NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Henderson JT, Vesco KK, Senger CA, et al. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021 Sep. (Evidence Synthesis, No. 205.)

Chapter 1 Introduction

Condition Background

Condition Definition

Preeclampsia is a pregnancy-specific disease that occurs after the 20th week of pregnancy and is defined as the new onset of hypertension (systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure [DBP] ≥90 mm Hg, on two occasions at least 4 hours apart) in a person with previously normal blood pressure, together with additional specified signs or symptoms.[1, 2] Although preeclampsia was historically diagnosed as hypertension accompanied by new onset proteinuria (300 mg/dL of protein in a 24-hour urine collection or a protein-to-creatinine ratio of 0.30 or more), in 2013 the American College of Obstetricians and Gynecologists (ACOG) revised the diagnostic criteria such that proteinuria is no longer requisite for diagnosis. In the absence of proteinuria, preeclampsia is diagnosed when hypertension is accompanied by any of the following signs or symptoms: thrombocytopenia; impaired liver function as indicated by elevated blood concentrations of liver enzymes and severe persistent right upper quadrant or epigastric pain unresponsive to medication; renal insufficiency; pulmonary edema; new-onset headache unresponsive to medication; or visual disturbances.[1] The presence of any of these systemic signs or symptoms, or of severe hypertension (systolic ≥160 mm Hg or diastolic >110mmHg), also define the clinical designation of "preeclampsia with severe features."[1]

Gestational hypertension alone (i.e. new onset hypertension after 20 weeks of gestation that is not accompanied by the additional signs and symptoms that define preeclampsia), is also associated with adverse pregnancy outcomes and an increased risk for future chronic hypertension and cardiovascular disease.[1] Gestational hypertension is defined as new onset of elevated blood pressure (SBP of 140 mm Hg or more or DBP of 90 mm Hg or more, on two occasions at least 4 hours apart) after 20 weeks gestation in the absence of proteinuria or other signs or symptoms of preeclampsia.[1] Gestational hypertension requires enhanced surveillance as up to 50 percent of women develop proteinuria or other signs of preeclampsia, and progression is more likely if hypertension arises prior to 32 weeks of gestation.[1] Chronic hypertension with superimposed preeclampsia is diagnosed when there is new onset of proteinuria beyond 20 weeks in a woman with chronic hypertension but without prior proteinuria, or sudden onset of the following: substantial sustained increases in protein excretion, exacerbation of hypertension with need to escalate antihypertensive medication dose, or manifestation of systemic signs and symptoms associated with preeclampsia.

Preeclampsia can remain stable until delivery, but occasionally can quickly and unpredictably take a more serious turn. Severe hypertension; eclampsia; hemolysis, elevated liver enzymes, and low platelet counts (HELLP syndrome); and other organ or systemic complications can lead to maternal or fetal injury and death.[2, 3] There is some variation in the diagnostic criteria for HELLP syndrome, but the following are widely agreed upon: lactate dehydrogenase elevated to 600 IU/L or more, aspartate aminotransferase and alanine aminotransferase elevated more than twice the upper limit of normal, and platelet counts less than 100×10^9/L.[1, 4,9] The majority of HELLP syndrome cases are seen in the third trimester, but about a third of cases present or progress postpartum. The primary symptoms of HELLP syndrome include right upper quadrant pain and generalized malaise, with nausea and vomiting seen in approximately half of cases.

Prevalence and Burden

Preeclampsia and eclampsia are the second and third most common causes of maternal morbidity and mortality worldwide, respectively.[5–7] Access to standard medical care has been shown to greatly improve health outcomes, as demonstrated by higher proportions of maternal mortality attributed to hypertensive disorders of pregnancy in lower income countries.[8]

In the United States, preeclampsia occurs in about 1 in 25 pregnancies that continue beyond 20 weeks of gestation. In a large retrospective cohort analysis of nearly 37 million deliveries (n=36,985,729) in the United States from 2006 to 2015, 3.8 percent received a diagnosis of preeclampsia. Severe preeclampsia increased as a proportion of preeclampsia cases over the study period, as did superimposed preeclampsia (preeclampsia arising in women with pre-existing chronic hypertension).[9] A rising trend in the proportion of hospital deliveries in the US complicated by preeclampsia and/or preeclampsia is evident from Healthcare Cost and Utilization Project data on all hospital deliveries in the United States, a 21 percent increase from 38.4 per 1,000 deliveries in 2005 to 46.6 per 1,000 deliveries in 2014).[10] Of over 175,000 deliveries with preeclampsia estimated in 2014 from these data, over one third (37%) were categorized as severe preeclampsia, 15 percent were cases among individuals with preexisting hypertension, and 1 percent resulted in eclampsia.[10]

In the United States, the risk of preeclampsia and of serious morbidity and mortality from the condition is greatest for Black women.[10, 11] Rates of preeclampsia are more than twice as high among Black women and more likely to manifest as severe disease. National estimates have shown that fewer than half of White women had severe preeclampsia whereas nearly two-thirds of cases among Black women were severe.[10, 12] Consequently, overall maternal mortality ratios and the contribution of preeclampsia/eclampsia to maternal mortality are higher for Black women.[13] Disparities in overall health, chronic health conditions, health care access, psychosocial stress, and systemic racial biases in health care are thought to contribute to the greater risk and worse outcomes of preeclampsia for Black women.[12, 14]

From 2011-2016, hypertensive disorders of pregnancy were responsible for 6.9 percent of pregnancy-related deaths in the United States.[13, 15] Significant maternal morbidities associated with preeclampsia include cerebrovascular bleeding, retinal detachment, and organ damage and failure complications from HELLP syndrome.[16, 17] Eclamptic seizures occur in approximately 1 to 2 percent of

preeclampsia cases, and can lead to death or serious complications such as brain damage, aspiration pneumonia, pulmonary edema, placental abruption, disseminated coagulopathy, acute renal failure, cardiopulmonary arrest, and coma.[5] Serious morbidity is more common than mortality; cohort data from obstetric patients attending 25 U.S.-based medical centers encompassing the Maternal-Fetal Medicine Units Network from 2008 to 2011 indicated that at least 21 percent of severe maternal morbidity (i.e., requiring surgical intervention, intubation, blood transfusion, or intensive care unit admission or diagnosed failure of at least one organ system) was attributable to hypertensive disorders of pregnancy.[18] The serious threat to maternal health associated with preeclampsia contributes to clinical decision-making related to the timing of delivery and other interventions to reduce maternal risk.

Preeclampsia increases the risk of adverse fetal, neonatal, and child health outcomes. These risks include intrauterine growth restriction, small for gestational age, low birth weight, preterm birth, placental abruption, stillbirth, and neonatal death.[2] The majority of preeclampsia cases occur after 34 weeks, but perinatal morbidity and mortality are greatest for early onset disease.[19] Due to the fact that the only effective treatment for preeclampsia is delivery, the condition is a leading cause of medically induced preterm birth and low birth weight. It has been estimated that preeclampsia contributes to 6 percent of preterm births and 19 percent of medically indicated preterm births.[20] Infants born before term (<37 weeks of gestation) are at increased risk of morbidity and mortality, with risks rising dramatically with earlier delivery.

There is also growing evidence that having preeclampsia is associated with increased risk of maternal chronic hypertension and cardiovascular disease later in life, including congestive heart failure,[21] myocardial infarction, and stroke.[22] The risk appears to be greatest among women who have experienced preeclampsia in more than one pregnancy,[23] required preterm delivery, or had a pregnancy complicated by fetal growth restriction.[24] Other data suggest that having had any hypertensive disorder of pregnancy may also be associated with long-term cardiovascular health risk.[25, 26] It is not yet clear whether this is due to common underlying risk factors for cardiovascular conditions across the life span, or whether the occurrence of a hypertensive disorder in pregnancy alters risk and predisposes one to future cardiovascular disease.

Etiology and Natural History

The underlying cause of preeclampsia is not fully understood, however, the placenta is thought to play a central role in its development. Preeclampsia can occur even in pregnancies without fetal development (e.g. hydatidiform mole) and it does not appear to regress until the placenta is removed or resorbed.[27] While delivery is important for curing the disease, its manifestations may take days or weeks postpartum to resolve, resulting in some cases presenting or being diagnosed in the postpartum period. The development of preeclampsia is usually presented as involving at least two stages—the placental stage and the maternal stage. The placental stage involves abnormal placentation, which contributes to early-onset preeclampsia (delivery<34 weeks gestation), and/or placental microvillus overcrowding, which develops with advancing pregnancy and is thought to contribute to late-onset of preeclampsia.[28, 29] The consequence of these changes is reduced placental perfusion, leading to hypoxia, placental ischemia, oxidative stress, and ultimately the release of damaging factors (i.e., cellular debris, oxidized lipids, antiangiogenic factors, soluble endoglin) into the maternal blood stream.[27, 30–32] The second, “maternal” stage involves the development of systemic maternal sequelae resulting from placental dysfunction.[27, 30] Placental damage leads to activation of platelets and the maternal clotting system,[33] and a systemic inflammatory response.[28] Changes in the renin-angiotensin-aldosterone system and increased sensitivity of blood vessels to contractile agents result in vasoconstriction.[30] Reduced perfusion, resulting from vasoconstriction, vascular occlusion by microthrombi, reduced vascular volume from leaking of fluid from the intravascular compartment, and vascular inflammation affect virtually every maternal organ in a women with preeclampsia.[27, 29] Placental perfusion abnormalities may also affect the fetus, leading to increased-risk of fetal growth restriction among women with preeclampsia.

Risk Factors

It is not clear why abnormal placentation occurs and preeclampsia develops, but the process may be influenced by maternal genetic, environmental, and immunologic factors.[27, 30, 34] In addition, the observation of heightened risk of preeclampsia during first pregnancies and in women who undergo in vitro fertilization with donor eggs has led to numerous investigations regarding the potential interaction of maternal physiology with fetal/paternal genes.[2, 35]

Factors associated with risk of preeclampsia can be classified into those obtained by clinical history, clinical exam, laboratory tests, and imaging. Patient characteristics associated with increased risk for preeclampsia include high pre-pregnancy BMI; nulliparity; [10, 36]maternal age greater than 35 years; family history of preeclampsia, specifically a mother or sister with preeclampsia; and family history of early-onset cardiovascular disease. In addition, Black race has been identified as risk marker because Black individuals have higher rates of preeclampsia and are at risk for more serious complications.[10, 36] These inequities have arisen from historical and present-day manifestations of racism and structural disadvantage that influence environmental exposures, access to health resources, and overall health status.[37] Current or past medical conditions that increase the risk of preeclampsia include preeclampsia, placental abruption, or stillbirth in a prior pregnancy; the presence of multifetal gestation; autoimmune disease, such as systemic lupus erythematous or antiphospholipid antibody syndrome; pregestational diabetes mellitus; chronic hypertension; renal disease; and conception via assisted reproductive technology.[38] Rates of preeclampsia associated with different risk factors vary. The medical history risk factors described above are more strongly associated with incidence of preeclampsia than patient characteristics such as nulliparity and maternal age, doubling or tripling the risk of developing preeclampsia. The presence of multiple risk factors, whether personal characteristics or medical history risk factors, further heightens risk for the condition. Individuals at lowest risk are those who have previously had an uncomplicated term pregnancy and do not have any conditions or circumstances known to increase risk.

Various maternal measures, including lab tests, blood pressure response to a stimulus, and ultrasound assessments of uterine artery blood flow, have been evaluated as means to identify women at increased risk of developing preeclampsia. In addition, several models have been developed that aim to identify women who are at risk of developing preeclampsia. Many of these models include variables

for medical history, patient characteristics, blood serum biomarkers (e.g., serum placental growth factor), mean arterial pressure (MAP), and ultrasound readings (e.g., Doppler uterine artery pulsatility index). The most extensively researched of these are various iterations of the Fetal Medicine Foundation (FMF) model; a recent publication provides the most complete development and validation evidence to date.[39] As in earlier studies of the model, performance was best for prediction of the more rare cases of preeclampsia requiring delivery early in pregnancy (<34 weeks). Evidence to support clinical application of available risk prediction models is limited, as there are very few external validation and implementation studies, and it is unclear whether risk prediction models are superior to risk assessment based on clinical history taking.[40]

Treatment Approaches

The only curative treatment for preeclampsia is delivery of the placenta. Current recommendations for delivery of patients with preeclampsia consider the risks and benefits both to the mother and the fetus. For women with gestational hypertension and preeclampsia without severe features, delivery is recommended when the patient reaches 37 0/7 weeks of gestation. For preeclampsia with severe features, delivery is recommended at 34 0/7 weeks of gestation, or at the time it occurs if after 34 0/7 weeks. Given the serious morbidity associated with HELLP syndrome, delivery is recommended regardless of gestational age at which it arises. Similarly, women with eclampsia should be delivered in a timely manner once the patient is stabilized. Close antenatal surveillance of women with gestational hypertension or preeclampsia without severe features arising prior to 37 weeks of gestation is required to assess for worsening disease or fetal compromise that might require more expedient delivery.[1]

Secondary prevention measures to avoid serious complications from preeclampsia include administration of antihypertensive medications to prevent stroke and administration of magnesium sulfate to prevent eclamptic seizures.[1, 41–44]

Preeclampsia Prevention

Interventions aimed at reducing the risk of preeclampsia have focused on several of the pathways potentially involved in its development, including vasoconstriction and platelet aggregation as well as metabolic abnormalities and nutritional deficiencies such as inadequate dietary calcium.[45] In a systematic review of 27 randomized trials of calcium supplementation for the prevention of preeclampsia, high-dose calcium supplementation (≥1 g/day) was shown to reduce the risk of preeclampsia and preterm birth, among women with a history of a low calcium diet (<900 mg/day).[46] Currently, the World Health Organization[47] recommends daily calcium supplementation (1.5-2.0 g oral elemental calcium) for pregnant women with low dietary calcium intake to reduce the risk of preeclampsia, whereas ACOG does not.[1] Medications such as heparin, metformin, sildenafil, and statins, nutritional supplements, and dietary modifications have been or are being explored for the prevention of preeclampsia, but, aside from calcium, none have been identified as efficacious.[48–53]

Acetylsalicylic acid (aspirin) demonstrates inhibitory effects on cyclooxygenases (COX) leading to shifts in the synthesis of prostacyclin and thromboxane A2.[54] This results in a two-fold action, reducing both platelet aggregation and vasoconstriction. Aspirin also leads to reduction in the synthesis of other prostaglandins, such as PGE2, which are involved with inflammation, contributing to aspirin's effect as an anti-inflammatory agent.[55] The inhibition of platelet aggregation and reduced vasoconstriction, as well as aspirin's anti-inflammatory effects[56] are thought to provide the basis by which aspirin administration may reduce the risk of development of gestational hypertension and preeclampsia.[54, 57, 58]

While no interventions eliminate preeclampsia risk, evidence from a moderate-sized body of trial evidence that includes several large trials has established that aspirin modestly reduces the risk of preeclampsia in increased-risk populations.[59–61] Trials conducted among average-risk populations where preeclampsia prevalence ranges from 3 to 5 percent have not consistently demonstrated preventive benefits, and concerns about potential bleeding from aspirin use as well as lack of data regarding long-term effects on the offspring[56] have supported guidelines focused on increased-risk populations.[1, 62] There have, however, been modeling studies and clinical discussions in recent years arguing for broader use of aspirin for prevention of preeclampsia. Most recently, a large multisite trial conducted in low income and middle income countries reported a statistically significant benefit of low dose aspirin use for prevention of preterm birth and perinatal mortality among nulliparous individuals.[63]

Previous USPSTF Recommendation and Recommendations of Others

In 2014, the USPSTF concluded with moderate certainty that there is a substantial net benefit of daily low dose aspirin use to reduce the risk for preeclampsia, preterm birth, and intrauterine growth restriction in women at high risk for preeclampsia, and recommended the prescription of low dose (81 mg/d) aspirin after 12 weeks of gestation to asymptomatic pregnant women who are at high risk for preeclampsia (B recommendation).

The USPSTF recommendation of low dose aspirin for women at high risk of preeclampsia was evaluated in a retrospective cohort study using a database of deliveries from two hospitals within a single academic institution.[64] Rates of recurrent preeclampsia for women with a history of preeclampsia in a prior pregnancy were compared for periods before and after the 2014 recommendation, spanning recommendation August 2011 to June 2016. Results showed that the risk of recurrent preeclampsia was 30% lower in the "after" group (adjusted relative risk, 0.70; 95% CI, 0.52, 0.95).[64]

Aspirin for women at high risk of preeclampsia is currently the only recommended method of prevention.[1] Low dose aspirin is recommended by the World Health Organization,[65] the American College of Obstetricians and Gynecologists,[66] the National Institute for Health and Clinical Excellence,[67] and the American Heart Association/American Stroke Association (Table 1).[68]

Table 1

Existing Clinical Recommendations.

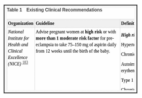

Table 1 Existing Clinical Recommendations

Organization	Guideline	Definit
National Institute for Health and Clinical Excellence (NICE) [1]	Advise pregnant women at **high risk** or with **more than 1 moderate risk factor** for pre-eclampsia to take 75-150 mg of aspirin daily from 12 weeks until the birth of the baby.	*High ri* Hyperte Chronic Autoim erythem Type 1

[Copyright Notice](#)

Bookshelf ID: NBK574452