 2022), <https://www.cms.gov/files/document/qso-22-22-hospitals.pdf>; *see also Reinforcement of EMTALA Obligations specific to Patients who are Pregnant or are Experiencing Pregnancy Loss*, CENTERS FOR MEDICARE & MEDICAID SERVICES (Sept. 17, 2021), <https://www.cms.gov/files/document/qso-21-22-hospital.pdf>.

25. EMTALA contains an express preemption provision, which preempts State laws “to the extent that the requirement directly conflicts with a requirement of this section.” 42 U.S.C. § 1395dd(f).

IDAHO’S ABORTION LAW

26. In 2020, Idaho enacted a law that severely restricts abortions and threatens criminal prosecution against anyone who performs an abortion. The law, codified at Idaho Code § 18-622, is currently set to take effect on August 25, 2022, which is 30 days after issuance of the judgment in *Dobbs v. Jackson Women’s Health Organization*, 142 S. Ct. 2228 (2022). *See* Idaho Code § 18-622(1)(a).

27. Under Idaho’s abortion law, “[e]very person who performs or attempts to perform an abortion . . . commits the crime of criminal abortion.” *Id.* § 18-622(2). The crime of “criminal abortion” is a felony, punishable by two to five years imprisonment. *Id.*

28. Idaho’s law also requires that “[t]he professional license of *any* health care professional who performs or attempts to perform an abortion or who assists in performing or attempting to perform

an abortion in violation of this subsection shall be suspended by the appropriate licensing board for a minimum of six (6) months upon a first offense and shall be permanently revoked upon a subsequent offense.” *Id.* (emphasis added).

29. The Idaho law defines “[a]bortion” to mean “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.” *Id.* § 18-604(1).

30. The *prima facie* criminal prohibition in Idaho’s law does not contain any exceptions for when the pregnant patient’s health or life is endangered. Thus, the mere performance of an abortion—even in an emergency, life-saving scenario—would subject a provider to criminal prosecution and require the provider to raise one of the law’s narrow affirmative defenses at trial.

31. Idaho’s abortion law provides for only two affirmative defenses, either of which the provider must prove by a preponderance of the evidence. In other words, once a prosecutor or licensing authority proves the *prima facie* case of an abortion having been performed, an accused physician may try to avoid conviction, incarceration, and loss of license by raising one of two affirmative defenses, but bears the burden of proving the defense to a jury, along with the expense and uncertainty that flow from that burden.

32. Specifically, the accused physician would have to prove to a jury: (1) that “[t]he physician determined, in his good faith medical judgment and based on the facts known to the physician at the time,

that the abortion was necessary to prevent the death of the pregnant woman,” or (2) in cases of rape or incest, that the woman, or, if a minor, the woman or her parent or guardian, “has reported the act of rape or incest to a law enforcement agency” and the physician, prior to performing the abortion, received a copy of a police report (or, in the case of a minor, a police report or report to child protective services) regarding “the act of rape or incest.” Idaho Code § 18-622(3)(a)(ii), (b)(ii)-(iii).

33. There is no affirmative defense applicable in circumstances where an abortion is necessary to ensure the health of the pregnant patient—even where the patient faces serious medical jeopardy or impairment—if the care is not “necessary to prevent the death” of the patient.

34. In addition, it is a requirement for both affirmative defenses, and thus the physician would have to prove, that the physician “performed or attempted to perform the abortion in the manner that, in his good faith medical judgment and based on the facts known to the physician at the time, provided the best opportunity for the unborn child to survive, unless, in his good faith medical judgment, termination of the pregnancy in that manner would have posed a greater risk of the death of the pregnant woman.” *Id.* § 18-622(3)(a)(iii), (b)(iv).

IDAHO’S ABORTION LAW CONFLICTS WITH EMTALA

35. Within the State of Idaho, there are approximately 43 hospitals that voluntarily participate in Medicare. Approximately 39 of those

hospitals have emergency departments that are required to comply with EMTALA.

36. Idaho’s criminal prohibition of all abortions, subject only to the statute’s two limited affirmative defenses, conflicts with EMTALA. Idaho’s criminal prohibition extends even to abortions that a physician determines are necessary stabilizing treatment that must be provided under EMTALA.

37. In particular, EMTALA’s definition of an emergency medical condition—for which the hospital would be required to facilitate stabilizing treatment—is broader than just those circumstances where treatment is “necessary to prevent . . . death” under Idaho law. For example, EMTALA requires stabilizing treatment where “the health” of the patient is “in serious jeopardy,” or where continuing a pregnancy could result in a “serious impairment to bodily functions” or a “serious dysfunction of any bodily organ or part.” 42 U.S.C. § 1395dd(e)(1)(A)(i)-(iii). Idaho has criminalized performing abortions in those circumstances, even when a physician has determined that an abortion is the necessary stabilizing treatment for a patient’s emergency medical condition. The Idaho law therefore conflicts with federal law and is, in this respect, preempted.

38. The Idaho law also conflicts with EMTALA because the only limited protection it affords for even life-saving abortions is in the form of an affirmative defense where the provider bears the burden of proof at trial. Idaho’s law subjects every provider who performs an abortion to the threat of indictment, arrest, and criminal prosecution. The law likewise subjects every provider and employee who performs

or assists in performing an abortion to potential loss of their medical license. By threatening providers with criminal prosecution and license revocation proceedings for *every* abortion, regardless of whether it was “necessary to prevent . . . death,” the Idaho law will deter physicians from performing abortions they have determined are medically necessary and thus must be provided under federal law. This is true even in the limited situations in which the abortions could be deemed defensible at a physician’s criminal trial. “Where a prosecution is a likely possibility, yet only an affirmative defense is available,” there “is a potential for extraordinary harm and a serious chill” upon protected conduct. *Ashcroft v. ACLU*, 542 U.S. 656, 670-71 (2004). Here, the law’s obvious chilling effect on providers’ willingness to perform abortions, even when abortions are determined to be necessary medical treatments, is itself an impediment to the accomplishment of EMTALA’s goal of ensuring that patients receive emergency care. The Idaho law is therefore preempted.

IDAHO’S ABORTION LAW CAUSES INJURY TO FEDERAL INTERESTS

39. The Idaho abortion law will become effective on August 25, 2022.

40. Following the Supreme Court’s decision in *Dobbs*, the Governor of Idaho issued a press release stating that “Idaho has been at the forefront of enacting new laws” to restrict abortion, and specifically referencing § 18-622 as a bill that the

Governor “signed into law” and “will go into effect later this summer.”²

41. Before filing this lawsuit, on July 29, 2022, the United States sent a letter to the State of Idaho, expressing the United States’ view that § 18-622 was contrary to federal law. The United States did not receive a substantive response.

42. Once the law goes into effect on August 25, 2022, providers will immediately be subject to the threat of arrest, imprisonment, criminal liability, and loss of license for providing federally required care.

43. Severe harm will result from Idaho’s law, which violates the Supremacy Clause. *See New Orleans Pub. Serv., Inc. v. Council of City of New Orleans*, 491 U.S. 350, 366-67 (1989) (assuming that irreparable injury may be established “by a showing that the challenged state statute is flagrantly and patently violative of . . . the express constitutional prescription of the Supremacy Clause” (citation omitted)).

I. Idaho’s Abortion Law Threatens Severe Public Health Consequences

44. If Idaho’s abortion law is allowed to take effect, physicians in Idaho will be threatened with prosecution under a state law that prohibits them from providing necessary stabilizing medical treatment required by EMTALA. Physicians will be faced with an untenable choice—either to withhold critical stabilizing treatment required under

² <https://gov.idaho.gov/pressrelease/gov-little-comments-on-scotus-overrule-of-roe-v-wade/>

EMTALA or to risk criminal prosecution and potential loss of their professional licenses. As a result of Idaho's physicians being placed in this position, patients will suffer—including by having their care delayed or losing access to necessary health care that is guaranteed under federal law. Particularly in emergency circumstances, or when dealing with considerations of risk to an individual's life or health, delayed health care can pose serious harms and is exactly what EMTALA's requirements are designed to prevent. In short, the Idaho law threatens severe public health consequences.

45. For example, pregnant patients sometimes arrive at a hospital's emergency department with an emergency medical condition for which physicians reasonably determine that the appropriate stabilizing treatment is an emergency abortion. Physicians facing a threat of criminal prosecution for performing an emergency abortion may be reluctant to perform the procedure—even when their medical judgment leads them to conclude that the procedure is necessary. The loss of that necessary treatment will result in irreversible damage to the health of a pregnant patient in some instances, and in other cases could lead to death.

46. The Idaho law will deprive pregnant patients of necessary treatment required by EMTALA notwithstanding the Idaho law's affirmative defense for abortions "necessary to prevent the death of the pregnant woman." Idaho Code § 18-622(3)(a)(ii). Because that defense is available only during criminal prosecution or licensing proceedings, the law still subjects providers to the threat of criminal prosecution and potential loss of license for

performing a life-saving abortion. And even the law's affirmative defense does not allow for abortions in emergency situations where pregnancy can reasonably be expected to place the health of the pregnant patient in serious jeopardy, seriously impair the pregnant patient's bodily functions, or cause serious dysfunction of any bodily part or organ.

II. Idaho's Law Interferes with EMTALA Obligations under the Federal Medicare Program

47. As discussed above, Idaho's abortion law directly conflicts with the important federal policy reflected in EMTALA, 42 U.S.C. § 1395dd, through which Congress codified a guarantee of necessary stabilizing medical treatment for patients with emergency medical conditions, including pregnant patients, who seek care at emergency departments. *See id.* § 1395dd(a), (b), (e)(1), (g).

48. Congress intended EMTALA to govern nationwide in every hospital that accepts Medicare funds, as confirmed by its express preemption of conflicting State laws. *Id.* § 1395dd(f). Idaho's law frustrates Congress's objective of guaranteeing nationwide emergency medical care at Medicare hospitals, because Idaho law prohibits a particular form of medical treatment—even when that treatment is necessary to stabilize a patient experiencing an emergency medical condition. The United States has a strong sovereign interest in ensuring that States may not disrupt the federal objectives embodied in EMTALA, particularly when States seek to hold physicians criminally liable for

providing stabilizing emergency treatment required under federal law.

49. The United States has an interest in protecting the integrity of the funding it provides under Medicare and ensuring that hospitals who are receiving Medicare funding will not refuse to provide stabilizing treatment to patients experiencing medical emergencies. From 2019 to 2020, HHS paid approximately 74 million dollars for emergency department care in Idaho hospitals enrolled in Medicare. A condition of hospitals' enrollment in Medicare is that they agree to comply with EMTALA. *See id.* § 1395cc(a)(1)(I)(i). Thus, part of the United States' bargain when it agrees to provide Medicare reimbursement to hospitals is that those hospitals will, in return, provide all forms of stabilizing treatment to emergency department patients, consistent with EMTALA.

50. Idaho's law prevents the United States from receiving the benefit of its bargain, however, by affirmatively prohibiting Idaho hospitals from complying with certain obligations under EMTALA. Thus, Idaho's law undermines the overall Medicare program and the funds that the United States provides in connection with that program, by precluding the United States from receiving one of the benefits to which it is entitled under the Medicare program.

51. Idaho's law also improperly interferes with the United States' pre-existing agreements with hospitals under Medicare. Under these agreements, each hospital (including those in Idaho) must certify that it "agrees to conform to the provisions of section

1866 of the Social Security Act and applicable provisions in 42 CFR,” CMS Form 1561, and those referenced provisions likewise include obligations to comply with EMTALA.³

52. Approximately 43 hospitals in Idaho have signed Medicare agreements, and approximately 39 of those hospitals have emergency departments that must comply with EMTALA. Compliance with Idaho’s law would force these hospitals to violate their agreements with the United States because Idaho criminalizes the provision of stabilizing medical services required by EMTALA, and thus Idaho’s law likewise interferes with the United States’ interests.

53. Waiting to initiate federal enforcement actions directly against physicians or hospitals would likely have significant negative consequences on public health, including because such actions could be pursued only after physicians or hospitals had first denied emergency care to an individual in need. Unless the action is filed against a state-run hospital, the State would not be a party to a federal enforcement action, and the State’s absence would further delay the resolution of this issue. Meanwhile, patients would be denied important life-saving and stabilizing medical care, resulting in needless suffering and even loss of life. Physicians and hospitals should not be placed in the untenable position of risking criminal prosecution under state law or subjecting themselves to enforcement actions under federal law. Pregnant patients who arrive at an emergency department are entitled to the stabilizing

³ <https://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/cms1561.pdf>

emergency care ensured under federal law when experiencing life- or health-threatening conditions.

54. The law likewise stands as an obstacle to Congress's goal of ensuring that patients receive effective emergency care by threatening the professional license of *any* health care professional who "assists" in performing or attempting to perform an abortion. Idaho Code § 18-622(2). In particular, the law threatens a six-month suspension of the license of any health care professional who assists in an abortion or, on a second offense, threatens to permanently bar these providers from their professional practice. A pregnant patient who arrives in the emergency department with an emergency condition is likely to encounter not just emergency department physicians but also triage nurses, scrub nurses, lab techs, radiologists, anesthesiologists, and others whose role in any procedure could constitute "assisting" in the performance of an abortion. By threatening the license of other hospital employees whose care is critical to providing emergency department care, Idaho's law impedes EMTALA's goal of ensuring that patients receive effective emergency care.

CLAIM FOR RELIEF

Preemption Under the Supremacy Clause and EMTALA

55. Plaintiff hereby incorporates paragraphs 1 through 54 as if fully set forth herein.

56. The Supremacy Clause provides that "[t]his Constitution, and the Laws of the United States which shall be made in Pursuance thereof . . . shall be

the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.” U.S. Const. art. VI, cl. 2.

57. EMTALA expressly preempts State laws “to the extent that the requirement directly conflicts with a requirement of this section.” 42 U.S.C. § 1395dd(f). Idaho Code § 18-622 violates the Supremacy Clause and is preempted to the extent it is contrary to EMTALA.

58. The law imposes requirements that are contrary to EMTALA and impedes the accomplishment and execution of the full purposes and objectives of federal law and is therefore preempted.

59. The Idaho law therefore violates the Supremacy Clause and is preempted under federal law to the extent that it conflicts with EMTALA.

PRAYER FOR RELIEF

WHEREFORE, the United States respectfully requests the following relief:

- a. A declaratory judgment stating that Idaho Code § 18-622 violates the Supremacy Clause and is preempted and therefore invalid to the extent that it conflicts with EMTALA;
- b. A declaratory judgment stating that Idaho may not initiate a prosecution against, seek to impose any form of liability on, or attempt to revoke the professional license of any medical provider based on that provider’s performance of an abortion that is authorized under EMTALA;

- c. A preliminary and permanent injunction against the State of Idaho—including all of its officers, employees, and agents—prohibiting enforcement of Idaho Code § 18-622(2)-(3) to the extent that it conflicts with EMTALA;
- d. Any and all other relief necessary to fully effectuate the injunction against Idaho Code § 18-622's enforcement to the extent it conflicts with EMTALA;
- e. The United States' costs in this action; and
- f. Any other relief that the Court deems just and proper.

Dated: August 2, 2022	Respectfully submitted,
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EXHIBIT A to Plaintiff's MPI

**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 preeclampsia/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(l).

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.

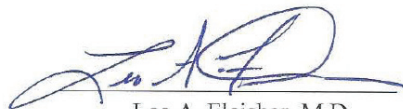
36. As described above, these conditions frequently require emergency care, including abortion, and given these nationwide numbers, it is not surprising that pregnant patients in Idaho are among persons who require treatment for medical conditions that frequently present as medical emergencies. For example, 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.

A handwritten signature in blue ink, appearing to read "Lee A. Fleisher", with a stylized flourish extending to the right.

Lee A. Fleisher, M.D.

FLEISHER DECLARATION: EXHIBIT B

Interim Update

**ACOG PRACTICE BULLETIN****Clinical Management Guidelines for Obstetrician–Gynecologists**

NUMBER 193, MARCH 2018

*(Replaces Practice Bulletin Number 191, February 2018)***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 trans- vaginal 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 ultra-sonography. 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/m² 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/m² 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^t

- Administer methotrexate at a dose of 50 mg/m² intramuscularly on day 1
- Administer second dose of methotrexate at a dose of 50 mg/m² 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/m² 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/m² 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 folic acid 0.1 mg/kg intra-muscularly 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 non-pregnancy 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.

This information is designed as an educational resource to aid clinicians in providing obstetric and gynecologic care, and use of this information is voluntary. This information should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations in practice may be warranted when, in the reasonable judgment of the treating clinician, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology. The American College of Obstetricians and Gynecologists reviews its publications regularly; however, its publications may not reflect the most recent evidence. Any updates to this document can be found on www.acog.org or by calling the ACOG Resource Center.

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FLEISHER DECLARATION: EXHIBIT C

Interim Update

**ACOG PRACTICE BULLETIN****Clinical Management Guidelines for Obstetrician–Gynecologists**

NUMBER 222

*(Replaces Practice Bulletin No. 202, December 2018)***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

Pregestational 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 X 10⁹/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 is 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 A₂ (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 those 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.

tration. 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 A₂ 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 A₂ 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; $P=0.004$). 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 [†]	<ul style="list-style-type: none"> • 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 [‡]	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 because these agents can temporarily lead to increased blood pressure (118).

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.

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 preeclampsia: 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
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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 $70 \times 10^9/L$ 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 $70 \times 10^9/L$ 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, sympatho-

mimetic 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 anti-inflammatory 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 $400,000 \times 10^9/L$ (164). Women with HELLP syndrome are also at increased risk of pulmonary edema, acute respiratory distress syndrome and renal failure (65).

- ▶ *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 $100,000 \times 10^9/L$); 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 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 $70 \times 10^9/L$ 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.

Published online on May 21, 2020.

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**American College of Obstetricians and
Gynecologists**

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Gestational hypertension and preeclampsia. ACOG Practice Bulletin No. 222. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2020;135:e237–60.

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FLEISHER DECLARATION: EXHIBIT D**ACOG PRACTICE BULLETIN****Clinical Management Guidelines for Obstetrician–Gynecologists**

NUMBER 212

Presidential Task Force on Pregnancy and Heart Disease**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 the Presidential Task Force on Pregnancy and Heart Disease members Lisa M. Hollier, MD, James N. Martin Jr., MD, Heidi Connolly, MD, Mark Turrentine, MD, Afshan Hameed, MD, Katherine W. Arendt, MD, Octavia Cannon, DO, Lastascia Coleman, ARNP, CNM, Uri Elkayam, MD, Anthony Gregg, MD, MBA, Alison Haddock, MD, Stacy M. Higgins, MD, FACP, Sue Kendig, JD, Robyn Liu, MD, MPH, FAAFP, Stephanie R. Martin, DO, Dennis McNamara, MD, Wanda Nicholson, MD, Patrick S. Ramsey, MD, MSPH, Laura Riley, MD, Elizabeth Rochin, PhD, RN, NE-BC, Stacey E. Rosen, MD, Rachel G. Sinkey, MD, Graeme Smith, MD, PhD, Calondra Tibbs, MPH, Eleni Z. Tsigas, Rachel Villanueva, MD, Janet Wei, MD, and Carolyn Zelop, MD.

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-birth-weight 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 over-load (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 pre-pregnancy 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 pre-pregnancy) 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 pre-pregnancy 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*‡
	Reassure	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 lightheadness 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
mWHO Risk Class I		Delivery Location
No detectable increased risk of maternal	<ul style="list-style-type: none"> ● Uncomplicated small, or mild ○ Pulmonary stenosis 	<ul style="list-style-type: none"> ● Prepregnancy/ pregnancy counseling ● Care at local hospital

<p>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</p>	<ul style="list-style-type: none"> ○ 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 	<ul style="list-style-type: none"> ● Delivery at local hospital*
<p>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</p>	<ul style="list-style-type: none"> ● Unoperated atrial or ventricular septal defect ● Repaired Tetralogy of Fallot or aortic coarctation ● Most arrhythmias (supraventricular arrhythmias) ● Turner syndrome without 	<ul style="list-style-type: none"> ● Prepregnancy/ pregnancy counseling ● Pregnancy Heart Team* consultation/counseling ● Care at local hospital ● Delivery at local hospital

	congenital cardiac disease	
mWHO Risk Class II and III	<ul style="list-style-type: none"> ● Mild left ventricular impairment (EF >45%) ● Hypertrophic cardiomyopathy ● Native or bioprosthetic valve disease not considered 	<ul style="list-style-type: none"> ● Prepregnancy/ pregnancy counseling ● Pregnancy Heart Team* consultation/counseling ● Care at appropriate level hospital (critical members of the Pregnancy Heart Team* available depending on cardiac disease) ● Delivery at an appropriate level hospital*†
Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity (11-19% maternal cardiac event rate)	mWHO Risk Class I or IV (mild mitral stenosis, moderate aortic stenosis)	
Follow-up: Cardiology, every trimester	<ul style="list-style-type: none"> ● 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 	

<p>Pre-mWHO Risk Class III</p> <p>Significantly increased risk of maternal mortality or severe morbidity (20-27% maternal cardiac event rate)</p> <p>Follow-up: Cardiology, every 1-2 months)</p>	<ul style="list-style-type: none"> ● 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 	<ul style="list-style-type: none"> ● Prepregnancy/ pregnancy counseling ● Pregnancy Heart Team* consultation/counseling ● Care at appropriate level hospital[†] ● Delivery at an appropriate level hospital^{**}
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	<ul style="list-style-type: none"> ● 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/m²; Tetralogy of Fallot <50 mm) ● Ventricular tachycardia 	
mWHO Risk Class IV	<ul style="list-style-type: none"> ● 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 	<ul style="list-style-type: none"> ● 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**
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)		

- Systemic right ventricle with moderate to severely decreased ventricular function
- Severe aortic dilation (>45mm in Marfan syndrome or other HTAD; >50 mm in bicuspid aortic valve; Turner syndrome ASI >25 mm/m²; Tetralogy of Fallot >50 mm)
- Vascular Ehler-Danlos
- Severe (re)coarctation
- Fontan circulation with any complication

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 Classificati on I	Modified WHO Pregnancy Risk Classificati on II	Modified WHO Pregnancy Risk Classificatio ns III and IV
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Pregnancy Heart Team Members	Obstetrician, family medicine practitioner, internist Cardiologist consultation	Obstetrician, family medicine practitioner, internist Maternal-fetal medicine subspecialist Cardiologist consultation	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* Interventional cardiologist* Cardiac surgeon* Neonatologist* Geneticist* Mental health specialist* Pharmacist*
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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 post-partum 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 Zwanger-schap 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	Breast-feeding
<i>Inotropic Agents</i>			
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
<i>Vasodilators</i>			
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

*Antiotensin Converting Enzyme Inhibitors and
Angiotensin Receptor Blockers*

	Yes	Contra indicated Associated with fetal renal failure, growth restriction, malformatio ns and death	Probably compatible No published information
<i>Beta-blockers</i>			
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
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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

Antirhythmic 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	Probably compatible

		disease of the newborn	
Amiodarone	No	May be associated with fetal thyroid toxicity	Hazardous
Flecainide	Yes Limited human informa tion	Limited human information	Probably compatible Limited information
Sotalol	No Limited human informa tion	Human data suggest fetal risk	Possibly hazardous

AV Note Blocking Agents

Adenosine	No informa tion	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 Does not cross placenta	Probably compatible

Unfractionated heparin	No	No adverse fetal effects Does not cross placenta	Probably compatible
Clopidogrel	No Limited human information	Limited human information	Probably compatible No published information
<i>Direct Factor Xa Inhibitors (revaroxaban or apixaban)</i>			
	No	Product labeling warns about abnormal bleeding risk Crosses placenta	Possibly hazardous No published information
<i>Diuretics</i>			
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 post-partum 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,

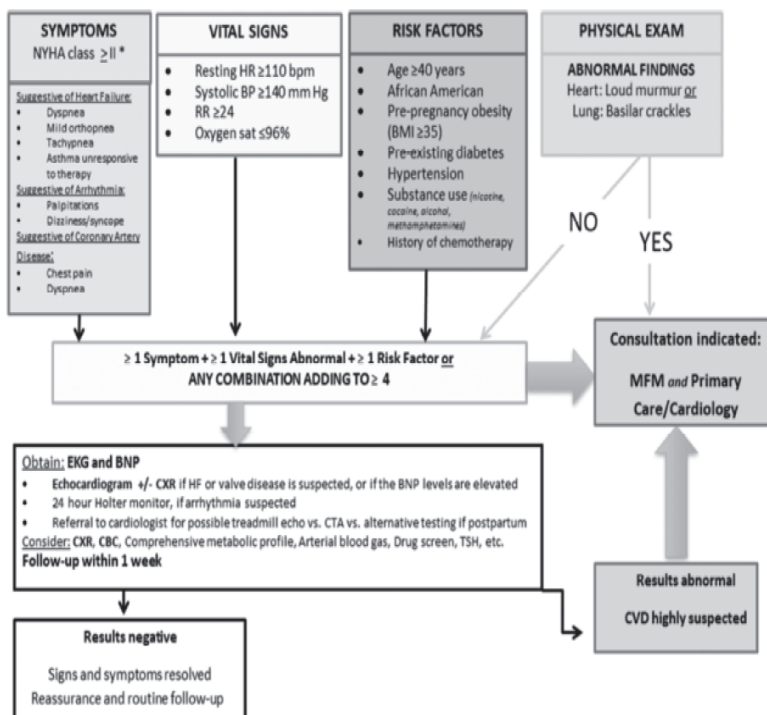


Figure 1. Cardiovascular Disease Assessment in Pregnant and Postpartum Women. *The NYHA Functional Classification is available at http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp. Abbreviations: BMI, body mass index; BNP, brain natriuretic 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 non-diagnostic. 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. Breast-feeding 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 pre-natal 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 post-partum 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 Syndrom	Surveillance Frequency	Suggested Mode of Delivery
Normal-sized aorta	Each trimester	Vaginal
Dilated ascending aorta <40 mm	4-6 weeks	Vaginal
Ascending aorta 40-50 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 trans-plantation 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 re-perfusion, 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

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)

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 un- witnessed, 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.

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 resuscitation skills and scenarios through simulation training (128).

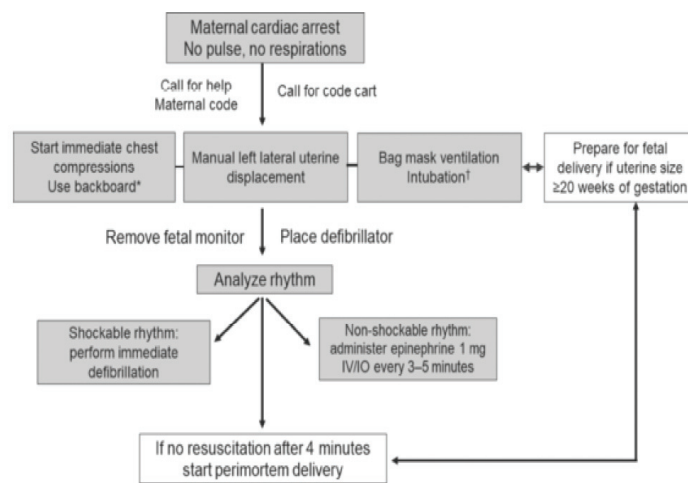


Figure 2. Maternal Resuscitation Algorithm. Abbreviations: IO, Intraosseous; IV, intravenous. *High-quality chest compressions on a backboard are performed at a rate of 100–120 per minute. †Prioritization of bag mask ventilation with 100 percent oxygen. Oxygenation remains a primary goal using a ratio 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.)

- ***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 post-partum 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 anti-coagulation 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

			athy and stenotic valvular lesions especially aortic stenosis
Terbutaline	Tachycardia Hypotension Arrhythmias Myocardial ischemia	Hypertrophic obstructive cardiomyopathy Patients at risk of arrhythmia or ischemia Stenotic valvular lesions especially mitral stenosis	Do not use beyond 48-72 hours
Methylergoline	Coronary artery vasospasm Hypertension Arrhythmias	Coronary artery disease or risk for ischemia Aortopathies	Do not give intravenously
Carboprost Tromethamine	Hypertension Palpitations Pachycardia Vasodepressor syncope Pulmonary hypertension	Pulmonary hypertension Cyanotic congenital heart disease	Can cause bronchospasm Do not give intravenously

Pulmonary
edemaTranexamic
AcidUse with
caution in
uncorrecte
d
cardiovasc
ular
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). Intra-muscular 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 (pre-eclampsia, eclampsia, or hemolysis, elevated liver enzymes, and low platelet count syndrome)
- Chronic disease (chronic hypertension or pre-gestational 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 as 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 non-permanent 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.

Published online on April 23, 2019.

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American College of Obstetricians and Gynecologists
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Pregnancy and heart disease. ACOG Practice Bulletin No. 212. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2019;133:e320-56.

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

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 217

(Replaces Practice Bulletin Number 188, January 2018)

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 Robert Ehsanipoor, MD and Christian M. Pettker, MD.

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 neo-natal 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 abruption 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 manage-

ment 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 pre-term 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†

Perivable (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.

§Perivable 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 assess-

ment 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 ultra-sonographic 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, cortico-steroids, 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 in 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 cortico-steroids 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 pre-term 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 anti-biotics 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 non-randomized 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 abruption 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 pre-term 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 (ferning) 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 de- signed 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.

Published online on February 20, 2020.

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American College of Obstetricians and Gynecologists 409 12th Street SW, Washington, DC 20024-2188

Prelabor rupture of membranes. ACOG Practice Bulletin No. 217. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2020;135:e80-97.

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Exhibit B to Plaintiff's MPI
UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF IDAHO
SOUTHERN DIVISION

UNITED STATES OF AMERICA, <p style="text-align: center;">Plaintiff,</p> v. THE STATE OF IDAHO, <p style="text-align: center;">Defendant.</p>	Case No. 1:22-cv-329 DECLARATION OF DR. EMILY CORRIGAN
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DECLARATION OF DR. EMILY CORRIGAN IN SUPPORT OF THE UNITED STATES' MOTION FOR A PRELIMINARY INJUNCTION

I, Emily Corrigan, being first duly sworn under oath, state and depose upon personal knowledge as follows:

1. I am a board-certified Obstetrician-Gynecologist ("Ob-Gyn") physician at Saint Alphonsus Regional Medical Center in Boise, Idaho. In that capacity, I specialize in, among other aspects of care, inpatient management of complicated pregnancies and emergency assessment and management of pregnant women. Saint Alphonsus Regional Medical Center is a tertiary care medical center with a trauma designation and a Level 3 Neonatal Intensive Care Unit. Thus, it is a regional referral center for complicated pregnancies and frequently cares for patients with traumatic injuries during pregnancy. I submit this declaration in support of the Motion for Preliminary Injunction filed

by the United States in the above-captioned matter. Unless otherwise stated, the facts set forth herein are true of my own personal knowledge, and if called as a witness to testify in this matter, I could and would testify competently thereto.

2. I graduated from the University of California, San Francisco (“UCSF”) School of Medicine in 2006 and subsequently completed my residency in Obstetrics and Gynecology at the University of Maryland Medical Center in 2011. I am Board Certified in General Obstetrics and Gynecology by the American Board of Obstetrics and Gynecology.

3. In 2019, I moved to Idaho after accepting my current employment position as an Obstetric Hospitalist at Saint Alphonsus Regional Medical Center in Boise, Idaho. I have subsequently been elected to the position of Vice Chair of the Department of Obstetrics and Gynecology.

4. My family and I were drawn to Idaho for its natural beauty—including vast mountains and beautiful forests and all the recreation opportunities incumbent therein—along with its desirable pace of life and friendly communities. I also came to Idaho, in part, to fill a serious need for physicians generally, and especially Ob-Gyns, in the state.

5. There are zero residency programs in Obstetrics and Gynecology in the State of Idaho, meaning that all Ob-Gyns must be recruited from out of state. Idaho also has one of the fastest growing populations in the country. This dynamic has created a significant shortage of Ob-Gyns in our state.

6. Over the course of my nearly 15-year career as a practicing Ob-Gyn, I have treated thousands of pregnant women and delivered thousands of healthy babies.

7. Although as physicians we work to help our patients to experience normal pregnancies, culminating in the delivery of a healthy baby, not all pregnancies are as simple and complication-free as physicians and patients would like.

8. At Saint Alphonsus Regional Medical Center, we do not perform purely elective abortions, which are abortions performed in pregnancies that do not seriously threaten the health or life of the mother. However, there are situations where pregnancy termination in the form of an abortion is the only medical intervention that can preserve a patient's health or save their life. I will describe several recent examples of patients my colleagues and I have treated, which illustrate the dire circumstances that can make it medically necessary to terminate a pregnancy. Currently, our institution cares for patients in circumstances like these once every several months. However, I expect that this number will increase once Idaho Code § 18-622 goes into effect.

Jane Doe 1

9. Jane Doe 1 is a woman in her mid-20s who lives in a rural part of the state hundreds of miles away from Boise. I treated her and the facts I describe here were either personal observations I made or facts relayed to me for the purpose of treating Jane Doe 1.

10. Jane Doe 1 has two children of her own. Like many other women in our state, she decided to become a surrogate (also called gestational carrier) to provide additional income for her family and to help others who are unable to produce their own children. The intended parent and biological father of Jane Doe 1's pregnancy lives overseas.

11. When Jane Doe 1 was at 19-weeks' gestation, she was diagnosed with a pregnancy complication called preterm premature rupture of membranes ("PPROM"). PPRM is a premature breaking open of the amniotic sac. It increases the risk of life-threatening intra-amniotic infection (chorioamnionitis) and also increases the risk that the fetus will not develop normally due to a decrease in the amount of amniotic fluid.

12. Jane Doe 1 consulted with her personal obstetrician after the diagnosis of PPRM but was not advised that evacuation of the uterus was appropriate or necessary. Instead, she was incorrectly advised that terminating the pregnancy was illegal in Idaho following the Supreme Court's decision in *Dobbs* (which had occurred one week prior) due to Idaho's trigger law (even though Idaho Code § 18-622 was not yet in effect).

13. As her condition worsened, Jane Doe 1 spent several days in consultation with her surrogacy agency to determine her options. Eventually, she drove to Boise and presented to the emergency department at another hospital in the area. At this point, Jane Doe 1 had been experiencing cramps and chills for three days—signs of infection. The treating

physician gave her oral antibiotics and told her to return to her regular physician in a week.

14. Administration of oral antibiotics and discharge home is not the medically accepted standard of care for suspected chorioamnionitis. At this point, Jane Doe 1 was experiencing an increased risk of sepsis (a life-threatening condition) and a deepening infection of the uterus that, in addition to the deficient amniotic fluid, would have a direct negative impact on the fetus. In such cases, evacuation of the uterus and intravenous (“IV”) antibiotics is the only medically acceptable form of treatment.

15. Eventually, Jane Doe 1 presented to the Labor and Delivery Unit at Saint Alphonsus Regional Medical Center, where I first met her. She had been diagnosed with PPRM almost two weeks prior to presentation and had been experiencing worsening uterine cramping and chills for the past three days. I informed Jane Doe 1 that although fetal cardiac activity was still present, termination of pregnancy was the necessary course of action to preserve her life. The overseas intended parent for whom Jane Doe 1 was carrying the baby agreed with Jane Doe 1 that terminating the pregnancy was the best course of action due to the serious risks to both Jane Doe 1’s life and the health of his future child. I discussed with her medical and surgical options for uterine evacuation, and she chose a medical termination.

16. Shortly after she was given medication to induce labor, Jane Doe 1 spiked a high fever. She delivered the fetus after several hours; however, the placenta would not detach from the uterus, causing

her to start hemorrhaging. I transferred Jane Doe 1 to the operating room for a uterine curettage to remove the retained placenta. She was also given multiple medications to decrease the bleeding from her uterus. Still, she lost almost two liters of blood and required a blood transfusion. She was continued on IV antibiotics for another 24 hours and was discharged home in stable condition on hospital day number three.

17. Had Jane Doe 1 not received medical care to terminate her pregnancy, her intraamniotic infection would likely have led to sepsis thereby significantly increasing her chance of death.

18. If Idaho Code §18-622 was in effect when Jane Doe 1's case presented, I would have felt the need to consult with a lawyer in addition to the ethics and medical professionals I had already consulted in her case. This additional consultation would have further delayed Jane Doe 1's treatment in addition to taking me away from treating other patients in need.

19. Jane Doe's case illustrates an additional reason why Idaho Code § 18-622 is especially dangerous: Idaho's status as a destination for surrogacy. In my experience, Idaho has a very significant number of women who carry babies as surrogates. The prevalence of surrogacy in Idaho means that many pregnancies in the state are initiated through in vitro fertilization ("IVF") and are likely to be high-risk pregnancies that carry an increased risk of serious health complications for both the mother and the fetus.

Jane Doe 2

20. One year and 8 months ago, Jane Doe 2 presented to an outlying hospital emergency department at 19-weeks' gestation experiencing significant bleeding. I eventually treated her and the facts I describe here were either personal observations I made or facts relayed to me for the purpose of treating Jane Doe 2.

21. Jane Doe 2 was diagnosed with a placental abruption. This condition occurs when the placenta begins separating from the wall of the uterus before birth. Placental abruption decreases the blood and oxygen supply to the fetus and usually results in vaginal bleeding in the mother.

22. During the time she was under observation at the outside hospital, Jane Doe 2's condition worsened, and she developed disseminated intravascular coagulation ("DIC"). This is a dangerous condition that creates a high risk of death for the mother due to the rapid loss of large volumes of blood. Given that the outside hospital has minimal amounts of blood products in their blood bank, they requested to transfer Jane Doe 2 to Saint Alphonsus Regional Medical Center.

23. I first met Jane Doe 2 in the intensive care unit ("ICU") at Saint Alphonsus Regional Medical Center. The risk of her death at that point was imminent and the fetus still had a detectable heart rate by ultrasound. Although Jane Doe 2 was receiving multiple blood products at this point, her coagulation factors and anemia continued to worsen. The only medically acceptable action to preserve her life was immediate termination of the pregnancy.

24. An emergent dilation and evacuation procedure (“D&E”) was advised, and Jane Doe 2 was taken to the operating room. The D&E procedure was uncomplicated. She remained intubated in the ICU overnight and continued to receive multiple blood products. By the next morning, the DIC had resolved and her anemia improved. Jane Doe 2 was transferred out of the ICU at that point and discharged from the hospital two days later.

25. Jane Doe 2’s case illustrates the fact that some cases are so critical that there is simply no time to consult with a lawyer and debate, under the law, whether the proper medical standard of care should be used.

Jane Doe 3

26. Ten months ago, Jane Doe 3 presented to the Emergency Department at an outside hospital at 17-weeks’ gestation. She was suffering from shortness of breath and high blood pressure. Like Jane Doe 1, Jane Doe 3’s pregnancy was the result of IVF. I did not personally treat Jane Doe 3, but I have studied her case in the normal course of my work as part of educational conferences in the Department of Obstetrics and Gynecology at Saint Alphonsus Regional Medical Center.

27. After ruling out other conditions including COVID-19, pneumonia, and a blood clot in her lungs, Jane Doe 3 was diagnosed with pleural effusions, sometimes called “water on the lungs,” a condition that causes fluid to accumulate between the tissues that line the lungs and chest. Further examination revealed that Jane Doe 3’s pleural effusions were

being caused by a case of preeclampsia with severe features. Her fetus had detectable cardiac activity.

28. Preeclampsia is a dangerous pregnancy complication that can result in serious and potentially fatal complications to both the mother and the fetus. It rarely occurs before 20-weeks' gestation. When it occurs before 20-week's gestation, as it did for Jane Doe 3, it is typically severe and carries a high risk of maternal and fetal death.

29. The only medically acceptable standard of care for preeclampsia with severe features in Jane Doe 3's case was to terminate the pregnancy through evacuation of the uterus. She underwent an urgent D&E procedure. The pleural effusions and high blood pressure immediately began to improve after the pregnancy termination, and she was discharged home in stable condition several days later.

30. Had Idaho Code § 18-622 been in effect, my colleague, Jane Doe 3's treating physician, would have been in the position of assessing her own legal liability instead of simply assessing the patient's best interest.

Idaho Code § 18-622 and the Impact on Providers and Patients

31. Idaho Code § 18-622 is already harming women in Idaho. Specifically, in my experience as I describe above, the threat of criminal prosecution has already deterred doctors from providing medically necessary, life-saving care.

32. Idaho Code § 18-622 is also making it even more difficult to recruit Ob-Gyns to the State of Idaho. As I said, we already have a shortage of Ob-Gyns in

Idaho. Idaho Code § 18-622 places physicians in a very difficult position because of a conflict between the State law and our ethical obligations to patients and our obligations under Federal law. If an Ob-Gyn can practice in a state without these conflicts and risks, it is only natural that they would be deterred from practicing here. In fact, at least one of my colleagues has already decided to stop her part-time work at our hospital due to the stress of complying with this law.

33. In addition, in emergency situations, many of which present in the middle of the night, physicians often do not have time to consult with lawyers about whether a decision they believe is warranted by the standard of care and therefore in the best interest of their patient will result in a financially ruinous investigation into their practice or in criminal liability. Also, time spent by physicians in court defending their medical decisions will keep them from their clinical duties for significant periods of time. This will add to the shortages in hospital and clinic coverage, increasing the workload of their practice partners as well as increasing wait times for patients.

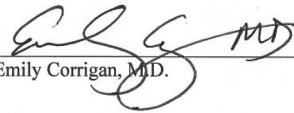
34. The fact that a doctor can defend herself in a criminal prosecution does not give me any comfort about the way the law will negatively affect patient care. Having to defend against such a case alone would be incredibly burdensome, stressful, costly, and accordingly, means that the availability of a defense really does not solve the problems presented by the law.

35. Idaho Code § 18-622's threatens to criminalize abortion, even in many medically

necessary circumstances, in a state where there is both a shortage of qualified physicians and a disproportionate number of high-risk pregnancies. This puts the health of Idaho women at significant risk.

I declare under penalty of perjury under the laws of the State of Idaho that the foregoing is to the best of my knowledge true and correct. Executed this 8th day of August 2022, in Boise, Idaho.

8/8/22
Date


Emily Corrigan, M.D.