Updates on Screening, Prevention, Treatment, and Genetic Markers for Preeclampsia

Moderator: Glenn E. Palomaki[1]*
Experts: James N. Martin, Jr.,[2] S. Ananth Karumanchi,[3]† and Liona C. Poon[4]

Preeclampsia is a serious disorder of pregnancy that occurs by 24 weeks of gestation or later and manifests in between 2% and 5% of all pregnancies. Nulliparity, maternal weight, advancing maternal age, multiple gestation, previous pregnancy with preeclampsia, and insulin-dependent diabetes are just some of the predisposing factors for developing preeclampsia. According to the American College of Obstetricians and Gynecologists (ACOG)[5], preeclampsia can be diagnosed by persistent high blood pressure that develops during pregnancy that is associated with high concentrations of protein in the urine or the new development of decreased blood platelets, trouble with the kidney or liver, fluid in the lungs, or signs of brain trouble such as seizures and/or visual disturbances. The only truly effective treatment is delivery. If not managed, preeclampsia can evolve into life-threating eclampsia for both the mother and fetus. Before 37 weeks, and especially before 34 weeks, of gestation, the diagnosis of preeclampsia poses a dilemma between preterm elective delivery and continuation of pregnancy with the potential for developing eclampsia.

Over the past few years, rapid developments and breakthroughs in screening, prevention, and treatment for preeclampsia have occurred. Genetic studies are just now providing new insights into the etiology of this disorder. In this Q&A, 3 world leaders in preeclampsia research and implementation discuss these new developments, roadblocks to implementation, and opinions on what might be expected in the near future.

Current screening tests and those in development that quantify the risk of developing preeclampsia later in pregnancy vary widely from simple queries regarding personal history and demographic factors, to more complex algorithms including biochemical and ultra-sound markers. What are the key factors you look for in evaluating such screening tests? Have ACOG and the UK National Institute for Health and Care Excellence (NICE) guidelines kept pace with the research findings for more comprehensive multivariate models such as used in the Aspirin vs Placebo in Pregnancies at High Risk of Preterm Preeclampsia (ASPRE) trial?

Liona Poon: I look for 3 factors in evaluating screening tests for preeclampsia. The first factor is screening performance. The performance of screening for preterm preeclampsia provided by a combination of maternal factors and biomarkers is superior to that achieved by current NICE guidelines. The current approach to screening for preeclampsia is to identify risk factors from maternal demographic characteristics and medical history. Such an approach essentially treats each risk factor as a separate screening test with additive detection and screen positive rates. An alternative approach uses Bayes' theorem to combine the background risk from maternal factors, derived by a multivariable logistic model, with the likelihood ratios of various biophysical and biochemical measurements. This allows estimation of patient-specific risks of preeclampsia requiring delivery before a specified gestational age. In response to an urgent need to improve existing methodology for the screening of preeclampsia, the UK National Institute for Health Research Efficacy and Mechanism Evaluation recently commissioned a study to compare the performance of screening using the Bayesian method vs the NICE protocol in 16747 women. The screen positive

rate by NICE was 10% with a detection rate for preterm preeclampsia of 41%. This was substantially lower than the 82% detection rate for the Bayesian method combining maternal risk factors, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor (PlGF).

The second factor is applicability and affordability. In my opinion, the Bayesian-based test can be implemented within an existing prenatal care infrastructure. However, compared with the NICE method, certain logistical arrangements must be considered. Essentially, the NICE method relies on the skills of healthcare professionals in eliciting and interpreting medical history, whereas the Bayesian-based method necessitates the use of software to calculate a patient-specific risk. Additional screening components include the measurement of mean arterial pressure, which can be undertaken by healthcare assistants after minimal training, with inexpensive equipment and taking only a few minutes to perform. Serum PlGF can be measured on the same blood sample and by the same machines used for Down syndrome screening. Lastly, the measurement of the uterine artery pulsatility index can be performed within a few minutes by the same sonographers and ultrasound machines used as part of the current routine 11 to 13 weeks' scan.

The third factor is whether there is a proven method of prevention in the high-risk women identified by the screening test. Recent evidence from a European multicenter randomized placebo-controlled trial indicated that effective screening for preterm preeclampsia at 11 to 13 weeks of gestation by the Bayesian-based method, followed by low-dose aspirin prophylaxis given to high-risk women before 16 weeks of gestation, would reduce the rate of preterm preeclampsia by 60%.
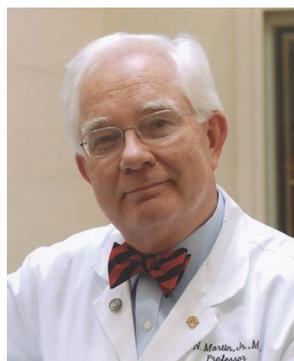
James Martin: I can't speak for ACOG, but I believe ACOG practice guidelines are carefully constructed to reflect evidence-based practice that shows value for a given intervention. One such example is screening for preeclampsia. Evaluation of a recommendation includes not only the science behind it but also the practice implications and financial considerations for use by the >60000 ACOG members. Until the work is done to evaluate the value and costs of any proposed screening test(s) for preeclampsia, and to show that its use makes a measurable difference in patient outcomes, no screening test will likely gain entry to recommended maternity care. In addition, an effective intervention useful to initiate after a positive screening test is needed to warrant the cost of screening. We lack this evidence at present. It is costly to undertake such research in the US, presenting a major hurdle to progress in this arena.

Ananth Karumanchi: A screening test that can be used in conjunction with other clinical variables to identify the vast majority of women with preeclampsia (>90% detection rate) with relatively low false-positive rates (<5% false-positive rates) would be most useful. To be clinically meaningful, screening tests must be coupled with an interventional strategy, such as a therapeutic or change in clinical practice pattern that is beneficial to patients. In this regard, the multivariate model with novel biochemical tests and other clinical variables used by the ASPRE investigators is robust. ASPRE investigators demonstrated that aspirin reduced preterm preeclampsia by 62% in the women at highest risk for preeclampsia. These are impressive results that demonstrate aspirin to be highly effective in select individuals with certain biophysical and biochemical measurements when administered early in pregnancy. In the US, societies such as ACOG have not kept up with the Europeans. Biochemical tests such as PlGF (used in the ASPRE algorithm) are not yet approved by the US Food and Drug Administration (FDA) and, therefore, are not routinely available for clinical use. Furthermore, uterine artery flow studies are not routinely obtained by clinicians in the US.

Prediction and preventive models (such as early aspirin for high-risk pregnancies) choose varying definitions of what the main outcome measure should be. For example, preterm delivery may be defined as <32, <34, or <37 weeks. Outcome may also include early delivery of infants with growth retardation. What outcome or set of outcomes do you think should be targeted as having the most relevance regarding the identification and management of preeclampsia that might target/prevent these severe adverse outcomes?

Ananth Karumanchi: Adverse maternal outcomes include hepatic dysfunction, hematological abnormalities such as thrombocytopenia, placental abruption, pulmonary edema, cerebral hemorrhage, seizures, acute renal insufficiency, or maternal death. The adverse fetal/neonatal outcomes include prematurity-related fetal outcomes (such as necrotizing enterocolitis, respiratory distress syndrome, and retinopathy of prematurity), small

for gestational age birth weight (≤10th percentile for gestational age), fetal death, and neonatal death. Because most of these adverse outcomes occur during the preterm period (<37 weeks) or during the early-onset period (<34 weeks), it seems reasonable to use extension of pregnancy as a surrogate of these adverse outcomes in therapeutic clinical studies.

James Martin: ACOG has gone to great lengths to standardize terminology in obstetrics and gynecology. An example is the definitions of early term, late preterm and early preterm. Not mentioned is the commonly used differentiation of preeclampsia into early onset before 34 weeks of gestation vs that of so-called late-onset preeclampsia that presents from the 34th week thereafter. The reduction of both early-onset and late-onset preeclampsia is important, perhaps most important for the early-onset secondary to fetal/perinatal considerations. With standardization of terminology for maternal morbidity and mortality, plus the emphasis on inclusion of core measures/outcomes in publications, we should derive better evidence for or against any screening test and the effectiveness of its implementation to improve outcomes.

Liona Poon: Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. Preterm preeclampsia (with delivery at <37 weeks of gestation) is associated with a higher incidence of fetal growth restriction and both short-term and long-term maternal and perinatal mortality and morbidity. Obstetricians managing cases of preeclampsia are faced with the challenge of balancing the need for achieving fetal maturation with the risks to mother and fetus from continuing pregnancy. For the mother, short-term risks include progression to placental abruption, HELLP syndrome (a group of signs in pregnant women including hemolysis, increased liver enzymes, and low platelet count), eclampsia, cerebrovascular accident, and death. Additionally, the condition is associated with an increased risk of death from future cardiovascular disease, hypertension, stroke, and diabetes, and the life expectancy of women affected by preterm preeclampsia is reduced, on average, by 10 years. For the fetus, preterm delivery is associated with higher mortality rates and increased morbidity resulting from thrombocytopenia, bronchopulmonary dysplasia, cerebral palsy, and an increased risk of various chronic diseases in adulthood. I believe the ability to effectively screen for preterm preeclampsia has short- and long-term benefits for both the mothers and the babies.

Given the success of daily aspirin treatment in reducing the incidence of early preeclampsia outcomes (preeclampsia plus delivery <37 or <34 weeks), what proportion of all pregnancies (or all preeclampsia) should be targeted? Would it make sense, especially in countries where routine measurement of serum and ultrasound measurements might be difficult, to consider widespread aspirin-based prevention? What would be reasonable contraindications for treatment?

James Martin: There is a burgeoning body of literature on the issues surrounding low-dose aspirin use for preeclampsia reduction. There is general agreement that it should be used in various categories of patients at risk of developing preeclampsia. The standard low-dose aspirin tablet in the US contains 81 mg of drug; outside the US, some other formulations include 100 mg or 150 mg. In general, the benefit is somewhere between a 7% and 14% reduction in the overall occurrence of preeclampsia, although numbers differ quite a bit among various patient populations studied, dosage of drug used, and time of initiation during pregnancy. Part of the problem for practitioners is risk assessment of patients and treating some because they meet criteria. However, we have learned through the hard road of experience in the US that we need to treat all patients the same—to screen them all—to detect early evidence of gestational diabetes and to prevent group B *Streptococcus* infections around delivery. Given the exceedingly low occurrence of patient complications associated with low-dose aspirin use for preeclampsia prevention and the potential for major adverse perinatal and maternal complications coincident with the development of preeclampsia, the case has been made for universal treatment of all prenatal patients, thus obviating the laboratory costs and logistic hurdles of screening and selective treatment. Obviously, this could be extended to inclusion of low-dose aspirin as 81 mg or 100 mg in prenatal vitamins given to all prenatal patients. This is especially attractive in middle and lower socioeconomic healthcare environments. Such an approach might be appropriate while we continue the search for why preeclampsia occurs at all and how we can best manage it. A last consideration is that preterm birth and preeclampsia have both been shown to be reduced with low-dose aspirin treatment, certainly a win-win in maternity care.

Ananth Karumanchi: It has been argued that because the cost of aspirin is low, perhaps aspirin should be given to every pregnant woman. However, aspirin is not entirely benign. Aspirin therapy is associated with some bleeding risk, and a recent epidemiological study suggested excess asthma risk in the offspring of women taking aspirin during pregnancy. In the absence of long-term safety data, it is prudent to administer aspirin only to women at the greatest risk for developing preeclampsia-related adverse outcomes. In this regard, ASPRE trial investigators have provided a robust algorithm, with a low false-positive rate, that combines imaging, biomark-

ers, and clinical factors to identify most patients who would develop preterm preeclampsia. In countries such as the UK, where the algorithms and biomarkers are available, it seems reasonable to screen women during the first trimester and recommend aspirin therapy to women at greatest risk. In countries like the US, we do not yet have biomarkers such as PlGF, and obstetricians do not routinely perform uterine artery Doppler evaluations. Because of these limitations, ACOG has recommended aspirin therapy only for women with history of previous preeclampsia.

Liona Poon: The success of the ASPRE trial relates to the ability to identify a specific group of high-risk women who respond very well to early administration of low-dose aspirin. This does not mean that low-dose aspirin should be given to all pregnant women universally. Furthermore, we should consider the issue of compliance. Although aspirin is considered safe in drug trials, nonetheless, it is a drug with known side effects; therefore, women at high risk for preterm preeclampsia should be identified and compliance with aspirin prophylaxis should be monitored throughout pregnancy. Universal first trimester screening should be advocated, and in high-risk women, low-dose aspirin should be commenced before 14 + 6 weeks of gestation. To achieve the best prediction and prevention of preterm preeclampsia, screening ideally should be done with evaluation of maternal history, measurements of mean arterial pressure, uterine artery pulsatility index, and serum PlGF. In the absence of 1 or 2 of the biomarker(s), risk calculation can still be done, but the detection rates for preterm preeclampsia will be reduced, in turn leading to a reduction in the treatment effect size by the aspirin prophylaxis. Currently, the contraindications for aspirin prophylaxis are bleeding disorders such as von Willebrand's disease, peptic ulceration, and hypersensitivity to aspirin.

What is the potential impact of genetic markers in identifying preeclampsia, or the angiogenic factors in newer treatment modalities? Might such findings be more useful in further exploring the etiology of preeclampsia?

Ananth Karumanchi: Preeclampsia heritability is estimated at approximately 55%. Although there has been some success in large genome-wide association studies, these associations explain only a small percentage of preeclampsia cases. With improvements in exome and whole genome sequencing methods, rare variant studies using large sample sizes will be complementary to genome-wide association studies that may identify other causal pathways to help explain the heritability of preeclampsia. Using transcriptional profiling, discovery and character-

ization of the antiangiogenic pathways in preeclampsia have provided improved understanding of the disease pathophysiology and have directed predictive and therapeutic efforts. In the clinic, recent evidence supports the utility of the soluble fms-like tyrosine kinase-1 and PlGF for predicting adverse maternal and perinatal outcomes for preterm patients, for ruling out preeclampsia in patients with suspected disease, and for predicting which high-risk patients are at low risk for severe adverse outcomes. Availability of these angiogenic biomarkers on automated platforms has also provided investigators with a robust surrogate that can be used in therapeutic studies.

James Martin: There is great potential here because preeclampsia affects huge numbers of mothers worldwide. The response to the first question above is apropos to this consideration. As soon as the required research is done to identify biomarkers, test their use, and assess their benefit and costs in the US, we can make substantial progress.

Liona Poon: Despite recent major advances in the development of effective screening and prevention strategies for preterm preeclampsia, this process is somewhat hindered by the lack of a full understanding of the underlying cause of the disorder. A strong genetic component for the development of preeclampsia is implicated; therefore, it is reasonable to assume that the unraveling of the genetic root of preeclampsia would further advance our efforts in predicting and preventing this disorder. Existing studies that have examined genetic changes and variations in women with preeclampsia using various approaches have demonstrated inconsistent results. Future direction should aim to evaluate molecular subtypes and specific biomarkers of preeclampsia for risk stratification, leading to personalized therapy.

The most recent NICE and ACOG guidelines for preeclampsia have not recommended biochemical, genetic, or ultrasound markers to help identify risk for preeclampsia. Do you believe that this will change in the near future?

James Martin: As mentioned previously, I think that both NICE and ACOG would be willing to recommend any biomarker that has been tested to show efficacy for reducing maternal and perinatal morbidity and mortality related to preeclampsia following the demonstration of cost and risk benefit to patients and healthcare systems. The biomarkers to identify risk for preeclampsia have little value if we do not have interventions demonstrated to be effective in reducing that risk at reasonable cost for patients, providers, insurers, and healthcare systems.

Liona Poon: The UK has already commissioned a study to evaluate the screening performance of the Bayesian approach. Data have shown this latter approach to be superior to that achieved by current NICE guidelines. I would envision that the NICE guideline will be updated in due course.

Ananth Karumanchi: I believe in the US, biomarkers proposed in the ASPRE algorithm, such as PlGF, are not currently available, and evaluating flow abnormalities of the uterine artery is not yet standard practice. For these reasons, there is limited generalizability of the ASPRE study to current practice in the US. A follow-up clinical trial in the US should be undertaken that includes biomarkers such as PlGF, known clinical risk factors, and perhaps ultrasound findings to evaluate aspirin's effect on prevention of preeclampsia and improvement of perinatal outcomes. I remain optimistic that this trial will occur.

What are the critical challenges you see relating to improving the range of services for screening prevention and management of preeclampsia? What research priorities would you most strongly support? What potential breakthroughs might be on the horizon?

Liona Poon: The introduction of biophysical and biochemical components to preeclampsia screening requires planning, training, and continuous monitoring. One decade ago, effective first trimester screening for Down syndrome was implemented in all maternity hospitals in the UK within a few months of the appropriate decision being taken by the National Screening Committee and NICE. That same infrastructure can now be used to expand the aims of first trimester screening to include identification of women at high risk of developing preterm preeclampsia. Research priorities that I would most strongly support include prospective validation of the Bayes' theorem-based screening method for preeclampsia. There is also an ongoing need to identify new biomarker(s) for improving the existing prediction model for both preterm and term preeclampsia, as well as other therapeutic measures for the prevention of preeclampsia.

James Martin: It is less costly to test biomarkers and treatments in markets outside the US, and very costly to do it here. A commitment is needed to test the most promising biomarkers and potential treatments shown to be of value elsewhere in the world, before I expect the FDA would recommend their use here. Like the major investments by the National Institutes of Health and the March of Dimes in prematurity research, the same sort of commitment is needed for progress to be made in preeclampsia research.

Ananth Karumanchi: The current gold standard criteria for preeclampsia diagnosis (hypertension and proteinuria) are suboptimal because they have low predictive value for the detection of adverse outcomes related to preeclampsia. Therefore, we need to better phenotype patients in clinical studies—pathology, imaging, hemodynamic, and biomarker data—so we can develop accurate new tools that can be used in conjunction with other clinical measures for the early detection of preeclampsia-related adverse outcomes. The research and clinical communities also need to engage with the National Institutes of Health, pharmaceutical industry partners, and the FDA to jointly identify and validate promising biological targets for therapeutics, like what is being done by the Accelerating Medicines Partnership for diseases such as Alzheimer's and rheumatoid arthritis. Large-scale human genetic studies to look for rare variants in the maternal and fetal genome (causal or protective variants) with big effect sizes are needed in this field. During the past decade, basic science and translational studies have suggested that the adverse outcomes related to preeclampsia may be largely explained by placental antiangiogenic factors that circulate in maternal blood. Novel strategies to block the toxic effects of these antiangiogenic factors such as RNA interference-based drugs and/or selective depletion of these factors with targeted apheresis are being evaluated in preclinical studies, and I remain optimistic that these targeted strategies will be helpful for some women with very preterm preeclampsia. I would also strongly support development of large animal models of preeclampsia that closely mimic the human situation, so novel therapeutic drugs can be better evaluated before first in-human studies. Another promising area of research is to evaluate the role of immune cells and dysregulated decidualization in the etiology of preeclampsia. Focusing on these early events of placentation may lead to improved preventive strategies. Finally, a disturbing trend in the US is a marked decrease in young scientists getting independent National Institutes of Health grants in biological research and especially in the reproductive biology field. Universities and the government will need to engage with the next generation of scientists early and provide them long-term support, as most major medical breakthroughs in basic sciences are made by scientists during their 30s and 40s.