Consensus Statement

Gottesfeld-Hohler Memorial Foundation Risk Assessment for Early-Onset Preeclampsia in the United States

Think Tank Summary

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Preeclampsia is responsible for significant maternal and neonatal morbidity and is associated with a substantial economic burden. Aspirin has been shown to be effective in decreasing the risk of preterm preeclampsia; however, there is no consensus on the target population for aspirin prophylaxis. In May 2018, the Gottesfeld-Hohler Memorial Foundation organized a working group meeting with the goal of identifying the optimal preeclampsia risk-assessment strategy and consequent intervention in the United States. The meeting brought together experts from the leading professional societies. We discussed available literature and trends in preeclampsia risk assessment, current professional guidelines for identifying women at risk for preeclampsia, prophylactic use of aspirin in the United States and Europe, cost-effectiveness data, and feasibility of implementation of different assessment tools and preventive strategies in the United States. We identified specific

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This article represents a consensus on risk assessment for early-onset preeclampsia in the United States formulated during a conference held in Ft. Lauderdale, Florida, May 11–12, 2018.

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knowledge gaps and future research directions in preeclampsia risk assessment and prevention that need to be addressed before practice change.

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Preeclampsia complicates about 5% of pregnancies in the United States and is one of the leading causes of maternal and perinatal morbidity and mortality, carrying both short-term and long-term health consequences.[1–5] Preeclampsia is responsible for much of the prematurity seen in the United States, with rates of 12.4%, 22.3%, and 13% in women delivering at less than 28 weeks of gestation, 29–33 weeks, and 34–36 weeks, respectively (Lee HCB MVG S, Butwick, AJ, Druzin, M, Melsop, K, Ton, TGN. The burden of preeclampsia on preterm birth [abstract]. Presented at the American Academy of Pediatrics 2016 National Conference and Exhibition.).[6] Further, in the United States, approximately 16% of all maternal deaths are related to hypertensive disease of pregnancy.[7–9] The rate of preeclampsia in the United States is rising rapidly.[10,11] Given the rising incidence, preeclampsia represents a growing economic burden on the U.S. health care system. In 2012, the cost of preeclampsia in the first 12 months after birth was estimated at $1.03 billion for mothers and $1.15 billion for infants.[6]

Preeclampsia causes adverse maternal and neonatal outcomes, and recent data suggest that aspirin appears to delay or reduce this risk.[12,13] Early risk stratification can help identify women at increased risk for preeclampsia. Despite professional organizations in the United States (the American College of Obstetricians and Gynecologists [ACOG] and the U.S. Preventative Services Task Force) and throughout the world (the National Institute for Health and Care Excellence and the International Federation of Gynecology and Obstetrics) recommending aspirin prophylaxis for women with risk factors for preeclampsia, determining which women are at sufficient risk to warrant treatment and at what dose and timing is unclear.[14–18]

In May 2018, the Gottesfeld-Hohler Memorial Foundation, a nonprofit organization dedicated to research and education in obstetric and gynecologic ultrasonography, organized a meeting with invited participants including members of several obstetrics and gynecology professional organizations, with the goal of determining the appropriate preeclampsia risk-assessment strategy and to consider consequent treatments and interventions for the U.S. population. The following organizations had representatives in attendance: ACOG, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the Society for Maternal-Fetal Medicine (SMFM), the American Institute for Ultrasound in Medicine, the Fetal Medicine Foundation, and the International Society for Ultrasound in Obstetrics and Gynecology. In addition, content experts were invited by the Gottesfeld-Hohler Memorial Foundation. This summary includes background and position information from some participants, in addition to summarizing discussion regarding implementation of any new processes in the United States.

The American College of Obstetricians and Gynecologists recommends risk assessment for preeclampsia by taking an appropriate medical history for risk factors, such as those listed in the Table 1.[19] This recommendation was reiterated in ACOG Practice Bulletin No. 202, "Gestational Hypertension and Preeclampsia" (published January 2019).[14] The American College of Obstetricians and Gynecologists also recommends that women with one or more high-risk factors or more than one moderate risk factor for preeclampsia (Table 1) should be offered low-dose aspirin (81 mg daily) prophylaxis beginning between 12 and 28 weeks of gestation (optimally before 16 weeks) and continued until delivery.[14] In the absence of risk factors for preeclampsia, ACOG concludes that current evidence does not support the use of aspirin for the prevention of other adverse pregnancy outcomes such as early pregnancy loss, fetal growth restriction, stillbirth, or preterm birth. Factors considered in these recommendations include cost, cost-effectiveness, utility, feasibility, and potential risks of implementation and interpretation.

The U.S. Preventative Services Task Force makes recommendations for screening and prevention of a wide range of conditions to improve the health of all Americans; recommendation grades are listed in Box 1.[20] In 1996, the U.S. Preventative Services Task Force recommended obtaining blood pressure for preeclampsia risk assessment at the first prenatal visit and periodically throughout the remainder of the pregnancy (grade B).[21] This statement was reaffirmed and strengthened in 2017 to recommend blood pressure measurements for all pregnant women throughout pregnancy (grade B).[22] They did not find adequate evidence regarding other molecular, biochemical, or physiologic tests to recommend for or against such screening.[18] Similar to ACOG, the U.S. Preventative Services Task Force also recommends the use of low-dose aspirin for the prevention of preeclampsia in women at elevated risk (grade B).[23] The U.S. Preventative Services Task Force also identified several

Table 1. Clinical Risk Assessment for Preeclampsia*

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

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

† Single risk factors that are consistently associated with the greatest risk for preeclampsia. The preeclampsia incidence rate would be approximately ≥8% in a pregnant woman with ≥1 of these risk factors. See Henderson JT et al. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 112. AHRQ Publication No. 14-05207-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014 *and* Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2014;160:695–703.

‡ A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk for preeclampsia. These risk factors are independently associated with moderate risk for preeclampsia, some more consistently than others. See Henderson JT et al. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 112. AHRQ Publication No. 14-05207-EF-1. Rockville, MD: Agency for Healthcare Research and Quality.

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

Reprinted with permission from Final recommendation statement. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: preventive medication. U.S. Preventive Service Task Force; Rockville, MD. September 2014. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/low-dose-aspirin-use-for-the-prevention-of-morbidity-and-mortality-from-preeclampsia-preventive-medication.

research gaps, including the need for better understanding of the complex pathophysiology of preeclampsia, risk-assessment tools targeting the various subtypes of preeclampsia, descriptive studies to better characterize variations in current practices, and identification and validation of screening algorithms and new markers using rigorous methodology.[15]

American College of Obstetricians and Gynecologists and U.S. Preventative Services Task Force recommendations share the advantages of being relatively easy and inexpensive to implement, because they are based on patient characteristics and medical history. They also share the disadvantage of not basing treatment recommendations on an individualized risk assessment.

The London-based Fetal Medicine Foundation has developed an algorithm that estimates individualized risk for preeclampsia with severe features necessitating delivery before 32 weeks of gestation.[24] Specifically, in 61,174 pregnancies, the algorithm overall identified 90% of pregnancies in which preeclampsia was first diagnosed at or before 32 weeks of gestation (early), 75% between 32 and 36 weeks (preterm), and 41% at or after 37 weeks (term). This model distinguishes between preeclampsia diagnosed before and after 32 weeks of gestation, because the former exposes the maternal–fetal dyad to greater risk with greater health care expenditure. The algorithm uses data collected at 11 0/7–13 6/7 weeks of gestation, including maternal history, mean arterial pressure (MAP), uterine artery pulsatility index, and serum biochemical markers (placental growth factor [PlGF] and pregnancy-associated plasma protein A [PAPP-A]). The most predictive pattern seen in women who develop preeclampsia requiring delivery before 32 weeks of gestation includes elevations in the multiples of median of the uterine artery pulsatility

Box 1. The U.S. Preventive Services Task Force Recommendation Grade Definition

Grade	Definition
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined

USPSTF, U.S. Preventative Services Task Force.
Modified with permission from Grade Definitions. U.S. Preventive Services Task Force; Rockville, MD. June 2016. https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions.

index and MAP and decreased PlGF and PAPP-A levels, although PAPP-A does not add further to the model.

The maternal characteristics included in the Fetal Medicine Foundation model are listed in Box 2 and are based on National Institute for Health and Care Excellence guidelines, which consider the maternal risk factors for preeclampsia as independent variables and are similar to those included in the ACOG and U.S. Preventative Services Task Force recommendations.[25] In a study that included 120,492 singleton pregnancies, with a screen-positive rate of 11% based on National Institute for Health and Care Excellence guidelines, the new model predicted 40%, 48%, and 54% of total preeclampsia, preeclampsia requiring delivery at less than 37 weeks of gestation, and preeclampsia requiring delivery at less than 34 weeks of gestation, respectively, which were significantly higher than the 35%, 40%, and 44% achieved by standard application of risk factors.[26]

Box 2. Maternal Characteristics Included in the A Priori Risk Calculation in the Fetal Medicine Foundation's Algorithm for Preeclampsia Requiring Delivery at Less Than 32 Weeks of Gestation

List of Maternal Characteristics

- Age
- Racial origin
- Height and weight
- Parity
- Number of fetuses
- Method of conception
- Cigarette smoking during pregnancy
- Chronic hypertension
- Type 1 or 2 diabetes mellitus
- Systemic lupus erythematosus
- Antiphospholipid syndrome
- History of preeclampsia in a previous pregnancy
- History of preeclampsia in the patient's mother

Data from The Fetal Medicine Foundation. Risk assessment: risk for preeclampsia. Available at: https://fetalmedicine.org/research/assess/preeclampsia/first-trimester. Retrieved September 8, 2019.

Using a Bayesian approach, these maternal characteristics are used to calculate the a priori risk, which then is adjusted by the first-trimester data (MAP, uterine artery pulsatility index, PlGF, PAPP-A) to arrive at an individual posterior risk.[27] This model calculates individual patient risk for preeclampsia at any desired gestational age cutoff or prespecified time interval from assessment. The calculated individualized risks of early-onset preeclampsia necessitating delivery were developed based on assessment of 35,948 patients.[27]

The predictive performances for preeclampsia using the Fetal Medicine Foundation algorithm and National Institute for Health and Care Excellence guidelines were compared prospectively in 16,747 patients as a part of the U.K.-based Screening Program for Preeclampsia trial. For a false-positive rate of 10%, the preterm preeclampsia detection rate of the National Institute for Health and Care Excellence approach was 41%, whereas the Fetal Medicine Foundation algorithm identified 82% of cases.[28] The accuracy of the Fetal Medicine Foundation algorithm then was tested again prospectively in 8,775 patients as a part of a multicenter, multinational nonintervention trial.[29] The detection rate obtained prospectively at a 10% false-positive rate was 100% (95% CI 80–100) for preeclampsia diagnosed at less than 32 weeks

of gestation (predicted detection rate 89%), 75% (95% CI 62–85) for preeclampsia diagnosed at less than 37 weeks of gestation (predicted detection rate 75%), and 43% (95% CI 35–50) for preeclampsia diagnosed at greater than 37 weeks of gestation (predicted detection rate 47%).

Studies that have adhered to the conditions under which the Fetal Medicine Foundation algorithm was developed have shown a generally consistent test performance. In Australia, Park et al[30] report a detection rate of 91.7% (95% CI 61.6–98.6%) of early-onset preeclampsia cases (less than 34 weeks of gestation) at a 10% false-positive rate, with a positive predictive value of 3.6% and negative predictive value of 99.9%, although this trial did not include PlGF. Lobo et al[31] applied the Fetal Medicine Foundation algorithm to a Brazilian population and observed an 86% detection rate for a 10% false-positive rate. In Belgium, Guizani et al[32] found 81% and 83% detection rates of preeclampsia diagnosed at less than 37 and less than 34 weeks of gestation, respectively, for a 10% false-positive rate. In an unselected U.S. population, Sonek et al[33] predicted 85% of preeclampsia occurring before 34 weeks of gestation at a false-positive rate of either 5 or 10%, although the number of positive diagnoses was small (n=13).

Other investigators have not been as successful, reporting detection rates of 55–72% for early-onset preeclampsia at a false-positive rate of 10%.[34,35] External trials validating the biomarker methods have had varying results.[36] The reason for the discrepancy is unclear but may reflect different populations, varying techniques for uterine artery Doppler sampling, and the need for local adjustments of logistic regression. Furthermore, the application of various elements of the Fetal Medicine Foundation algorithm in some of these studies was inconsistent.

PREVENTION: WHY ASPIRIN?

Aspirin, a cyclooxygenase inhibitor, is postulated to decrease preeclampsia risk through its antiplatelet and antiinflammatory properties by attenuating disordered autocrine and paracrine eicosanoid activity.[37–39] Accordingly, low-dose aspirin, 81 mg daily in the United States and 150 mg or more in other countries, has been employed as a prophylactic treatment. Many randomized trials have evaluated this strategy, although most results from individual trials did not show a statistically significant reduction in the incidence of preeclampsia.[38,40] Despite the negative studies, the point-estimate for the effect related to aspirin treatment was in the direction of benefit. An individual patient data meta-analysis using data from multiple trials including more than 30,000 women demonstrated a 10% reduction in the frequency of preeclampsia associated with antepartum aspirin therapy (P=.004).[13] In that meta-analysis, there was no difference in the effect of aspirin prophylaxis whether a patient was considered low-risk or high-risk or based on particular high-risk factors. Based on these findings as well as considerations regarding the number needed to treat to prevent disease, aspirin has been routinely recommended for women with risk factors for preeclampsia. However, it remains unclear which women are considered high-risk enough to require aspirin and what is the best approach to establish risk for preeclampsia, a surrogate for adverse pregnancy outcomes.

ASPIRIN TRIAL DATA

The ASPRE trial, published in 2017, included a screened population of 26,941 gravid patients, of whom 2,642 screened positive for preeclampsia at a risk greater than 1 in 100 and 1,776 (67%) consented to participate.[12] The high-risk patients were randomized to either 150 mg of aspirin nightly (n=798) or placebo (n=822) from 11 to 14 weeks of gestation until 36 weeks of gestation. The primary outcome was preeclampsia diagnosed at less than 37 weeks of gestation. Preterm preeclampsia occurred in 1.6% of women in the aspirin group compared with 4.3% of those in the placebo group (adjusted odds ratio 0.38, 95% CI 0.20–0.74; P=.004). The comparison between the aspirin and placebo groups was based on adjusted analysis, which does not appear to have been prespecified in the published protocol. Aspirin use had no appreciable effect on term preeclampsia. No maternal or pregnancy-related adverse outcomes were noted, with reported compliance (defined as taking greater than 85% of the required number of tablets) in 79.9% of the participants.

In the ASPRE trial, the total number of neonatal intensive care unit admissions in the aspirin and the placebo groups was not statistically different. However, a subsequent secondary analysis that was not specified a priori demonstrated a 68% (95% CI 20–86%) decrease in length of stay for the neonates in the treatment compared with the placebo arm.[41] This is a reflection of a decrease in deliveries before 32 weeks of gestation in the treatment arm, with shorter mean lengths of stay in neonates admitted to the neonatal intensive care unit (aspirin vs placebo: 11.1 vs 31.4 days), a reduction of 20.3 days (95% CI 7.0–38.6; P=.008). It should also be noted that the ASPRE trial did not show a difference in overall rates of preeclampsia, rather just in preeclampsia requiring

delivery before 37 weeks of gestation, which may be affected by variations in practices and indications for delivery (eg, diagnosis of fetal growth restriction or fetal Doppler findings) between the United States and other countries.

The gestational age at which aspirin prophylaxis was initiated (by 14 weeks of gestation), the dosage of aspirin used (150 mg), and the time of day when aspirin was administered (nightly) are all important aspects of the ASPRE trial design, and each has a scientific basis. It is generally recognized that preeclampsia, especially preterm, is associated with placentation abnormalities and that the uteroplacental interface is mostly established before 18 weeks of gestation, so initiation in the first trimester (ie, by 14 weeks of gestation) to target the developing placental unit has biological plausibility.[13,42,43]

The current consensus in the United States for preeclampsia prophylaxis is aspirin 81 mg daily, whereas the Fetal Medicine Foundation recommends 150 mg daily.[12,14] Support for aspirin doses higher than 100 mg daily comes from both laboratory studies and meta-analyses.[43–45] There is significant interpersonal variation in platelet aggregation in response to a given dose of aspirin.[46] These differences may be due to either aspirin resistance or heterogeneity in platelet function. In a study of pregnant women at risk for preeclampsia, approximately 30% of patients showed an inadequate response to 81 mg of aspirin daily in platelet aggregation testing. This was reduced to approximately 5% by doubling the dose to 162 mg daily.[47] Although there is no apparent increase in maternal risk with higher-dose aspirin, the data on fetal and neonatal risks are still limited. Aspirin can alter platelet function in the fetus, and, although term births can be protected from this effect by stopping aspirin at 36 weeks of gestation, preterm neonates would not benefit from that approach.[48]

When considering changes to medical practice, such as the acceptance of the Fetal Medicine Foundation algorithm or implementation of universal preeclampsia prophylaxis with aspirin, matters of implementation, such as efficacy, cost, and anticipated compliance rate, ought to be considered. The efficacy of the Fetal Medicine Foundation risk-assessment and treatment algorithm is dependent on both the timing at which the test is performed and the specific components of the algorithm that are ultimately implemented. The addition of biomarkers to standard maternal risk factors and MAP assessments comes with an additional cost. It remains undetermined whether these algorithms would provide the same results if applied to a large U.S. population with the potential for different management approaches to preeclampsia.

The prediction of cost when no primary economic evaluation is available can be estimated through decision modeling. By using existing peer-reviewed literature, it is possible to estimate downstream costs and outcomes that occur when a practice has been changed. A decision model from Israel compared first-trimester risk assessment for preeclampsia (using clinical history, uterine artery Doppler studies, and serum measures of placental protein 13 and PlGF) with history-based risk assessment.[49] When the model assumed a combined prevalence of term and preterm preeclampsia of 1.7%, a cost of $112, a false-positive rate of 10%, and a first-trimester detection rate of 90% for preeclampsia diagnosed before 34 weeks of gestation and 70% for preeclampsia diagnosed beyond 34 weeks of gestation, first-trimester risk assessment cost $66,949 (not including delivery) to prevent one case of preeclampsia. After accounting for hospital-related charges with delivery and discharge, the costs of first-trimester assessment and history-based assessment were equal.

Another decision model built using Canadian costs and care patterns compared the cost-effectiveness of first-trimester preeclampsia risk assessment using the Fetal Medicine Foundation algorithm with history-based risk assessment.[50] This analysis suggested that the implementation of risk assessment using the Fetal Medicine Foundation algorithm could prevent 1,096 cases of early-onset preeclampsia (diagnosed at less than 34 weeks of gestation) in Canada in 1 year and lead to health care savings of $14,386,982 per year.

Although both decision models are well designed, their applicability to the U.S. health care system and U.S. costs is uncertain, because their assumptions are not consistent with the U.S. populations or practices. The Israeli model assumed a preeclampsia prevalence of 1.7%, which is much lower than the estimated U.S. preeclampsia prevalence, and the Canadian model compared first-trimester risk assessment with current Canadian preeclampsia risk assessment.

Thus far, the only U.S. decision model available to assess costs of preeclampsia risk assessment compared different historical risk factor strategies.[51] This decision model assessed both the cost of preeclampsia and the cost-effectiveness of risk assessment by comparing the U.S. Preventative Services Task Force approach with three other models: no risk assessment, the ACOG approach of history-based risk assessment and subsequent aspirin prophylaxis for those at high

risk, and the use of universal aspirin administration. The U.S. Preventative Services Task Force approach resulted in direct annual medical cost savings in the United States of $364,495,520 when compared with the ACOG approach, and $12,424,360 when compared with universal prophylaxis. When evaluating cost-effectiveness, this model estimated the cost needed to gain the most neonatal quality-adjusted life-years through each strategy. In this case, universal aspirin prophylaxis was the most cost-effective compared with the U.S. Preventative Services Task Force strategy, costing $8,174 per quality-adjusted life-year gained.

Because there is no U.S. model that compares first-trimester risk assessment using the Fetal Medicine Foundation algorithm and universal prophylaxis, an in-progress model was presented at the Gottesfeld-Hohler Memorial Foundation meeting and at the SMFM annual meeting.[52] This decision model compares the cost per preeclampsia case prevented using four possible policies: no risk assessment, the U.S. Preventative Services Task Force guidelines, the Fetal Medicine Foundation risk-assessment tool, and universal aspirin administration. Initial analysis of this model suggested that universal aspirin administration is a dominant strategy, because it costs the least and has the greatest clinical benefit. Compared with risk assessment using the Fetal Medicine Foundation strategy, universal aspirin administration costs approximately $19,000,000 less and prevents 829 additional cases of preterm preeclampsia for every 100,000 pregnant women treated. After varying several inputs widely, the model appears to be sensitive only to compliance with aspirin use. This model used any aspirin exposure rather than stratifying by different aspirin doses, so it cannot be used to determine the optimal dosage of aspirin.

All of the decision models described above have significant limitations. In particular, the models are limited by a lack of real-world data on universal aspirin administration. We do not know how often pregnant women would take aspirin if it was universally prescribed. Furthermore, although low-dose aspirin has been relatively safe in study settings, the exact rate and type of complications that might be encountered were it to be prescribed to 3,855,500 pregnant women annually in the United States are uncertain. To truly understand the most cost-effective strategy to prevent preeclampsia, further trials are warranted. Specifically, these trials should include a universal aspirin arm, measure compliance with risk assessment and treatment, and evaluate side-effects specifically related to universal aspirin use.

CURRENT RESEARCH IN THE UNITED STATES

Preeclampsia research is supported through many private grants and institutes at the National Institutes of Health and the NICHD. Large studies and initiatives include the NuMOM2b study (https://numom2bhhs.rti.org/Learn), the Human Placenta Project (https://www.nichd.nih.gov/research/supported/HPP/default), and studies conducted through the Obstetric-Fetal Pharmacology Research Centers (https://www.utmb.edu/nichd-oprc/) and the Maternal Fetal Medicine Units Network (https://mfmunetwork.bsc.gwu.edu/PublicBSC/MFMU/MFMUPublic/). Data from all NICHD-supported studies are planned to be publicly housed on a single site to facilitate access for all investigators to data and specimens at the NICHD Data and Specimen Hub (https://dash.nichd.nih.gov/).

Other ongoing research aims to better understand predictors of preeclampsia, including biomarkers, genetics, and epigenetics. Point-of-care devices for early detection of preeclampsia, new and novel therapies to prevent and treat preeclampsia, and analyses that provide insight into the long-term effects of preeclampsia on the health of both mother and child are under investigation. Leveraging data and banked samples from completed and ongoing studies, developing new data sets, and using the infrastructure of network and data sets to support translation are all opportunities for investigators. Mechanistic and etiology investigation includes human and animal studies on factors that influence the growth of blood vessels in pregnancy, mechanism and function of the placenta, genetic factors affecting blood pressure during pregnancy, characteristics and factors that cause or contribute to the progression of preeclampsia, and the long-term effects of the diagnosis.

RESEARCH GAPS

Preeclampsia has been used as the surrogate outcome measure of aspirin prophylaxis. However, we recommend that severe maternal and neonatal outcomes could be more appropriate, given that preeclampsia is, in actuality, just a proxy. Nevertheless, we still have to improve our understanding of appropriate aspirin dosage and the consequences of assessment for high-risk characteristics. This and a better understanding of cost analysis will be the keys to determining the best approach to risk stratification. Investigations of maternal cardiovascular aspects of risk assessment (ie, peripheral resistance), the therapeutic value of statins, and risk assessment for prediction of late preeclampsia are ongoing. Does the administration of low-dose aspirin to prevent preterm preeclampsia have its effect by shifting the disease to term preeclampsia? That would have a great benefit in reduced risks of

prematurity if there are no harms from the longer administration of aspirin. Is there any role for aspirin in the prevention of term preeclampsia? What are the unintended consequences of risk assessment in those with a false-positive result? A large-scale, randomized controlled trial comparing aspirin administration based on risk-factors alone, the Fetal Medicine Foundation algorithm, and universal aspirin stratified by dose (81 vs 162 mg daily) may be necessary to reach a clear recommendation on the best course of action.

Although we have sought to understand the importance of and focus on women's' experiences during pregnancy, a significant research piece missing has been the patient perspective on prophylaxis and the consequences of risk assessment. The NICHD along with partners recently launched PregSource, a study using crowdsourcing to understand both normal and abnormal pregnancy (https://pregsource.nih.gov/). Women are able to provide information about their pregnancy experience in real time, including questionnaires on hypertension and other pregnancy-related conditions. This novel research opportunity will provide insight on both normal and abnormal pregnancy.

DISCUSSION

The rate of preeclampsia has risen over the past decade, despite garnering substantial investigative attention. Significant inroads have been made in better understanding its pathogenesis and in developing methods to predict the condition, especially early-onset preeclampsia with severe features. Published data suggest that the Fetal Medicine Foundation paradigm of history, physical characteristics (MAP), and biochemical markers outperforms either history alone or history and blood pressure and identifies more than 80% of cases of early-onset preeclampsia with severe features. However, implementing the Fetal Medicine Foundation protocol in the present U.S. health care system would add new expenses to prenatal care, with challenges to implementation including broad geographic availability of sonologists who can perform the required uterine artery Doppler measurements accurately and reliably. Based on time lags for implementation of other population risk-assessment recommendations in the U.S. obstetric community, there would be an inevitable time lag to implementation of this protocol as well.

Most studies have shown low-dose aspirin, especially when administered early, to have some efficacy in reducing the incidence of early-onset preeclampsia, but uncertainty remains regarding optimal dosage (81 vs 162 mg or 150 mg) despite laboratory evidence showing the higher dosage better inhibits platelet aggregation. Studies comparing various clinical protocols have not included a prevention arm of universal aspirin administration, which has the benefit of circumventing expensive risk assessment. However, efficacy of universal aspirin administration may suffer from patient noncompliance or the possible maternal and fetal adverse effects that could accrue from giving a medication, the safety of which has not been completely proven, to nearly 4 million pregnant women in the United States. Certainly, universal low-dose aspirin prophylaxis should be an arm of future efficacy studies, as well as compliance and psychological acceptance of any preventive protocol.

Last, although awaiting results from further investigation suggested above or already in progress, it is strongly advised to identify patients at high risk for preeclampsia at least by the guidelines of ACOG, SMFM, the U.S. Preventative Services Task Force, or the Fetal Medicine Foundation criteria. Offering prophylactic low-dose aspirin starting in the late first or early second trimester, and close scrutiny of these women throughout pregnancy, may help to avert or mitigate the severe complications for the mother, fetus, and neonate that can result from preeclampsia.

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