Prediction and Prevention of Early-Onset Preeclampsia

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So, what should clinicians do based on these findings? While, I do not think one can counsel women that by lowering the GWG, they will definitively lower their risk of GDM, it can be included as an outcome that may be improved along with the many other impacts that have been identified. Studies have found that physician counseling can increase the proportion of women who gain within the IOM recommendations. In particular, there have been dietary and exercise recommendations that have been studied with some benefit (Cochrane Database Syst Rev 2015;6:CD007145).

A consultation with a nutritionist for those who have a poor understanding for the components of a healthy diet and how to achieve such would be reasonable. Giving feedback to women at every prenatal visit is likely to be useful so they can get a sense of what rate of weight gain is expected. While, in the end, we may not dramatically lower GDM rates with better GWG counseling, but given the preponderance of the evidence related to excess GWG, routine, consistent counseling regarding GWG during prenatal visits is worth the effort.—ABC

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**Prediction and Prevention of Early-Onset Preeclampsia: Impact of Aspirin After First-Trimester Screening**


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**ABSTRACT**

Preeclampsia (PE) continues to be a significant cause of maternal and fetal mortality and morbidity in both developed and developing societies. The aim of the study undertaken was to assess the value of intervention with low-dose aspirin after first-trimester prediction of early PE in an unselected population. The authors validated The Fetal Medicine Foundation early PE algorithm by using a combination of maternal demographic, biophysical (maternal mean arterial pressure [MAP] and uterine artery Doppler pulsatility index), and biochemical (pregnancy-associated plasma protein A [PAPP-A]) parameters. It was confirmed in the study that this algorithm predicted 92% of early PE in women who developed it, at a false-positive rate of 10%. This was a retrospective analysis of 2 consecutive cohorts of women screened for early PE. The first cohort (3066 women), screened between April 16, 2010, and March 9, 2012, was observed and used to validate the algorithm. The second cohort of women (2717 women) was screened, using the same algorithm, between April 1, 2012, and June 5, 2013. The first cohort was observed to determine whether algorithms developed to screen for PE at 11 to 13 + 6 weeks' gestation could be applied to the population. High-risk women in the second cohort were advised on their risk and offered aspirin (150 mg at night), with treatment starting immediately after screening. Preeclampsia was defined as de novo hypertension, arising after 20 weeks' gestation, returning to normal postpartum, with proteinuria (24-hour urine protein of $\geq 300$ mg or spot urine protein/creatinine ratio of $\geq 30$ mg protein/mmol creatinine). The demographic features of the observational and interventional groups were compared using the Mann-Whitney $U$ test for nonparametric data, $t$ test for normally distributed continuous data, and $\chi^2$ test for categorical data. Data analysis was done through SPSS version 22. Multiples of the median for MAP, uterine artery Doppler pulsatility index, and PAPP-A were all significantly higher in the interventional cohort. The prevalence of early PE and the proportion of women with PE delivering at 34 to 37 weeks' gestation were compared between the cohorts. A total of 3013 women (98.3%) in the observational group and 2666 (98.1%) in the interventional group had a live birth and were included in the
subsequent analysis. In the interventional cohort, 264 women (9.9%) had a risk of early PE ≥2% and were advised to take aspirin, and one of them (prevalence, 0.04%) developed early PE ($\chi^2 P = 0.01$). There were no cases of early PE reported among low-risk women in the interventional cohort. Among all women with PE delivering before 37 weeks, 25 (0.83%) were in the observational cohort and 10 (0.37%) in the interventional cohort ($P = 0.03$). A strategy of first-trimester screening for early PE coupled with prescription of aspirin to the high-risk group seems to be effective in reducing the prevalence of early PE.

**EDITORIAL COMMENT**

(Many previous studies have evaluated the potential benefit of low-dose aspirin for prevention of PE, with varied results. Recent meta-analyses have suggested that, provided treatment is started before 16 weeks, there is a reduction in early-onset PE and that this leads to a reduction in perinatal death and morbidity. However, although overall there seems to be benefit for patients at high risk based on medical history, whether there is a benefit for patients who are at risk based on serum, ultrasound, and other screening tests remains uncertain.

In this abstracted article, the authors report on a type of natural history experiment and 2 cohorts of patients. In the first, they validated an algorithm for the early detection of risk for PE, whereas in the second they treated women identified as high risk based on the algorithm with 150 mg of aspirin (ASA) daily. The algorithm included measurement of MAP, Doppler assessment of the uterine artery, and measurement of PAPP-A. Women were screened at the time of nuchal translucency ultrasound (11–13 + 6 weeks’ gestation), and those identified as high risk were treated with ASA until 34 weeks. Those high-risk women in the second cohort had a significantly lower risk of severe, preterm PE of 0.04% (1/2717) versus 0.4% (12/3066) in the first cohort.

To quote the authors, “reviewing the use of low-dose aspirin as a therapeutic agent for reducing the prevalence of PE reveals a tortuous path littered with periods of excitement and disappointment.” That was a colorful way of saying there have been many studies of low-dose aspirin to prevent PE, with results that are all over the map—some demonstrate benefit (Lancet 1985;1:840–842), others demonstrate no benefit (Lancet 1993;341:396–400; N Engl J Med 1993;329:1213–1218; Lancet 1994;343:619–629), and still others raise concern for harms such as abruption and increased bleeding (N Engl J Med 1998;338:701–705; Br J Obstet Gynaecol 1998;105:293–299). Importantly, criteria for entry, the dosage of aspirin, the timing of enrollment, and other factors have varied widely between these prior studies.

The authors of this current report hypothesize a few major contributors to the success of their protocol, as compared with those published previously. They undertook a preliminary evaluation and validation of their screening protocol, which they report detected 92% of early PE, at a false-positive rate of 10%. They screened women early in gestation (late first trimester) and instituted ASA early; data support the benefit of starting ASA before 16 weeks. They also provided a dose of 150 mg, as some evidence indicates that many individuals do not benefit from the lower dose preparations that are often used (J Obstet Gynaecol Can 2009;31:1022–1027; Am J Obstet Gynecol 1999;180:135–140). Finally, they advised women to take ASA at bedtime because this has been reported in some studies to be more beneficial (Hypertension 1999;34:1016–1023). Which of these variables are most important remains uncertain, but the combination certainly seems to have been very effective.

Despite the variable findings of the prior studies, a recent meta-analysis of all relevant randomized controlled trials showed a small, but modest, benefit of using aspirin to prevent PE (Lancet 2007;369:1791–1798), and the US Preventive Health Services Task Force now recommends this for women at high risk based on a number of factors, primarily maternal history and comorbidities. Those recommendations do not discuss risk based on biochemical or ultrasound screening parameters, although it is well known that such factors can also indicate an increased risk. Whether women who have abnormal serum screening without increased MAP or abnormal uterine artery Doppler would benefit from ASA is unclear. However, given the low-risk profile of ASA in

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pregnancy, treating such women seems reasonable, although further studies are definitely warranted. One could also argue for just giving low-dose ASA, which is inexpensive and very safe to all women, although it is argued that compliance improves if women are recognized to be high risk. In any event, it seems that either these authors have finally solved the riddle and found the truly beneficial utility, or we will once again fall into the pit of aspirin despair.—MEN)

Noninvasive Prenatal Diagnosis for Cystic Fibrosis: Detection of Paternal Mutations, Exploration of Patient Preferences, and Cost Analysis

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ABSTRACT

Cystic fibrosis (CF) is a severe, autosomal recessive, multisystem condition affecting the respiratory and digestive systems. It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. Prenatal diagnosis of CF currently requires an invasive test to obtain fetal genetic material and carries a small risk of miscarriage. Noninvasive prenatal diagnosis (NIPD) based on analysis of cell-free fetal DNA in maternal plasma has been reported to exclude the paternal mutation in couples carrying different CF mutations. This study describes the development of a next-generation sequencing assay designed to detect or exclude 10 of the most common CF mutations, for use when each parent carries a different CFTR mutation, and the paternal mutation is one of the 10 included in this panel. A cost analysis of NIPD for CF is reported to inform implementation strategies. Normal and heterozygous genomic DNA (gDNA) control samples with known CFTR mutations were used to assess test performance, before testing on maternal plasma samples collected, as part of a larger program designed to develop standards for NIPD from women undergoing invasive diagnostic prenatal testing because of a risk of CF. The presence of fetal DNA was confirmed by the detection of paternal CFTR sequences, ZFY, or paternal HLA-type sequences in the maternal plasma. The total test-related costs of 3 different clinical pathways (the current invasive testing only pathway, NIPD for the paternal CF mutation, and NIPD for direct diagnosis) were estimated to assess the economic consequences of implementing NIPD for CF. Total test-related costs were estimated for the current care pathway and were compared with those incorporating NIPD by using uptake data from a study exploring views on NIPD for CF. All 8 mutations in the gDNA samples from CF carriers were reliably detected at an allele frequency of 50%. A questionnaire-based study of stakeholder views and preferences was undertaken to estimate the uptake of invasive testing and NIPD with detailed results published elsewhere. Most participants (n = 130; 94.9%) said that they would choose NIPD for CF, and 90% would be prepared to pay for it, with 49.2% prepared to pay up to £50, 39.0% prepared to pay £100 to £200, and 10.3% prepared to pay more than £200. The total cost for this pathway per 100 women was £57,185. Using these potential uptake data, the incremental costs of NIPD over invasive testing per 100 pregnancies at risk of CF are £9025 for paternal mutation exclusion and £26,510 for direct diagnosis. The authors have successfully developed a next-generation sequencing assay to allow NIPD to be used for risk stratification in a significant proportion of CF families. Consideration of stakeholders' views and cost-effectiveness alongside test development indicates that introduction of NIPD for CF would be welcomed and uptake is likely to be high. These findings may have