EDITORIAL

Biomarkers and the Risk of Preeclampsia

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Over the past few decades, while the global incidence of preeclampsia has risen, the number of maternal and perinatal deaths due to hypertensive disorders of pregnancy has declined.[1] In 2011, international agencies, including the World Health Organization and the UK's National Institute for Health and Care Excellence, issued recommendations for daily low-dose aspirin to reduce the incidence of preeclampsia based on maternal demographics and medical history (collectively termed *maternal factors*).[2] By 2013, similar recommendations were adopted in the US based on guidance from the US Preventive Services Task Force (USPSTF), American College of Obstetricians and Gynecologists, and Society for Maternal-Fetal Medicine. These guidelines arose from systematic reviews and meta-analyses demonstrating a reduction in preeclampsia, preterm birth at less than 37 weeks, and fetal and neonatal deaths for patients in whom low-dose aspirin, 75-100 mg, was initiated between 12 and 16 weeks' gestation.[3-5]

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In this issue of *JAMA*, Mendoza et al[6] investigated the discontinuation of low-dose aspirin for preeclampsia prophylaxis at 24 to 28 weeks of gestation and the risks of preterm preeclampsia and hemorrhage in a noninferiority trial conducted at 9 hospitals across Spain. The authors identified patients at increased risk of preeclampsia based on first trimester screening for maternal factors, uterine artery pulsatility index (UTPI), mean arterial pressure (MAP), and serum pregnancy-associated plasma protein A (PAPP-A), who were treated with 150 mg/d of low-dose aspirin prior to 16 weeks and had ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) measurements performed between 24 and 28 weeks' gestation. A total of 968 participants were assessed to be at low risk of preterm preeclampsia based on an sFlt-1:PlGF ratio of 38 or less and were randomized in a 1:1 ratio to aspirin discontinuation between 24 and 28 weeks of gestation or aspirin continuation until 36 weeks' gestation.

Mendoza et al[6] found that early discontinuation of 150-mg aspirin was noninferior to continuation until 36 weeks with regard to their primary outcome: incidence of preterm preeclampsia (1.48% in the aspirin discontinuation group vs 1.73% in the aspirin continuation group). Consistent with their rationale for conducting this trial, they found a higher incidence of minor antepartum hemorrhage in the continuation group (7.61% in the low-dose aspirin discontinuation group vs 12.31% in the low-dose aspirin continuation group; absolute difference, −4.70 [95% CI, −8.53 to −0.87]).

Though well-designed and provocative in its findings, this study is difficult to interpret in a US population. Key differences in US preeclampsia prevention guidelines compared with the practices specified by the investigators of this work include (1) the exclusive use of clinical maternal factors in the US as opposed to molecular biomarkers for screening for low-dose aspirin prophylaxis; (2) a difference in the dosage of aspirin prescribed by US (81 mg daily) compared with international (150 mg daily) societies; and (3) no recommendation in the US to discontinue prophylactic low-dose aspirin at 36 weeks' gestation.

Given the current reliance on maternal factors in the US for selection of pregnancies for low-dose aspirin prophylaxis, the adoption of the risk assessment paradigm applied in the Mendoza et al[6] study (ie, maternal factors, UTPI, MAP, and PAPP-A for universal first-trimester screening followed by second-trimester reassessment using sFlt-1:PlGF) would represent a marked change in practice accompanied by a substantial increase in cost. Moreover, low-dose aspirin–related bleeding complications may not be relevant to the US population, where accepted guidelines recommend an aspirin dose of 81 mg daily, which some meta-analyses have found to have similar efficacy to the 150-mg dose in prevention of preeclampsia.[3,5] Given the conflicting evidence in the literature to date, it remains unclear whether low-dose aspirin is associated with a clinically significant increase in antepartum bleeding.[3] Without an increase in bleeding complications, there is no rationale to recommend discontinuation of low-dose aspirin for preeclampsia prevention prior to delivery.

Since the initial publication of guidelines recommending the use of low-dose aspirin for prevention of preeclampsia, screening algorithms designed to improve prediction of preeclampsia have continuously evolved.[7] When used in combination with maternal factors, first-trimester MAP, UTPI, PAPP-A, and PlGF have been shown to predict up to 82% of cases of preterm preeclampsia and 54% of all cases of preeclampsia (with a fixed false-positive rate of 10%).[8-11] This predictive power is markedly better than maternal factors alone, which predict 43% of preterm preeclampsia cases and 40% of all preeclampsia cases.[8] The landmark ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial was conducted in 5 European countries and Israel and used maternal factors, MAP, UTPI, PAPP-A, and PlGF to identify patients at increased risk of preterm preeclampsia, who were randomized in a double-blind trial to aspirin, 150 mg, daily vs placebo from between 11 to 14 weeks' and 36 weeks' gestation. ASPRE demonstrated a 62% reduction in the incidence of preterm preeclampsia in the low-dose aspirin group compared with the placebo group, leading to the revision of international guidelines to add biophysical and

molecular parameters to the original maternal factor–based first-trimester risk assessment approach.[12-14]

Besides first-trimester algorithms for risk assessment in asymptomatic persons, there have been efforts (mostly outside of the US) to identify biomarkers for triaging care in pregnancies with signs and/or symptoms of preeclampsia. The PROGNOSIS study showed that an sFlt-1:PlGF ratio of 38 or less has a high negative predictive value (99.3%) for ruling out preeclampsia during the following week in patients in the second or third trimesters with suspected preeclampsia.[15] In a nested case-control study from the multicenter PREDO study (Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction) Project, including 26 high-risk participants who developed preeclampsia, 26 high-risk participants who did not develop preeclampsia, and 52 participants without risk factors who did not develop preeclampsia, high sFlt:PlGF measured between 26 and 28 weeks' gestation was able to predict all cases of early-onset preeclampsia.[16] Importantly, this PREDO substudy served as the rationale for preeclampsia risk assessment between 24 and 28 weeks using the sFlt-1:PlGF ratio in the Mendoza et al[6] study.

While the benefit of low-dose aspirin in preeclampsia prevention is well-established, the most effective daily dose for prevention of preeclampsia remains unknown. Some analyses have suggested that daily doses of 75 mg or higher show benefit in reducing the risk of preeclampsia, but that the magnitude of reduction is greater with a dose of 150 mg, particularly with regard to prevention of preterm preeclampsia.[17,18] Other reviews demonstrated overlap in the effect size for preeclampsia risk reduction between lower and higher doses, suggesting that there may not be a difference.[3,5] However, many of these meta-analyses are limited by the inability to control for trial effects and inconsistencies in the use of aggregated data (which overestimate the effect of aspirin) vs individual patient data. No trials have directly compared low-dose aspirin dosages, leaving the optimal dosage uncertain.

In the trial by Mendoza et al,[6] the rationale for focusing on preterm preeclampsia requires careful consideration. Although preterm preeclampsia overwhelmingly contributes to adverse fetal, neonatal, and maternal outcomes related to hypertensive disorders of pregnancy, limiting outcomes to preterm preeclampsia minimizes the absolute contributions of all subtypes of preeclampsia to perinatal and maternal outcomes. Early-onset preeclampsia at less than 34 weeks occurs in just 0.38% of pregnancies, while 3% to 5% are affected by late-onset preeclampsia.[7] Though the odds of adverse perinatal and maternal outcomes are higher with preterm preeclampsia, due to its overall higher incidence, late-onset preeclampsia has a higher overall impact on perinatal and maternal morbidity and mortality.[19]

This important study challenges a growing body of evidence trending toward increasingly widespread use of low-dose aspirin in pregnancy. A recent analysis of the 2019 birth certificate data from the US National Center for Health Statistics showed that at least 50.4% of pregnancies were eligible for low-dose aspirin based on USPSTF recommendations.[20] Perhaps unsurprisingly, owing to potential barriers to selective implementation and the perceived safety of low-dose aspirin, support is growing in the US for its use in all pregnancies.[21,22] Of note, application of the USPSTF recommendations would have identified less than 50% of the at-risk population that was identified to be eligible for low-dose aspirin in the Mendoza et al[6] study. The authors' use of biophysical and molecular factors to more accurately risk stratify patients for initiation of low-dose aspirin prophylaxis in the first trimester, as well as their application of a growing mass of data that highlights the exceptional negative predictive value of second-trimester biomarkers, points to potential opportunities to develop improved guidelines for personalized pregnancy management.

By implementing an individualized approach to low-dose aspirin prophylaxis, Mendoza et al[6] highlight the potential to apply multimodal approaches for risk assessment and management to reduce the burden of major complications of pregnancy. This paradigm is poised to capitalize on ongoing efforts, including several in the US, to identify molecular biomarkers with high sensitivity and predictive value for all types of preeclampsia (not just preterm preeclampsia), as well as for other important complications of pregnancy, such as stillbirth, preterm birth, and fetal growth restriction. US practitioners and professional societies should reconsider current risk assessment strategies, which are largely based on maternal factors, and evaluate whether incorporation of molecular biomarkers would improve maternal and fetal/neonatal outcomes.

ARTICLE INFORMATION

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