



Preeclampsia: a report and recommendations of the workshop of the Society for Maternal-Fetal Medicine and the Preeclampsia Foundation

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Preeclampsia is a substantial cause of perinatal and maternal morbidity and mortality. The prevalence of this condition has increased over the past several decades. Additional opportunities are needed to foster interdisciplinary collaborations and improve patient care in the setting of preeclampsia. In recognition of the Preeclampsia Foundation's 20th anniversary and its work to advance preeclampsia research and clinical agendas, a 2-day virtual workshop on preeclampsia was cosponsored by the Society for Maternal-Fetal Medicine and the Preeclampsia Foundation and held January 25-26, 2021 in conjunction with the 41st annual pregnancy meeting. Leaders with expertise in preeclampsia research, obstetrical care, primary care medicine, cardiology, endocrinology, global health, and patient advocacy gathered to discuss preeclampsia prediction, prevention, management, and long-term impacts. The goals of the workshop were to review the following issues and create consensus concerning research and clinical recommendations:

- To present innovative opportunities for research on predicting, preventing, and managing preeclampsia
- To review the benefits and challenges associated with various strategies for preeclampsia prediction, prevention, management, and postpartum follow-up
- To identify research gaps for the prediction, prevention, management, and postpartum follow-up of preeclampsia
- To discuss needs and opportunities for research, increasing awareness, and risk mitigation of the long-term effects of preeclampsia

This report, developed collaboratively between the SMFM and the Preeclampsia Foundation, presents the key findings and consensus-based recommendations from the workshop participants.

Key words: maternal morbidity, maternal mortality, preeclampsia

Background

Evidence presented at the workshop demonstrates that although preeclampsia is associated with substantial health risks during and after pregnancy, there are opportunities to improve the prediction, prevention, management, and postpartum follow-up of patients with this disorder. Speakers highlighted the following:

- Although much remains to be elucidated regarding the heterogeneity in the incidence and manifestations of preeclampsia, this disorder is widely understood to be related to placental dysfunction and syncytiotrophoblast stress resulting from placental malperfusion. The root

cause of early severe forms has been attributed to abnormal placentation. Premature senescence or cellular aging has been proposed to underlie preeclampsia that manifests later in gestation.^{1,2}

- Preeclampsia is prevalent, occurring in 5% to 7% of pregnancies, representing approximately 10 million pregnancies per year worldwide.¹
- The incidence of preeclampsia increased by 25% between 1987 and 2004, potentially related to population-level increases in known risk factors for preeclampsia, such as prepregnancy overweight and obese status, diabetes mellitus (DM), multiple pregnancy, and advanced maternal age.³
- Hypertensive disorders are responsible for 14% of maternal deaths worldwide, representing the second leading direct obstetrical cause globally,⁴ and 7.8% of maternal deaths in the United States.⁵

- American Indian or Alaskan Native, Black, and Hispanic birthing people in the United States are at increased risk of maternal death in the context of hypertensive disorders of pregnancy compared with White birthing people secondary to multiple factors, including disproportionate burden of comorbidities, racial bias, structural racism, and inequitable treatment.⁵
- In low- and middle-income countries, a history of chronic hypertension (HTN) is associated with an approximately 8-fold increased risk of preeclampsia, and preeclampsia is associated with a 4.5-fold increased risk of maternal death highlighting the importance of increased detection and management of this comorbidity.⁶
- Preeclampsia is associated with a 3-fold increased risk of developing cardiovascular disease (CVD) later in life, which merits heightened awareness, risk mitigation, and improved postpartum follow-up.^{7,8}
- Studies have found an association between sleep-disordered breathing^{9,10} in pregnant patients and the development of preeclampsia.
- Higher rates of mental health disorders, including post-traumatic stress disorder (PTSD), depression, and anxiety,^{11–13} are also observed among patients who had preeclampsia. Prioritization and assessments of targeted risk assessment and interventions could reduce this risk, but more research is also needed to understand resilience factors.¹⁴
- Studies have reported associations of adverse neurodevelopmental and cardiovascular outcomes in offspring in association with in utero exposure to preeclampsia.^{15–17}
- Low-dose prenatal aspirin use has been found in many studies to decrease the risk of preeclampsia^{18,19}; however, optimal strategy for implementation (eg, eligible pregnancies, dosing, or gestational age at initiation and discontinuation) is still an area of ongoing debate and study.^{20–26}
- Remote home blood pressure (BP) monitoring, which has increased in popularity during the COVID-19 pandemic, is feasible for the identification of subpopulations with BP elevations who benefit from greater monitoring and treatment, particularly those at higher risk of morbidity and mortality, such as Black birthing people.^{27–29} More work is needed to demonstrate the benefit of this intervention and, if clinically beneficial, optimize and support access to its use both before and after delivery.^{30–34}
- Guidelines, bundles, and collaboratives focused on optimizing the identification and management of hypertensive disorders in pregnancy have been promoted to decrease maternal morbidity and mortality.^{35–37} Further research is needed to determine the effectiveness of these strategies on patient outcomes and potential unintended consequences.
- Improving outcomes related to preeclampsia domestically and globally will require listening to and engaging patients and those close to them,^{38,39} ensuring access to quality care (eg, respectful care, medical homes, and patient safety bundles),^{40–43} addressing systemic and community factors affecting health outcomes (eg, health insurance coverage),^{43,44} and investing in innovative care delivery models (eg, multidisciplinary clinics and telemedicine).^{30,42,45}
- Concomitantly, support is needed for basic, translational, and clinical research efforts that aim to expand our fundamental knowledge of disease pathophysiology and phenotypes and to develop improved management strategies targeting those who are most likely to benefit from existing or novel therapies.

Key findings and recommendations

The following key findings related to research and clinical care emerged from the workshop discussions:

- Preeclampsia is a complex, heterogeneous disorder. The clinical syndrome is composed of multiple overlapping clinical phenotypes that continue to complicate the diagnosis and management of the disease.
- Although multiple pathophysiological mechanisms have been associated with preeclampsia, placental dysfunction seems to be a unifying characteristic of the disease.
- Current research areas include preeclampsia risk assessment and risk stratification using molecular analyses (eg, protein biomarkers and genetic variants) to identify high-risk patients and primary and secondary prevention strategies using existing medications.
- Future research in the area of preeclampsia prevention and treatment should (1) use consistent and contemporary clinical definitions of preeclampsia; (2) incorporate molecular biomarkers that reflect the risk of disease or subsequent disease severity to aid with objective recruitment of patients and reporting of intervention outcomes, respectively; and (3) recognize a spectrum of preeclampsia severity that acknowledges several distinct pathways that may result in the same pathologic endpoint.
- Several modifiable diseases that are implicated in preeclampsia and adverse health outcomes—obesity, chronic HTN, DM, and sleep disorders—are potential targets for reducing rates of preeclampsia during and after pregnancy.
- Qualitative studies that incorporate patient experiences with preeclampsia are needed.
- As novel strategies for preeclampsia prevention, treatment, management, and postpartum follow-up are developed, the appropriateness and feasibility of such interventions must be considered in various settings, especially in low- and middle-income countries where there is a disproportionate burden of disease and resource limitations.
- Partnership with family medicine, internal medicine and their subspecialties, and emergency medicine should be pursued in the development and implementation of HTN care practices because of the important role these specialists play in caring for pregnant and postpartum people.

- Technologies, such as remote BP monitoring, telemedicine, mobile and online health applications, and social media, may be increasingly important interventions to reach, educate, and empower patients and may be crucial to improving access to some aspects of health-care.⁴⁶ Larger, pragmatic studies are needed to determine the impact of these technologies on patient outcomes and potential unintended consequences.
- Clinical interventions with the potential to improve preeclampsia outcomes that warrant further research include the use of diuretics, complement inhibition, statins, more aggressive BP maintenance, postpartum and interpregnancy angiotensin-converting enzyme inhibitors, and optimal timing of delivery. Optimal delivery timing also remains an important area of uncertainty worthy of ongoing discussion.
- Patients with preeclampsia should have access to close clinical follow-up in the early postpartum period and care coordination with a primary care provider or cardiology for long-term risk assessment and mitigation.
- Patients and their loved ones are at higher risk of mental health sequelae (eg, anxiety and PTSD) after experiencing preeclampsia and merit related screening and trauma-informed care accordingly.
- Optimization of long-term cardiovascular risk stratification and mitigation for patients who experience preeclampsia is needed given the underestimation of risk by many existing tools.
- The immediate postpartum period is an important time for clinicians to target interventions for people with preeclampsia. The rates of maternal morbidity and mortality are the highest during this time frame, and safe, effective interventions exist.

Preeclampsia: “imitator” or “originator”?

Preeclampsia is often referred to as the “great imitator.” This description arises from the phenotypic similarities between preeclampsia and other diseases.⁴⁷ However, we argue that this label is flawed and that preeclampsia does not merely mimic other conditions. Alternatively, perhaps the mechanisms underlying its progression are shared or common to other diseases. We propose that reconceptualizing the framework for preeclampsia will be an important step forward towards its mechanistic origin.

Preeclampsia is associated with an increased risk of adverse health outcomes for pregnant people and their children later in life.^{7,8,15–17} Because of the potential implications for lifelong health, more fervor in understanding the mechanistic pathways and nidus of disease is needed. Clinicians and researchers are encouraged to disentangle and examine the various manifestations of preeclampsia instead of merging the diverse array of phenotypes into 1 category.⁴⁸ Approaching the mechanistic pathways underlying preeclampsia as “originators” of other conditions or a disease process with its origin, will generate findings that

benefit pregnant patients, their families, and the scientific community overall.

Preeclampsia prediction strategies and research needs

Role of predictive tools for preeclampsia

Research efforts have focused largely on the early prediction of preeclampsia or the development of adjunct diagnostic tests. Early detection of heightened risk of preeclampsia through early risk assessment has the potential to improve outcomes by identifying candidates for prophylaxis, such as acetylsalicylic acid and BP control, and those who might benefit from increased surveillance. Furthermore, early risk assessment would ideally enable researchers to detect disease earlier and define a target population for treatment. This approach—akin to cancer screening, risk mitigation, and treatment—not only is more cost-effective than enrolling all patients but also increases the likelihood of identifying true treatment effects by limiting the enrollment of candidates (nonresponders) who are unlikely to manifest preeclampsia or its severe sequelae.

The ideal early risk assessment strategy would be safe, valid, reliable, easy to perform, and cost-effective.⁴⁹ The disease should be medically important and clearly defined, and an intervention must be available; the burden of preeclampsia worldwide and the effectiveness of low-dose aspirin prophylaxis satisfy these criteria. Historically, national guidelines have endorsed the assessment for preeclampsia risk based on maternal factors, such as a history of preeclampsia, multifetal pregnancy, chronic HTN, or autoimmune disease.^{50–53} No combined risk assessment strategy (ie, which uses molecular biomarker or imaging modality in addition to clinical risk factors) has been universally endorsed because of unclear cost-effectiveness and the need for more evidence demonstrating robust performance, including validation studies with adequate sample size and diversity. In addition, the potential harms of high false-positive rates after combined early risk assessment require examination.⁵⁴

Several caveats regarding the use of early risk assessment for preeclampsia were discussed during the workshop. Although screening that identifies individuals who will develop early, severe forms of preeclampsia could avert the most severe adverse outcomes, a minority of preeclampsia cases fall into this category.⁵⁴ Another important discussion point regarding equity was that screening requires the early establishment of prenatal care. This approach may disproportionately preclude populations that have historically experienced barriers to healthcare, such as lack of insurance coverage and distance from a provider, but are nevertheless at high risk of developing preeclampsia. Furthermore, although there is general agreement that identification of appropriate candidates for low-dose aspirin prophylaxis is an important goal, in the United States, many patients will already meet the criteria for treatment based on

the US Preventative Services Task Force (USPSTF) criteria.^{18,55} Thus, despite some geotargeted analyses,⁵⁶ the added value and cost-effectiveness of universal screening beyond clinical risk factors in the United States remains undetermined, until other interventions are identified.

In addition, objective tests may have a role later in pregnancy during the evaluation for suspected preeclampsia as diagnostic and prognostic tools. When an individual presents to a clinic or labor and delivery triage with new-onset HTN or symptoms, prompt and accurate diagnosis and risk stratification are key. Biomarker tests have been studied extensively for their potential to improve clinical decision-making in this context by (1) increasing the confidence in and shortening the time to diagnosis of preeclampsia⁵⁷ and (2) identifying individuals at risk of disease progression and adverse outcomes.⁵⁸ These tests have the potential to help ensure appropriate surveillance (eg, high-risk patients are not inappropriately discharged from the hospital) and to aid in the decision to transfer to a higher-level center if needed. Moreover, there has been interest in their use as rule-out tests given their high negative predictive value. A test that reliably rules out development of severe disease or need for delivery within the next week could allow for safe outpatient monitoring of appropriately lower-risk patients and also provide reassurance to patients and clinicians.

Use of biomarkers for early risk assessment and prediction

Biomarkers have been studied alone and as part of combined strategies, such as the Fetal Medicine Foundation approach for preeclampsia screening.⁵⁹ Although several placenta-derived proteins have been evaluated, the best-studied and most robust predictive biomarkers for preeclampsia are the angiogenic factors placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1).⁶⁰ Consistent alterations in levels of these circulating factors in preeclampsia and other diseases of placental dysfunction (eg, fetal growth restriction [FGR], stillbirth, and placental abruption) occur before the manifestation of clinical disease and reflect shared underlying pathophysiology involving placental hypoperfusion and oxidative stress.⁵⁴ PlGF and sFlt-1 currently seem to be the best clinically available markers of placental reserve and are used in most commercial preeclampsia tests for both screening and diagnostic aids during the evaluation for suspected preeclampsia; however, no biomarker test for preeclampsia is currently available for commercial use in the United States.

Despite their potential and use in some countries (eg, the United Kingdom), some challenges have limited the widespread adoption of biomarker tests. Reference ranges are dependent on gestational age; thus, accurate gestational dating is essential. Different assays for the same protein may not be comparable because of differences in assay performance and specifications.⁶¹ Importantly, the presence of placental dysfunction is not sufficient to cause

disease, and poor positive predictive value remains a concern (ie, the maternal phenotype does not manifest in all cases of placental dysfunction). Fetoplacental-maternal interactions are complex, and disease phenotype depends on multiple factors, including maternal susceptibility (pre-existing chronic disease and genetic predisposition) and the adequacy of compensatory responses. The National Institute for Health and Care Excellence (NICE) is the only organization that currently recommends incorporating biomarkers into standard clinical assessment and subsequent clinical follow-up to assist with ruling out preeclampsia.⁶² Guidance from the American College of Obstetricians and Gynecologists (ACOG) in 2020, the Society of Obstetricians and Gynaecologists of Canada (SOGC) in 2014, and the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2018 states that the use of biomarkers and ultrasonography in the prediction of preeclampsia should remain investigational and cannot be recommended routinely until such screening has been shown to improve pregnancy outcome.^{50–52}

Novel tests and prediction models are being developed using data from transcriptomic and proteomic studies.^{63–65} Recent work has identified maternal cell-free RNA signatures associated with preeclampsia.^{64,66} Another example is the Congo red dot paper test based on proteomic studies showing that misfolded proteins are present in the urine of patients with preeclampsia.^{67,68} Although workshop participants agreed that basic science efforts and exploratory omics studies are important for the discovery of novel biomarkers, participants also expressed the desire to see in-depth study and validation of existing biomarkers given the substantial amount of effort it takes to bring any one candidate to clinical use. A major challenge arising from the complexity of preeclampsia and its heterogeneity and subphenotypes is the lack of validation of predictive algorithms. A recent study showed that protein-based prediction models derived from 2 cohorts from different geographic regions with disparate sociodemographic characteristics did not perform well when cross-validation was attempted.⁶⁹ Thus, multicenter studies that include diverse participants are necessary to develop prediction models that perform well for different populations and can be implemented beyond a local setting. In addition, the identification and separate investigation of disease subtypes will likely improve the accuracy of predictive tests.⁴⁸

Prediction research strategies

Various research strategies are being used to better predict who is most at risk of developing preeclampsia and subsequent adverse outcomes once a diagnosis has been established.^{67,70} Experimental studies in patients and animal models during the last decade have led to a better understanding of the pathophysiology of this disorder and therapeutic targets for treatment.¹ Placental ischemia caused by impaired placental spiral artery remodeling and reduced perfusion is thought to play a central role in the

pathophysiology of many, but not all, instances of preeclampsia.^{71,72} The release of antiangiogenic and proinflammatory placental factors from the ischemic placenta results in an up-regulation of the endothelin system, impaired production of nitric oxide, and vasoconstriction that contributes to disruptions in cardiac, cerebrovascular, renal, and hepatic function and, subsequently, the development of HTN.⁷¹ Workshop participants concluded that translational research incorporating findings from animal models, in vitro studies, and clinical studies is necessary to develop successful preeclampsia treatment and prediction strategies.

The application of machine learning for early detection of preeclampsia and identification of subtypes of the disorder and molecular targets for intervention is a relatively recent and new approach. By identifying patterns within large datasets, such as ultrasound imaging data, machine learning may be a useful strategy for predicting or classifying preeclampsia subtypes. Workshop participants emphasized that such an approach has been successful in cancer research, where the focus has shifted to classifying disease subtypes based on tumor genotype.

However, there is a potential for unintended consequences of machine learning. Because models are built by humans, they can be trained to reinforce existing biases related to race and ethnicity, age, or other variables. A reliance on machine learning or artificial intelligence has the potential to result in overtesting during pregnancy and removing the “human element” from clinical practice. Workshop participants cautioned that although a global, big data approach may help identify new mechanisms underlying the pathophysiology of preeclampsia, basic science approaches will still be necessary to test hypotheses generated through machine learning and from any exploratory experiments or datasets.

As noted previously, omics, including genomics, transcriptomics, proteomics, and metabolomics, have uncovered insights into disease pathophysiology and further highlighted the heterogeneity of preeclampsia. Preeclampsia is a complex genetic trait with heritability that has been estimated at 55% to 60%.⁷³ Genome-wide association studies (GWASs) have been used to identify variations in the maternal and fetal genome associated with an increased risk of preeclampsia.^{74–76} For example, results from a GWAS of 4380 offspring from pregnancies with preeclampsia compared with that of 310,238 controls suggest that multiple causal variants near the fetal *FLT1* locus may contribute to disease risk. This association is biologically plausible as *FLT1* encodes fms-like tyrosine kinase 1, which has been implicated in the pathology of preeclampsia.^{74,75} A meta-analysis of 8 GWASs comparing 9515 women with preeclampsia with 157,719 controls found 1 locus near the fat mass and obesity-associated gene with genome-wide importance in the risk of preeclampsia.⁷⁵ Moreover, this locus has been found to be important in the development of HTN and increased body mass index (BMI), supporting overlap among preeclampsia genetics with other traits.⁷⁵

Future omics studies will require large, well-phenotyped cohorts with genetic data to examine relationships among individual data points. Thus far, research in this area has been limited by cohorts without paired maternal-fetal or placental samples and studies of small sample sizes or with different methodologies. Sharing data and biosamples is necessary to acquire sufficient data and materials for omics studies. This sharing would be facilitated by common definitions and endpoints^{77–79} and the use of harmonized databases.⁸⁰

Future research

Exciting advances in preeclampsia research have revealed insights into the complex biology and mechanisms underlying the syndrome. However, our knowledge of disease biology and the optimal approach to clinical management remains incomplete. Improving our primitive understanding of preeclampsia requires the integration of basic science and clinical research through multidisciplinary collaborations between physicians and scientists. Advanced approaches in the laboratory, including comprehensive assessments of circulating placental factors during pregnancy, and the application of sophisticated analytical techniques, such as machine learning, are generating novel hypotheses and big data ripe for discovery. Simultaneous investigation of protein function and fundamental disease mechanisms using in vivo and in vitro model systems will continue to be important to validate and interpret findings from exploratory studies.

The identification of preeclampsia subtypes based on mechanism is crucial if we are to develop a classification scheme that is useful for clinical research. The recognition and subtyping of disease-based molecular phenotypes similar to the approach that has been taken in oncology would enable the move away from the suboptimal one-size-fits-all approach toward the ultimate goal of precision medicine—the right treatment for the right patient at the right time.⁸¹ In clinical research, the grouping of heterogeneous patients under the umbrella of “preeclampsia” has likely diluted effect sizes and undermined efforts to identify interventions effective for certain subtypes of preeclampsia. International consensus regarding a framework for preeclampsia diagnosis and classification is an important goal so that study results can be compared and for cross-validation efforts.

Preeclampsia prevention strategies and research needs

Aspirin

Aspirin has been studied extensively for its role in modification of cardiovascular health. Initial investigation of aspirin's role in preventing preeclampsia began in the 1980s. Since that time, it has emerged as a recommended medical treatment in the prevention of preeclampsia.

In 2013, the ACOG published the *Hypertension in Pregnancy Task Force Report*, which supported the use of

low-dose aspirin in people with a previous history of early-onset preeclampsia or multiple pregnancies complicated by preeclampsia. In 2021, the ACOG and the SMFM recommended the use of low-dose aspirin (81 mg/day) between 12 and 28 weeks of gestation in people at high risk of preeclampsia and those with multiple moderate risk factors.^{82,83} Many other large healthcare organizations have adopted recommendations regarding the use of antiplatelet agents for the prevention of preeclampsia, including the USPSTF, NICE, and World Health Organization (WHO).^{18,53,84} These recommendations are summarized in Table 1.

Antiplatelet therapy has some of the most robust evidence as a prevention strategy for preeclampsia. However, interpretation of the data has resulted in varying opinions regarding the optimal dose, timing, and target population, as reflected by the differing recommendations by national organizations, suggesting more research is needed to refine and standardize treatment guidelines. The earliest trials exploring the use of low-dose aspirin demonstrated a reduction in preeclampsia with doses between 60 and 100 mg daily; however, these trials were limited by small sample size.^{85–88} Initial randomized trials, such as the 1994 Collaborative Low-Dose Aspirin Study in Pregnancy trial and the 1998 National Institute of Child Health and Human Development (NICHD) Network of Maternal-Fetal Medicine Units trial called into question the efficacy of aspirin in preventing preeclampsia among women at risk of the condition.^{89,90} Other randomized trials of aspirin for the prevention of preeclampsia among healthy, nulliparous women demonstrated a very small or no effect on the incidence of preeclampsia in this population.^{91,92}

Since this time, however, several large studies have demonstrated a modest risk reduction with variable doses of aspirin. A 2007 Cochrane review of 59 trials noted an overall 17% reduction in preeclampsia with antiplatelet therapies. Subgroup analysis comparing those trials using ≤ 75 and > 75

mg of aspirin showed a greater relative risk (RR) reduction with higher doses (RR, 0.88 vs 0.64).¹⁹ In the same year, the Perinatal Antiplatelet Review of International Studies Collaboration—an individual patient data meta-analysis of 31 randomized trials—found an RR of 0.9 (95% confidence interval [CI], 0.84–0.97) for preeclampsia with doses of aspirin ranging from 50 to 150 mg daily.⁹³ The effects of a similar aspirin dose range (60–150 mg daily) were the subject of a systematic review by the USPSTF in 2021 that pooled data from 23 good- and fair-quality randomized trials. This review reported a 15% reduction in preeclampsia among patients administered aspirin compared with controls (16 randomized controlled trials [RCTs], $n=14903$; RR, 0.85; 95% CI, 0.75–0.95).¹⁸ The Aspirin for Evidence-Based Preeclampsia Prevention (ASPPE) trial—a recent multicenter randomized trial of 1776 at-risk patients—showed a decreased odds of developing preterm preeclampsia in the 150 mg per day aspirin group compared with the placebo group (odds ratio [OR], 0.38; 95% CI, 0.2–0.74; $P=.004$).⁹⁴ Conversely, a 2021 multicenter randomized trial of 898 at-risk patients in China failed to show a statistically significant reduction in the incidence of preeclampsia (RR, 1.220; 95% CI, 0.720–2.066; $P=.459$) among a high-risk pregnant population.⁹⁵

Most studies of low-dose aspirin for preeclampsia prophylaxis start intervention between 12 and 28 weeks of gestation. Large studies evaluating the timing of low-dose aspirin have consistently used 16 weeks of gestation to distinguish comparative groups. Several large aggregate meta-analyses have shown the greatest reduction of severe preeclampsia when low-dose aspirin is started before 16 weeks of gestation.^{96,97} However, a recent individual patient data meta-analysis showed consistent benefit regardless of the timing of low-dose aspirin, concluding that high-risk people should be offered prophylaxis even if their entry to prenatal care is beyond 16 weeks of gestation.⁹⁸ No study has demonstrated apparent benefit to discontinuing aspirin

TABLE 1
Recommendations for low-dose aspirin for prevention of preeclampsia

Organization	Dose recommendation
USPSTF (2021) ¹⁸	81 mg daily after 12 weeks of gestation with any high-risk condition or more than 1 moderate-risk condition
ACOG or SMFM (2021) ⁸³	81 mg daily between 12 and 28 weeks of gestation (ideally by 16 weeks) with any high-risk condition ^a or more than 1 moderate-risk condition ^b
WHO ⁸⁴	75 mg daily before 20 weeks of gestation with any high-risk condition
NICE (2019) ⁵³	75–150 mg daily after 12 weeks of gestation with any high-risk condition

ACOG, American College of Obstetricians and Gynecologists; NICE, National Institute for Health and Care Excellence; SMFM, Society for Maternal-Fetal Medicine; USPSTF, United States Preventive Services Task Force; WHO, World Health Organization.

^a High-risk factors: history of preeclampsia, especially when accompanied by an adverse outcome, multifetal pregnancy, chronic hypertension, pregestational type 1 or 2 diabetes mellitus, kidney disease, autoimmune disease (ie, systemic lupus erythematosus or antiphospholipid syndrome), or combinations of multiple moderate-risk factors.; ^b Moderate-risk factors: nulliparity, obesity (ie, body mass index of >30), family history of preeclampsia (ie, mother or sister), age of ≥ 35 years, personal history factors (eg, low birthweight or small for gestational age, previous adverse pregnancy outcome, and >10 -year pregnancy interval), and in vitro pregnancy. The moderate-risk factors Black race (as a proxy for underlying racism) and lower income are associated with increased risk of preeclampsia because of environmental, social, structural, and historic inequities shaping health exposures, access to healthcare, and the unequal distribution of resources, not biologic propensities, and low-dose aspirin can be considered if the patient has one of these moderate-risk factors.

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before delivery, and current guidelines recommend continuation until delivery.^{82,83}

Maternal risk stratification is common in most professional organization recommendations for determining the target population for low-dose aspirin prophylaxis.^{18,84} In a 2019 Cochrane review, the administration of aspirin led to a substantially greater reduction in the development of preeclampsia in high-risk pregnancies than in moderate-risk pregnancies, 25% vs 14%, respectively.¹⁹ Similarly, the analysis of risk group disease prevalence and treatment effect by the USPSTF suggests that a risk of preeclampsia of at least 8% be used to identify high-risk patients likely to benefit from low-dose aspirin.¹⁸ Because aspirin is inexpensive, is widely available, and has favorable maternal and fetal safety profiles, some experts have advocated for the universal administration of aspirin during pregnancy for the reduction of preeclampsia and other adverse perinatal outcomes.^{20,21,55,99}

Workshop participants emphasized that the potential benefits of aspirin therapy in the prevention of preeclampsia cannot be achieved without patient awareness and support. Discussion of the risks and benefits of low-dose aspirin therapy in pregnancy should be a component of the initial prenatal visit, especially for people at high risk of developing preeclampsia during their pregnancy. Educational resources for patients are available through organizations, such as MotherToBaby (<https://mothertobaby.org/fact-sheets/low-dose-aspirin>), the Preeclampsia Foundation (<https://www.preeclampsia.org/aspirin>), and the SMFM (<https://www.highriskpregnancyinfo.org/preeclampsia>). Moreover, providers should be aware of additional opportunities for delivering information and resources to at-risk individuals. Programs, such as Aetna Maternity Program—a collaboration between CVS Health and Aetna—use insurance claims data to identify people at high risk of preeclampsia. The Aetna program sends a kit containing educational materials and a bottle of 81 mg aspirin to patients to promote awareness of preeclampsia and encourage patient-initiated engagement with their prenatal providers on this topic.¹⁰⁰

Statins

Statins are another class of commonly used drugs that have become a focus for preeclampsia prevention research. Statins are classically known as cholesterol-lowering agents; however, their use in overall endothelial health is becoming more evident. Beyond their antiatherogenic properties, statins have also been implicated in the stabilization of atherosclerotic plaques, endothelial protection, and decreased inflammation.¹⁰¹ These characteristics contribute to the biologic plausibility of statins as agents to prevent the development of preeclampsia.

Pravastatin, a first-generation statin, was discussed during the workshop as a potential candidate for treatment in both animal and human trials. As a low-potency statin with limited transplacental transfer, pravastatin has consistently

shown a lack of teratogenicity in observational and randomized trials. Safety profiles have been well established in the nonpregnant adult population.¹⁰¹ A 2016 pilot randomized trial conducted by the *Eunice Kennedy Shriver* NICHD Obstetric-Fetal Pharmacology Research Units Network found a reduction in the rates of preeclampsia in the small group of patients with a previous history of preterm preeclampsia who received 10 mg pravastatin initiated between 12 and 16 weeks of gestation compared with placebo (40 vs 0%).¹⁰² The data are promising and signal a possible effective intervention but the small size of 10 patients per arm precludes definitive judgment. A 2021 double-blind placebo-control trial randomized 1120 high-risk patients between 35 and 36 weeks of gestation to pravastatin 20 mg vs placebo. Pravastatin in these patients did not reduce the incidence of delivery with preeclampsia in this study.¹⁰³

Although further trials will help define the role of pravastatin as an effective prophylactic treatment in the development of preeclampsia, other studies have examined its role as a therapeutic agent in pregnancies after the diagnosis of preeclampsia. The Statins to Ameliorate Early Onset Preeclampsia randomized trial did not find a difference in maternal sFlt-1 levels, latency to delivery, or other pregnancy outcomes.¹⁰⁴ Conversely, in a prospective study of women with antiphospholipid antibody syndrome, those who received pravastatin 20 mg in addition to standard of care at the time of preeclampsia diagnosis were found to have lower BPs, longer pregnancy latency, and higher infant birthweights.¹⁰⁵ Given the current body of literature, the use of statins for the prevention or treatment of preeclampsia is promising, but it remains investigational.

Novel therapeutics

Preeclampsia therapeutics is a burgeoning field within maternal care. There is insufficient evidence to recommend many of the proposed prevention modalities, including vitamin C, vitamin E, vitamin D, folic acid, fish oil, garlic supplements, and sodium restriction.⁵⁰ Metformin has been studied as a potential medical therapy with promising findings.¹⁰⁶ Similar to statins, metformin has been shown to alter angiogenic imbalance by reducing sFlt-1 and soluble endoglin.¹⁰⁷ A meta-analysis of studies in high-risk women with insulin resistance did not show a reduction in preeclampsia compared with placebo or control; however, there was a reduction noted among 8 randomized trials comparing metformin with insulin (RR, 0.68; 95% CI, 0.48–0.95; $P=.02$; $I^2=0\%$).¹⁰⁸ Moreover, non-pharmaceutical interventions are being explored as a strategy for preeclampsia treatment. In 2011, Thadhani et al¹⁰⁹ investigated single dextran sulfate cellulose apheresis treatment in women with very preterm preeclampsia and showed a reduction in circulating sFlt-1, proteinuria, and BP. Current use of metformin and plasma apheresis for the prevention and treatment of preeclampsia is limited to clinical trials.

Future research and clinical issues

Compelling evidence for any 1 prevention strategy for people at risk of preeclampsia has not yet been found, and given the heterogeneity in disease subtypes and phenotypes, it is unlikely that a single intervention will be beneficial in all cases. Even the best candidates for treatment regimens, including aspirin and statins, are met with conflicting results from trials often limited by small sample size or inconsistent definitions of disease. Future research in the area of preeclampsia prevention depends on establishing an objective framework for stratifying patients into trials (potentially using biomarkers) and selecting appropriate interventions based on risk factors and preeclampsia subtypes. In the past 30 years, our understanding of preeclampsia has evolved from a hypertensive disorder with renal dysfunction to a complex cascade of angiogenic and inflammatory dysfunctions resulting in a multisystemic syndrome. This evolution has seen multiple iterations of the definitions and clinical diagnostic criteria of preeclampsia. This fact alone confounds the interpretation of noncontemporary randomized trials and large meta-analyses and brings into question the actual disease and severity being assessed.

As such, future research in the area of preeclampsia prevention should (1) use strict, consistent, and contemporary clinical criteria for defining preeclampsia; (2) incorporate molecular biomarkers that reflect the risk of disease or subsequent disease severity to aid with objective recruitment of patients and reporting of intervention outcomes, respectively; and (3) recognize a spectrum of preeclampsia severity that acknowledges several distinct pathways that may result in the same pathologic endpoint.

Filling gaps in knowledge is a priority not only for improving the efficacy of current well-investigated prophylactic strategies but also for identifying potential innovations in preeclampsia prevention. Although low-dose aspirin is currently endorsed by the ACOG and the SMFM, additional large RCTs are needed, such as the ASPRE trial,¹¹⁰ that incorporate serum markers into maternal risk stratification. Head-to-head trials comparing different doses of aspirin will aid in determining optimal dosing and adjust for variations in dosing based on regional availability of drug formulations. Translational research of thromboxane and prostacyclin imbalance in preeclampsia not only will improve understanding of aspirin's mechanistic role in preeclampsia prevention but also may offer novel assays that can be used for risk stratification. Lastly, there is a paucity of data regarding the use of low-dose aspirin in the prevention of postpartum preeclampsia.

As studies continue to investigate the role of statins in the prevention of preeclampsia, a need for additional large, randomized trials will also be warranted to define the optimal statin drug, dose, timing, and target population. In addition, future studies comparing the effects of low-dose aspirin vs statin vs combination should be explored. Although safety data for pravastatin have been established during

pregnancy, it is prudent to follow long-term infant neurodevelopmental outcomes because of the intimate role of cholesterol in fetal brain development.

Abundant opportunity exists to study preeclampsia prevention strategies concerning population health and health-care disparities. Several modifiable diseases that are implicated in preeclampsia and adverse health outcomes—obesity, chronic HTN, DM, and sleep disorders—are potential targets for reducing rates of preeclampsia. Weight reduction and bariatric surgery have been associated with reduced rates of hypertensive disorders of pregnancy.¹¹¹ Similarly, the use of continuous positive airway pressure therapy in people with sleep-related breathing disorders may be an avenue to reduce preeclampsia and modify future cardiovascular risk long term.¹¹² Additional studies that reliably include race and ethnicity and address healthcare disparities, effects of systemic racism, and the role of psychosocial stressors not only contribute to data on preeclampsia prevention but also help ensure equity in population trials.¹¹³ Moreover, qualitative studies incorporating patient voices and their experiences with provider counseling on preeclampsia prevention are important to evaluate how evidence-based recommendations for prevention are performed on a practical level. Programs, such as the Preeclampsia Foundation's Cuff Kit Program, Aetna's Maternity Program, and various remote BP monitoring programs, can be leveraged to study ways to reduce disparities in patient education and intervention in high-risk populations. Lastly, it is crucial to continue to study efforts of preeclampsia prevention globally. Multinational data from the WHO have shown that an increased number of antenatal visits was protective for preeclampsia.⁶ As novel strategies for preeclampsia prevention arise, consideration of intervention cost and disease effect in low- and middle-income countries must be considered when formulating recommendations.⁶

Preeclampsia management strategies and research needs

Telehealth in preeclampsia

Telehealth and patient monitoring range from patient input of blood sugars and BP in the settings of DM and hypertensive disorders of pregnancy to face-to-face consultation using camera services.^{114–116} The COVID-19 pandemic necessitated the expansion of telehealth and showed its potential to provide a mechanism for improved provider-patient relationships and care continuation, including in the setting of preeclampsia. Research from before the pandemic showed that telehealth is useful.^{114–116} Telehealth may even provide equitable access to care by reducing geographic or social barriers posed by in-person visits. Patients can consult with clinical teams and seek expert opinion in other geographic regions. Moreover, it adds active patient participation and accountability via recording data points, such as BP and maternal weight. Therefore, it is not surprising that telehealth may be a

reasonable option for monitoring patients for preeclampsia, specifically in the postpartum period.^{27,31}

Similar to many areas of medicine, the use of telehealth must continue to be evaluated for overt and underlying disparities. For example, although institutions may report that telehealth visits are available to everyone, there may be disparities in access to mobile devices, wireless Internet and cell phone coverage, technology literacy, home BP monitors, and safe and private spaces to discuss medical care. Social media and electronic health records may be useful mechanisms for providing information to patients. However, clinicians should be aware that ease of use for patients with 1 technology may not translate to another. It is important for patients to receive information through methods and language that they can easily understand.

Bundles

Approximately 50% to 60% of pregnancy-related deaths are preventable.^{117,118} In a study of pregnancy-related deaths in California, 60% of preeclampsia deaths were preventable.¹¹⁹ Similar preventability has been observed for severe maternal morbidity (SMM), particularly in cases of preeclampsia and severe HTN.^{120–122} Provider factors, such as knowledge and referral, and system of care factors, such as communication, have been identified as key contributors to preeclampsia and eclampsia deaths.¹²³

Maternal safety “bundles” are 1 intervention aimed at reducing such preventable adverse outcomes.^{41,124} Bundles are developed from evidence-based guidelines and expert opinion and provide standardized approaches to managing obstetrical emergencies and complications. Bundles include patient information, provider information, and algorithms that include risk assessment tables and medication dosages. The national and international investments in maternal safety bundles, such as the severe HTN bundle, stem from the preventable nature of maternal morbidity and severe maternal mortality and the relatively simple measures for treating HTN.

The use of care bundles in obstetrics does show promise. Care bundles seem to be most effective in settings, such as intensive care units or trauma wards during procedures.^{125–127} Clark et al¹²⁴ showed a decrease in hypertension-related deaths in a large national database reviewing maternal mortality before and after safety bundle and protocol implementation (15 vs 3 deaths; $P=.02$). In Illinois, the implementation of a severe maternal HTN initiative between 2016 and 2017 led to an increase in the percentage of new-onset severe HTN cases treated within 60 minutes (41.5%–78.9%) across 98 hospitals.¹²⁸ In California, Nevada, and Arizona, the implementation of a toolkit aimed at reducing the incidence of eclampsia and SMM across 23 hospitals between 2015 and 2016 led to a decrease in the incidence of eclampsia by 42.6% ($1.15 \pm 0.15/1000$ to $0.62 \pm 0.09/1000$ births) and a decrease in SMM by 16.7% (2.40 ± 0.10 to 2.00 ± 0.15 ; $P < .01$).³⁷

Although the benefits of maternal safety bundles seem promising, gaps in success in protocolized hospitals could be the result of inequitable use of such safety bundles across hospital systems and within hospital systems with patients. Current data show that unconscious bias and systemic racism in medicine contribute to healthcare disparities, particularly for Black women.^{129–131} A research opportunity for collaborative hospitals and organizations should be to identify if these disparities exist internally in the ability or willingness of staff to implement a HTN safety bundle consistently. Finally, because pregnant and postpartum patients may be seen in the emergency department, labor and delivery triage, urgent outpatient care, or other community healthcare settings, partnership with primary care, internal medicine and their subspecialties and emergency medicine should be pursued in the development and implementation of HTN care bundles.

Preeclampsia criteria, hypertension management, and delivery timing

One of the challenges identified by workshop participants in implementing preeclampsia guidelines and protocols from other countries was the inconsistency in terminology, such as the criteria and management of severe disease (Table 2). For example, in the US classification system, the ACOG delineates 4 different classifications of preeclampsia.¹³² In contrast, the ISSHP does not have a specific classification for people with preeclampsia. The ISSHP states that the “severity” of preeclampsia is arbitrary, and it does not advocate for a clinical distinction between “mild” and “severe” diseases.^{52,133} The subtle differences in the ISSHP system could allow a person who once had severe-range HTN (preeclampsia with severe features [SFs]) to continue a pregnancy beyond 34 weeks of gestation as long as their BPs were controlled or allow a person with downtrending or improving laboratory parameters (eg, hemolysis, elevated liver enzymes, and low platelet count [HELLP] syndrome) to remain pregnant past betamethasone completion. Moreover, NICE does not recommend that all people with preeclampsia be admitted, and they delineate features consistent with more severe disease that requires admission.⁵³ Finally, similar to NICE and the ISSHP, the SOGC agrees that there is no international consensus on what defines “severe” preeclampsia. The SOGC characterizes the end-organ dysfunction of preeclampsia as either “adverse conditions” or “severe complications” and recommends timing of delivery based on maternal and fetal well-being (Figure 1).⁵²

Recommendations for the management of BP also differ by society and within institutions (Figure 1). The ISSHP, ACOG, NICE, and SOGC all agree that antihypertensive treatment should be initiated expeditiously for severe acute HTN (systolic BP of 160 mm Hg, diastolic BP of ≥ 110 mm Hg, or both) that is confirmed and persistent.^{50,51,53,134} Intravenous labetalol, hydralazine, and immediate-release oral nifedipine are all reasonable first-line agents in the

TABLE 2

Preeclampsia classification, definition, and management by academic society (as of January 2021)

Variable	Preeclampsia for expectant management to 37 weeks of gestation	Preeclampsia for expectant management to 34 0/7 to 36 6/7 weeks of gestation	Preeclampsia requiring delivery at betamethasone completion or immediate delivery
ACOG ⁵⁰	<p>Preeclampsia without SFs BP:</p> <ul style="list-style-type: none"> • SBP of ≥ 140 mm Hg or DBP of ≥ 90 mm Hg on 2 occasions at least 4 h apart after 20 weeks of gestation in a woman with a previously normal BP • SBP of ≥ 160 mm Hg or DBP of ≥ 110 mm Hg Proteinuria: • ≥ 300 mg per 24 h urine collection (or this amount extrapolated from a timed collection) • Protein or creatinine ratio of ≥ 0.3 • Dipstick reading of 2+ (used only if other quantitative methods not available) <p>In the absence of proteinuria or new-onset HTN with the new onset of any of the following:</p> <ul style="list-style-type: none"> • Thrombocytopenia: platelet count $< 100 \times 10^9/L$ • Renal insufficiency: serum creatinine concentrations of > 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 	<p>Preeclampsia with SFs</p> <ul style="list-style-type: none"> • SBP of ≥ 160 mm Hg or DBP of ≥ 110 mm Hg on 2 occasions at least 4 h apart (unless antihypertensive therapy is initiated before this time) • Thrombocytopenia • 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 RUQ or epigastric pain unresponsive to medications • Renal insufficiency • Pulmonary edema • New-onset headache unresponsive to medication and not accounted for by alternative diagnoses • Visual disturbances 	<ul style="list-style-type: none"> • Uncontrolled severe-range BPs (persistent SBP of ≥ 160 mm Hg or DBP of ≥ 110 mm Hg not responsive to antihypertensive medication) • Persistent headaches or refractory to treatment • Epigastric pain or RUQ pain unresponsive to repeat analgesics • Visual disturbances, motor deficit, or altered sensorium • Stroke • Myocardial infarction • HELLP syndrome • New or worsening renal dysfunction (serum creatinine of > 1.1 mg/dL or twice the baseline) • Pulmonary edema • Eclampsia • Suspected acute placental abruption or vaginal bleeding in the absence of placenta previa • Abnormal fetal testing • Fetal death • Fetus without expectation for survival at the time of maternal diagnosis • Persistent reversed end-diastolic flow in the umbilical artery
ISSHP ⁵¹	<p>No specific title other than preeclampsia:</p> <ul style="list-style-type: none"> • All preeclampsia cases not requiring immediate delivery or delivery at betamethasone completion 	<p>No specific management strategy</p>	<p>No specific title other than preeclampsia:</p> <ul style="list-style-type: none"> • Gestation at ≥ 37 weeks of gestation • Ongoing neurologic features, such as severe intractable headache, repeated visual scotomata, or eclampsia • Uncontrollable HTN despite using ≥ 3 classes of antihypertensives in appropriate doses • Maternal pulse oximetry of < 90 % • Progressive deterioration in liver function, renal function, hemolysis, or platelet count • Placental abruption • Reverse end-diastolic flow of the umbilical artery Doppler, a nonreassuring CTG, or stillbirth

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(continued)

TABLE 2

Preeclampsia classification, definition, and management by academic society (as of January 2021) (continued)

Variable	Preeclampsia for expectant management to 37 weeks of gestation	Preeclampsia for expectant management to 34 0/7 to 36 6/7 weeks of gestation	Preeclampsia requiring delivery at betamethasone completion or immediate delivery
SOGC ¹³⁴	<p>Preeclampsia with adverse conditions:</p> <ul style="list-style-type: none"> • Headache or visual symptoms, RUQ pain, or epigastric pain • Chest pain or dyspnea • Oxygen saturation of <97% • Elevated WBC, INR, or aPTT • Elevated serum creatinine or serum uric acid • Elevated serum AST, ALT, LDH, or bilirubin • Low plasma albumin • Low platelet count • Nausea or vomiting • Fetal growth restriction, oligohydramnios • Absent or reversed end-diastolic flow by Doppler velocimetry • Abnormal fetal heart rate 	There is no formal recommendation outside the guidance for delivery for severe complications	<p>Severe complications</p> <ul style="list-style-type: none"> • Eclampsia, PRES, cortical blindness, retinal detachment • GCS of <13, stroke, TIA, or RIND • Uncontrolled severe HTN (over a period of 12 h despite the use of 3 antihypertensive agents) • Oxygen saturation of <90%, need for ≥50% oxygen for >1 h, intubation (other than for cesarean delivery), or pulmonary edema • Positive inotropic support • Myocardial ischemia or infarction • Platelet count of <50 × 10⁹/L • Transfusion of any blood product • Serum creatinine of >150 micrometer with no previous renal disease • New indication for dialysis • INR of >2 in the absence of DIC or warfarin • Hepatic hematoma or rupture • Abruptio with maternal or fetal compromise • Reverse ductus venosus A wave • Stillbirth
NICE ⁵³	<p>No specific title other than preeclampsia:</p> <ul style="list-style-type: none"> • Any form of preeclampsia that does not meet the criteria for early birth 	There is no formal recommendation outside the guidance for delivery for severe complications	<p>Planned early birth before 37 weeks of gestation</p> <ul style="list-style-type: none"> • Uncontrolled HTN despite using ≥3 classes of antihypertensives in appropriate doses • Maternal pulse oximetry of <90% • Progressive deterioration in liver function, renal function, hemolysis, or platelet count • Ongoing neurologic features, such as severe intractable headache, repeated visual scotomata, or eclampsia • Placental abruptio • Reverse end-diastolic flow in the UA, nonreassuring CTG, or stillbirth

Adapted from the American College of Obstetricians and Gynecologists,⁵⁰ Brown et al,⁵¹ the National Institute for Health and Care Excellence,⁵³ and Magee et al.¹³⁴

ACOG, American College of Obstetricians and Gynecologists; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; CTG, cardiotocograph; DBP, diastolic blood pressure; DIC, disseminated intravascular coagulation; GCS, Glasgow Coma Scale; GFR, glomerular filtration rate; HELLP, hemolysis, elevated liver enzymes, and low platelet count; HTN, hypertension; INR, international normalized ratio; ISSHP, International Society for the Study of Hypertension in Pregnancy; LDH, lactate dehydrogenase; NICE, National Institute for Health and Care Excellence; PT, prothrombin; PRES, posterior reversible encephalopathy syndrome; RIND, reversible ischemic neurological disability; RUQ, right upper quadrant; SBP, systolic blood pressure; SF, severe features; SOGC, Society of Obstetricians and Gynaecologists of Canada; TIA, transient ischemic attack; UA, urinalysis; WBC, white blood cells.

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FIGURE 1

Comparisons of severity criteria and management for preeclampsia by various organizations

	ACOG	ISSHP	SOGC	NICE
Clinical Diagnosis	Preeclampsia without SF ----- Preeclampsia with SF	Preeclampsia	Adverse complications** ----- Severe complications***	Preeclampsia ----- Severe Preeclampsia
Hypertension Management	Do not initiate anti-hypertensives until SBP \geq 160, DBP \geq 110 SBP \geq 160, DBP \geq 110 treated acutely with anti-hypertensive	Treat blood pressures to keep SBP $>$ 110 and DBP $>$ 85 for both "adverse conditions" and "severe complications"	Anti-hypertensive therapy to maintain SBP 130-155 mmHg and DBP 80-105 mmHg	Initiate anti-hypertensive medication at SBP $>$ 140 and DBP \geq 90
Delivery Timing	Delivery \geq 37 weeks of gestation ----- Delivery \geq 34 weeks of gestation	Expectant management until 37 weeks of gestation ----- Immediate delivery*	Expectant management until 37 weeks of gestation ----- Immediate delivery	Expectant management until 37 weeks of gestation ----- Planned early birth \pm

The *asterisk* indicates the inability to control BPs on 3 classes of antihypertensive agents in appropriate doses; maternal pulse oximetry of $<$ 90%; progressive deterioration in liver function, renal function, hemolysis, or platelet count; ongoing neurologic features, such as severe intractable headache, repeated visual scotomata, or eclampsia; placenta abruption; or reversed end-diastolic flow. The *double asterisk* indicates headache, visual symptoms, chest pain or dyspnea, oxygen saturation of $<$ 97%, elevated white blood cells, elevated INR or activated partial thromboplastin clotting time, low platelet count, elevated serum creatinine, elevated serum uric acid, nausea or vomiting, right upper quadrant pain, elevated aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, or bilirubin, low plasma albumin, abnormal fetal heart rate, fetal growth restriction, oligohydramnios, or absent or reverse end-diastolic flow by Doppler velocimetry. The *triple asterisk* indicates eclampsia, posterior reversible encephalopathy syndrome, cortical blindness or retinal detachment, Glasgow Coma Scale of $<$ 13, stroke, transient ischemic attack, reversible ischemic neurologic deficit, uncontrolled severe hypertension in 12 hours, oxygen saturation of $<$ 90%, intubation, pulmonary edema, need for positive inotropic support, myocardia ischemia or infarction, platelet count of $<$ 50,000, transfusion of any blood product, acute kidney injury, creatinine level of $>$ 150 μ m with no previous renal disease, new indication for dialysis, hepatic dysfunction, INR of $>$ 2 in absence of disseminated intravascular coagulation or warfarin, hepatic hematoma or rupture, abruption with evidence of maternal or fetal compromise, reverse ductus A wave, or stillbirth. The *plus* indicates the inability to control BP despite using \geq 3 or more classes of antihypertensives; maternal pulse oximetry of $<$ 90%; progressive deterioration in liver function, renal function, hemolysis, or platelet count; ongoing neurologic features (headache, repeated visual, scotomata, or eclampsia); placental abruption, reverse end-diastolic flow in the umbilical artery, nonreassuring cardiotocography, or stillbirth. American College of Obstetricians and Gynecologists,⁵⁰ Brown et al,⁵¹ the National Institute for Health and Care Excellence,⁵³ and Magee et al.¹³⁴

ACOG, American College of Obstetricians and Gynecologists; BP, blood pressure; DBP, diastolic blood pressure; INR, international normalized ratio; ISSHP, International Society for the Study of Hypertension in Pregnancy; NICE, National Institute for Health and Care Excellence; SBP, systolic blood pressure; SF, sever feature; SOGC, Society of Obstetricians and Gynaecologists of Canada.

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treatment of severe HTN in the setting of preeclampsia.⁵² Although guidelines are clear to aggressively treat severe-range HTN, BP maintenance with antihypertensive medication is more nuanced. There is no current international agreement regarding the optimal BP ranges while undergoing expectant management or what BP management may be required to prevent reaching severe range pressures. Tighter BP control has been shown to reduce severe-range maternal HTN but not maternal or neonatal morbidity in preexisting HTN and gestational HTN.^{135,136} Data on aggressively managed BP control are lacking in active preeclampsia with SFs; thus, it is unclear if tight BP control

will prolong latency or decrease maternal or neonatal morbidity.

Regarding HELLP syndrome, the ISSHP does not recognize it as a separate disorder but rather within the spectrum of preeclampsia.¹³³ Although ISSHP recognizes there are inconsistencies in the definition of HELLP syndrome, they agree that platelet values of $<$ 100,000/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 2-fold the upper limit of normal, and elevated lactate dehydrogenase (LDH) 2-fold the upper reference limit are reasonable to define the illness.¹³³ Although it is clear that patients with HELLP syndrome can have a worse

overall prognosis, the use of these diagnostic parameters is questionable.¹³⁷ Hemolysis in preeclampsia and HELLP syndrome is associated with adverse outcomes but is rarely severe enough to destabilize a patient to necessitate delivery and be the sole driver of clinical care.¹³⁸ Clinically, LDH levels rarely drive patient care and are more an indication of end-organ damage. Moreover, AST and ALT can persist without clinical deterioration, as can low platelet levels that do not meet transfusion thresholds or cause disseminated intravascular coagulation. Lastly, some cohorts observed 30% of participants showing improvement or even normalization of laboratory values when expectantly managed; however, these patients still experienced preterm birth for worsening preeclampsia symptoms or BP control.^{139–142}

Future clinical management research

To move forward in both clinical management and research of preeclampsia, the criteria definition and classification must be reexamined. Workshop participants emphasized that the reliance on merging all clinical phenotypes into one definition of preeclampsia has led to uniform treatment and management strategies that either show no clinical difference or lead to early preterm birth and increased maternal morbidity and may lead to masking of effective therapeutics in a precision medicine approach. Better classification of phenotypic and biologic pathways may lead to advances in therapeutics targeted to specific populations that can improve both short- and long-term outcomes for the pregnant person and neonate.

Future research should focus on matching clinical phenotypes to available and emerging biomarkers. Although placental ischemia and the imbalance of sFlt to PlGF in the first trimester of pregnancy is the nidus of disease, other pathways may predominate later in pregnancy.^{2,74,143} For example, people with persistent, intractable HTN and signs of diastolic dysfunction on echocardiography may have abnormal angiotensin receptor autoantibody levels.^{144–146} Furthermore, patients with HELLP syndrome may have a preponderance of germline variants associated with other diseases of complement.^{147–150} Multiple studies have suggested that the complement system may be involved in the pathophysiology of preeclampsia and HELLP syndrome through excess complement activation, decreased complement regulation, or both.¹⁵¹ Unlike other biomarkers, the complement system may give biologic and mechanistic information via increases or decreases of certain regulator protein pathways. However, additional research is needed to determine the clinical use of complement protein biomarkers and complement genetic variants in the prediction, diagnosis, and management of preeclampsia. As with the other biomarkers discussed earlier in this report, a more in-depth understanding of how dysregulation of complement pathways contributes to the progression of preeclampsia and HELLP syndrome will allow for more accurate, tailored management of these

conditions and prolongation of pregnancy for this patient population.¹⁵²

Finally, the international consolidation of diagnostic criteria may provide an advantage in the collection of large global datasets that examine clinical outcomes, disparities in practice, and therapeutics and facilitate translation of research and clinical practices.

Long-term impacts of preeclampsia

Discussions during the workshop focused on the potential to affect the lives of those with the diagnosis of preeclampsia, their children, and the individuals who support them far beyond delivery. However, patients and their families and clinicians are often unaware of these risks and how to mitigate them.^{45,153} There is a need for scalable, evidence-based strategies and interventions to address the unique challenges faced by patients with preeclampsia and their families.^{44,45,154,155}

Cardiovascular health

Heart disease is the leading cause of death among women in the United States, awareness of which has declined in recent years to <50% among women.^{156,157} Birthing people who develop preeclampsia, particularly those with preterm, severe, and recurrent preeclampsia, are at a 2- to 3-fold higher risk of developing CVD, including coronary artery disease, myocardial infarcts, heart failure, and stroke.^{7,8,44,158} This increased risk of CVD is mediated at least in part through increased risk of comorbidities, including chronic HTN, hyperlipidemia (HLD), and DM, which are more common among those with a history of preeclampsia.

Although racial disparities in the prevalence of preeclampsia and chronic HTN are widely known, recent data have shown racial differences in early postpartum BP trajectories among patients with hypertensive disorders of pregnancy. These data highlight that Black patients have a heightened burden in both the immediate and long-term postpartum windows.^{159,160} Moreover, disparities exist in rates of maternal mortality through 1 year after delivery, with American Indian or Alaskan Native, Black, and Hispanic birthing people in the United States being at increased risk of maternal death in the context of hypertensive disorders of pregnancy compared with White women.⁵ These disparities necessitate greater emphasis on equity in postpartum care and outcomes by centering the distinct needs of these subpopulations.

Mental health

Increased rates of adverse mental health outcomes, including depression and PTSD, have been reported among those who develop hypertensive disorders in pregnancy.^{12,161} Unpublished data shared during the workshop from the Heart Health 4 Moms lifestyle intervention trial of 151 people with a history of preeclampsia revealed that 23% of participants had probable PTSD, which is higher than the

1.5% to 5.0% reported among a general population of birthing people and the 15% to 18% among those with severe complications, including stillbirth and emergency cesarean delivery.^{162–164} Increasing severity of disorders, from gestational HTN to eclampsia, has been associated with increased positive screening for PTSD and the prevalence of postpartum depression, suggesting increased mental health risk among those with the highest medical risk.^{11,12}

Offspring health

Evidence is growing regarding the associations between exposure to preeclampsia in utero and adverse health outcomes. The exact mechanisms for these associations have yet to be completely elucidated. Theories that in utero exposures have a causal relationship with ex utero diseases, such as the Barker hypothesis that FGR and prematurity have a causal relationship with the development of HTN and DM, are widely accepted.^{165,166} Potential differences in gene expression (eg, epigenetics), cell biology (eg, differentiation, proliferation, and programming), and other factors (eg, cytokine exposure) are thought to play a role.

Notable associations between in utero exposure to preeclampsia and offspring health reviewed during the workshop included adverse cardiovascular and neurologic outcomes. Findings from multiple studies have shown increased risks of elevated BP, higher BMI, and even distinct echocardiographic findings in children whose mothers had preeclampsia during their pregnancy compared with those whose mothers did not have preeclampsia during their pregnancy.^{15,167,168} Similarly, increased risks of neurodevelopmental disorders, including attention deficit hyperactivity disorder, autism spectrum disorder, epilepsy, and intellectual disability, have been associated with exposure to preeclampsia.^{16,17,169} However, emphasis was placed on the need for more evidence to understand the role of confounders, effect modifiers, and mechanisms of these associations to better determine the degree of causation and how to address it.

Opportunities and challenges to improving outcomes

The postpartum period provides unique opportunities to engage in counseling and risk reduction, given the greater access to care and the increased motivation to optimize one's own and family's health during this window. Workshop participants emphasized that the immediate postpartum period is an optimal time for clinicians to target interventions for people with preeclampsia, with most maternal deaths occurring in the first week after delivery.¹⁷⁰ Immediately after delivery, fetal health concerns are no longer included in the risk-benefit calculus for intervention, and most candidate drugs are compatible with breastfeeding. Actions clinicians and healthcare systems can take to reduce preventable maternal deaths because of preeclampsia include a timely response to changes in

symptoms or vital signs, effectively controlling HTN, educating staff and patients regarding BP management postpartum, and ensuring continuity of care.¹¹⁹ Table 3 highlights select national professional societies' key recommendations for care after delivery.

Workshop participants emphasized the need to empower patients and their families by providing information about their risks and how to mitigate them. Personal accounts shared by individuals who had preeclampsia highlighted the need to engage patient perspectives in disseminating data about long-term impacts of preeclampsia for those affected by this disease. Patients can benefit from being activated not only to engage in strategies to lower their risk but also to advocate for themselves. Workshop participants stressed that ongoing collaboration between professional medical societies and patient advocacy groups is necessary to facilitate such crucial awareness and capacity building.

The postpartum period is a crucial time to assess future pregnancy intention and family planning goals. Patients who have preeclampsia should be made aware of the risk of recurrence and advised of risk reduction strategies. In addition to highlighting the role of low-dose aspirin in their future pregnancies,⁸² patients should also be made aware that optimal control of certain comorbidities, such as chronic HTN, DM, and systemic lupus erythematosus, and achieving a healthy weight before their next pregnancy lower their risk of developing preeclampsia again. The ideal interpregnancy interval for patients with preeclampsia is not well defined, and some patients with very severe disease (eg, associated with cardiac compromise) may be cautioned against future pregnancy given concern for severe morbidity and mortality. However, a recommendation for avoiding interpregnancy intervals shorter than 6 months is reasonable given the association with adverse outcomes among the general birthing population.⁴⁰

Prioritization of CVD risk prevention among those with a history of preeclampsia is necessary because of the increased risk of disease progression in this population and the high mortality rates of first cardiovascular events in women.^{8,30,44} Fortunately, the progressive nature of CVD risk accrual affords patients and their providers time to address modifiable risk factors, including, but not limited to, cigarette smoking and secondhand smoke exposure, detection and management of comorbidities (eg, DM, HLD, and HTN), salt reduction, physical activity, and weight. Unfortunately, CVD risk models, such as the 10-Year Modified Framingham Risk Score and the Cardiometabolic Model, seem to underestimate the morbidity and early mortality associated with hypertensive disorders of pregnancy.¹⁷⁴ Large, long-term studies demonstrating effective strategies to decrease long-term morbidity and mortality specifically associated with preeclampsia are needed. However, extrapolation from other at-risk populations and expert opinion reveals postpartum care strategies with promise for improving long-term outcomes. Ongoing

TABLE 3
Recommendations for long-term postpartum care of patients with preeclampsia

Variable	ACOG (2019–2021) ^{40,50,171,172}	AHA (2021) ⁴⁴	FIGO (2016) ¹⁷³	ISSHP (2018) ⁵¹
Visits				
Maternal care visit	1–3 wk after delivery; comprehensive visit 4–12 wk after delivery	0–12 wk after delivery	Within 24 h after delivery, postpartum day 3, postpartum weeks 2 and 6	Within 1 wk after delivery if requiring antihypertensive medication on discharge; 3 mo after delivery
Primary care visit	Annually	8–12 wk after delivery	Referral to internal medicine or nephrology if difficult to control BP or 3–6 mo of proteinuria, decreased eGFR (<60 mL/min) or other indications of renal disease	Annual or regular
Assessments				
Initial BP check	3–10 d after delivery	—	3–6 d after delivery	Within 1 wk after delivery if requiring antihypertensive medication on discharge; 3 mo after delivery
CVD risk assessment Frequency Evaluation components	Within 3 mo and annually or sooner if there is an abnormality Medical history (smoking, physical activity, breastfeeding, comorbidities, and family history), resting BP and HR, BMI, WC, cholesterol or lipid profile, fasting glucose, urine protein, nutrition, or social determinants of health	At 6 wk, 8–12 wk, 6 mo, and 12 mo after delivery BP, lipids, fasting glucose, and BMI	No earlier than 3–6 mo after delivery Screening using national guidelines; evaluation of BP, BMI, lipid panel, or glucose intolerance screening	Annual or regular BP and periodic fasting lipids and blood sugar
Other laboratory testing	—	—	Confirmation that end-organ dysfunction resolution or facilitate further workup	Repeat abnormal laboratory tests the day after delivery and daily until stable; repeat any laboratory tests that were abnormal at 3 mo to determine if they have normalized or if further workup is needed
Mental health	Screen for postpartum depression and anxiety with a validated instrument	—	Evaluation and referral for postpartum psychological care	Assessment for depression, anxiety, or PTSD symptoms
Substance use screening and intervention	Screen for tobacco and other substances; encourage smoking cessation	Encourage smoking cessation	Encourage smoking cessation	—
Counseling				
Lifestyle modification	Actionable guidance on physical activity, diet, and weight	Heart-healthy diet and increasing physical activity	Heart-healthy diet, regular physical activity, reduce alcohol consumption, ideal body weight and WC, reduce salt intake, and smoking cessation	Aim to achieve prepregnancy weight by 12 mo after delivery, maintenance of healthy weight, and regular exercise

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(continued)

TABLE 3

Recommendations for long-term postpartum care of patients with preeclampsia (continued)

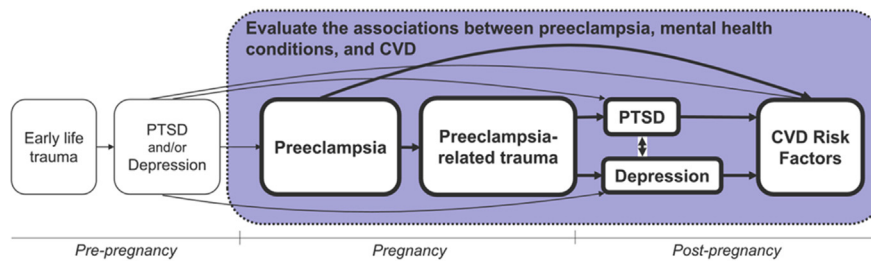
Variable	ACOG (2019–2021) ^{40,50,171,172}	AHA (2021) ⁴⁴	FIGO (2016) ¹⁷³	ISSHP (2018) ⁵¹
Infant feeding	Association of breastfeeding with decreased rates of HTN, HLD, T2DM, and CVD; compatibility of breastfeeding with select antihypertensive regimens	Association of lactation and breastfeeding with lower cardiometabolic risk; compatibility of breastfeeding with select antihypertensive regimens	Compatibility of breastfeeding with select antihypertensive regimens	Compatibility of breastfeeding with select antihypertensive regimens
Family planning	Avoid interpregnancy intervals of <6 mo and consider risks and benefits for intervals of <18 mo; shared decision-making regarding contraceptive options	—	—	—
Future CVD and other disease risk	Counseling regarding: CVD risk	Counseling regarding: CVD risk	Counseling regarding: CVD, renal disease, and mental health risks	Counseling regarding: CVD, DM, VTE, CKD, and mortality risk
Future pregnancy risk and prevention	Counseling regarding: recurrence risk; aspirin use in future pregnancy for prevention	Counseling regarding: recurrence risk; aspirin use in future pregnancy for prevention	Counseling regarding: risk of recurrent preeclampsia or gestational HTN; aspirin use and calcium use if intake is low in future pregnancy for prevention	Counseling regarding: risk of recurrent preeclampsia and SGA; aspirin use and calcium use if intake is low in future pregnancy for prevention
Future risk to newborn	—	—	Counseling regarding: potential long-term neurodevelopment, CVD, and pregnancy complications	—

Adapted from the American College of Obstetricians and Gynecologists,^{40,50,171,172} Parikh et al,⁴⁴ Brown et al,⁵¹ and Magee et al.¹⁷³

BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, heart rate; HLD, hyperlipidemia; HTN, hypertension; PTSD, posttraumatic stress disorder; SGA, small for gestational age; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism; WC, waist circumference.

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FIGURE 2
Interactions among preeclampsia, mental health conditions, and CVD



Reproduced with permission from Stuart JJ. The impact of preeclampsia on long-term mental health. Oral presentation at: Preeclampsia Workshop; 41st Annual Pregnancy Meeting; January 25, 2021; Virtual.

CVD, cardiovascular disease; PTSD, posttraumatic stress disorder.

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advocacy is needed to drive awareness of these recommended strategies among providers and patients.

Screening for postpartum depression and anxiety is widely accepted,⁴⁰ but the increased risk of PTSD seen among patients with preeclampsia and other pregnancy complications highlights the potential role of explicitly screening for PTSD.^{161,163} Patients with symptoms of these mental health disorders should be promptly referred for evaluation and treatment by a trained professional.

Collaborative care models, such as the medical home model and postpartum transition clinics, have demonstrated success in connecting patients to care, early risk assessment for CVD, and initiating prevention measures for patients at increased risk of later disease.^{8,45,175,176} The opportunity to leverage technology to facilitate care coordination both between the patient and the healthcare system and within the healthcare system was highlighted through examples, such as the Heart Health 4 Moms online lifestyle intervention.¹⁷⁷

Workshop participants emphasized the importance of engaging providers across specialties, particularly emergency medicine, primary care, and pediatrics. Given their frequent interactions with patients with a history of preeclampsia, specialists in these areas can provide risk assessment, care coordination, and patient education. Moreover, there was an emphasis on the opportunity to increase awareness and engagement of primary care and gynecologic providers in identifying patients with a history of hypertensive disorders of pregnancy as part of their standard medical history, even when individuals are beyond reproductive age. This identification is one step in ensuring that such patients receive appropriate cardiovascular health assessments and interventions (eg, modification of their 10-year atherosclerotic CVD risk estimate). In addition, the role of subspecialists, such as preventative cardiologists, was highlighted with the recognition that primary care providers are well positioned to triage patients to these experts.

Participants stressed that structural changes to the healthcare system are also needed. In the United States, health insurance coverage beyond 60 days after delivery was highlighted at multiple points as being crucial to mitigating some of the long-term risks that patients with preeclampsia and other pregnancy complications have by affording them the ability to engage in primary care.¹⁵⁵ Workshop participants recognized that insurance coverage does not equate to healthcare access. There is a need for more equitable infrastructure to enable patients to access diverse provider types and interventions, particularly around specialty care (eg, cardiology and psychiatry) and treatments (eg, mental healthcare). Financing and staffing of innovative care models were raised as potential barriers, particularly in areas with limited resources (eg, rural areas, public hospitals, and countries with limited resources). During the workshop, the importance of challenging long-term health disparities was also emphasized, both domestically and internationally, through targeted interventions and stratification of data to understand how disparities are being narrowed or exacerbated over time.

Workshop participants called for improved dissemination of best practices from research and clinics, hospitals, health systems, and larger collaborations. In response to this call to action, a small group of expert workshop participants is developing a toolkit compiling examples of clinical guidelines and tools (eg, CVD risk models), care models (eg, Kingston General Hospital Maternal Health Clinic's clinical workflow and select materials), and patient education materials (eg, Preeclampsia Foundation's video on how to take one's BP).

Areas for future research

Improving long-term health outcomes for people who experienced preeclampsia and their children will require additional research to guide practice improvements. Greater insights into which patients with a history of preeclampsia are at the highest risk of long-term adverse

outcomes (eg, stroke and PTSD) and thus would benefit the most from tailored interventions in the postpartum period are needed.

Regarding the risk of CVD, one challenge that was highlighted was the limitation of many models used to predict CVD risk, which often underestimates the risk for young women.^{8,178} Work to create improved models, particularly within populations with high rates of hypertensive disorders in pregnancy, is promising but has notable limitations (eg, reliance on administrative data and missing clinical variables, such as BP and echocardiogram parameters).¹⁷⁸ Given the heterogeneity in clinical presentation of preeclampsia (eg, preterm vs term, with vs without SFs), it is likely that models that account for nuances of the diagnosis might have better discernment for who has greater long-term risks. In addition, research is needed to understand how to optimally integrate more sensitive prediction models into clinical care and how they can guide the provision of interventions. It is not yet clear whether preeclampsia management during pregnancy, particularly around delivery timing after diagnosis, affects long-term CVD risk.^{179–182} If preeclampsia management decisions do have long-term health effects, how to incorporate that information into patient counseling about whether to prolong pregnancy is an opportunity for further investigation.¹⁸¹

The mechanisms through which racism (eg, interpersonal and structural) and related stressors (eg, socioeconomic and environmental) contribute to disparate hypertensive disease burdens inside and outside pregnancy need greater elucidation and targeted interventions. Exploration of the potential effect of promising efforts in other patient populations, including access to culturally appropriate and community-based interventions, may offer ways to mitigate these widely documented disparities, including the establishment of BP monitoring locations in nonclinical sites (eg, barbershops) and peer educators.^{183–187}

Associations among mental health conditions with biology (eg, cortisol levels), behaviors (eg, inactivity), and exposures (eg, trauma) complicate the understanding of the mechanism by which preeclampsia may increase the risk of mental health disorders and vice versa. Investigation into these complicated pathways (Figure 2) may help elucidate how to target interventions to improve mental health and cardiovascular outcomes (eg, assessment of adverse childhood experiences and subsequent referrals). More evidence is also needed to understand the effect of preeclampsia on the mental health of patients' social networks, particularly partners, given increased recognition of experiences of PTSD among those witnessing traumatic obstetrical births.¹⁸⁸ Finally, studies of interventions focused on both the prevention and treatment of psychological stress from preeclampsia (eg, biofeedback and mindfulness) are needed.

Although epidemiologic evidence links in utero exposure to preeclampsia with adverse cardiovascular and neurodevelopmental outcomes, more evidence is needed to

understand confounders (eg, maternal and paternal comorbidities), effect modifiers (eg, exposure to magnesium sulfate in utero and prematurity), and the mechanism underlying the pathophysiology to improve outcomes in offspring.

Workshop participants highlighted the importance of multidisciplinary teams to advance research to improve long-term outcomes for patients and families affected by preeclampsia. The importance of training programs and funding opportunities that promote such collaboration was emphasized. Moreover, participants highlighted the importance of advancing the systematic and widespread uptake of evidence-based practices to move the needle on population health, thus emphasizing the importance of implementation sciences research alongside basic science, clinical, and epidemiologic research.

Conclusion

Workshop participants proposed many recommendations for preeclampsia prediction, prevention, and management and identified several opportunities to improve postpartum and long-term follow-up care. It is hoped that this workshop serves as a catalyst for developing clinical guidelines and patient education strategies, generates new research questions, and strengthens relationships between researchers and clinicians to increase collaboration and support for patients with preeclampsia. ■

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The SMFM recognizes that obstetrical patients have diverse gender identities and is striving to use gender-inclusive language in all of its publications. The SMFM will be using terms such as “pregnant person or persons” or “pregnant individual or individuals” instead of “pregnant woman or women” and will use the singular pronoun “they.” When describing study populations used in research, the SMFM will use the gender terminology reported by the study investigators.

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