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First-Trimester Risk Assessment for Early-Onset Preeclampsia

ABSTRACT: Hypertensive disorders with adverse sequelae (including preterm birth, maternal morbidity and mortality, and long-term risk of maternal cardiovascular disease) complicate 5–10% of pregnancies. Early identification of pregnant women at risk of developing early-onset preeclampsia would theoretically allow referral for more intensive surveillance or application of preventive therapies to reduce the risk of severe disease. In practice, however, the effectiveness of such triage would be hindered by the low positive predictive value for early-onset preeclampsia reported in the literature. In spite of the modest predictive value of first-trimester preeclampsia risk assessment and the lack of data demonstrating improved clinical outcomes, commercial tests are being marketed for the prediction of preeclampsia in the first trimester. Taking a detailed medical history to evaluate for risk factors is currently the best and only recommended screening approach for preeclampsia; it should remain the method of screening for preeclampsia until studies show that aspirin or other interventions reduce the incidence of preeclampsia for women at high risk based on first-trimester predictive tests.

Recommendations

- Taking a detailed medical history to evaluate for risk factors is currently the best and only recommended screening approach for preeclampsia; it should remain the method of screening for preeclampsia until studies show that aspirin or other interventions reduce the incidence of preeclampsia for women at high risk based on first-trimester predictive tests.
- Current predictive tests for preeclampsia may harm more women than they benefit because of their low positive predictive value (PPV). These tests require a large number of women to be identified as high risk and to potentially undergo intensive surveillance in order to detect one case of early-onset preeclampsia.
- The American College of Obstetricians and Gynecologists does not recommend screening to predict preeclampsia beyond obtaining an appropriate medical history.

Introduction

In spite of the modest predictive value of first-trimester preeclampsia risk assessment and the lack of data demonstrating improved clinical outcomes, commercial tests are being marketed for the prediction of preeclampsia in the first trimester.

Hypertensive disorders with adverse sequelae (including preterm birth, maternal morbidity and mortality, and long-term risk of maternal cardiovascular disease) complicate 5–10% of pregnancies (1). Early-onset preeclampsia is associated with great risk for the mother and infant. Early identification of pregnant women at risk of developing early-onset preeclampsia would theoretically allow referral for more intensive surveillance or application of preventive therapies to reduce the risk of severe disease (2).

Clinical risk factors traditionally have been used to identify women at high risk of developing preeclampsia (Box 1). Several studies also have identified biophysical

Box 1. Clinical Risk Factors for Preeclampsia ⇦

- Primiparity
- Previous preeclamptic pregnancy
- Chronic hypertension, chronic renal disease, or both
- History of thrombophilia
- Multifetal pregnancy
- In vitro fertilization
- Family history of preeclampsia
- Type I diabetes mellitus or type II diabetes mellitus
- Obesity
- Systemic lupus erythematosus
- Advanced maternal age (older than 40 years)

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factors that may help predict hypertensive disorders of pregnancy (3–5). These studies have found associations between hypertensive complications and maternal body mass index, age, early pregnancy blood pressure, medical history, and biophysical markers such as pregnancy-associated protein A, placental growth factor, and uterine artery Doppler velocimetry. Such studies have used a variety of markers and risk factors, which limits the ability to synthesize the data available in the literature (6).

Limitations of Current Predictive Tests

In general, models that incorporate multiple predictive factors demonstrate better detection rates than those using only a single factor. Models also tend to have better predictive value (ie, proportion of patients with positive test results who develop preeclampsia) for early-onset preeclampsia and severe preeclampsia. Overall, most studies have reported modest PPVs. The case–control design, the small number of cases of early-onset preeclampsia, and the large number of predictors in available screening models raise concerns that reported detection rates are overly optimistic. These models also have not been validated independently in prospective cohorts.

For a predictive test for preeclampsia to be useful, it would need a high sensitivity and a high PPV, such that women who test positive would be at high risk of developing the disease. In addition, for a predictive test to be beneficial, detection before the onset of symptoms must improve clinical outcomes. In theory, referral of women at high risk of early-onset preeclampsia to specialists might allow for more intensive monitoring. In practice, however, the effectiveness of such triage would be hindered by the low PPV for early-onset preeclampsia reported in the literature. For example, investigators in a cohort study of 7,797 singleton pregnancies have reported detection rates for early-onset preeclampsia as high as 93% with models incorporating clinical risk factors as well as ultrasonographic and biochemical markers (4). However, of the 476 women who screened positive for early-onset preeclampsia, 32 developed the disease, giving a PPV of only 7% (4). Given the relatively low prevalence of early-onset preeclampsia, screening tests will need to have sensitivities and specificities well above what is currently achievable to produce meaningful PPVs. Moreover, current predictive tests for preeclampsia may harm more women than they benefit because of their low PPV. These tests require a large number of women to be identified as high risk and to potentially undergo intensive surveillance in order to detect one case of early-onset preeclampsia.

There are no randomized controlled trials of preventive therapy for women with an elevated risk of preeclampsia based on first-trimester biophysical screening. Taking a detailed medical history to evaluate for risk factors is currently the best and only recommended screening approach for preeclampsia; it should remain the method of screening for preeclampsia until studies show that aspirin or other interventions reduce the incidence of preeclampsia for women at high risk based on first-trimester predictive tests. Although a meta-analysis of studies of low-dose aspirin showed significantly reduced risk of severe preeclampsia, fetal growth restriction, and gestational hypertension in the subgroup in which treatment was initiated before 16 weeks (7), subjects in these studies were mostly identified by clinical risk factors rather than biophysical tests. Prediction–intervention studies based on first-trimester biophysical risk assessment are needed to determine whether women identified based on first-trimester screening might benefit from low-dose aspirin. In its 2014 recommendation for aspirin to prevent preeclampsia, the U.S. Preventive Services Task Force concluded that predictive models based on biophysical assessment "have not shown sufficient accuracy for clinical use" (8).

Conclusions

The American College of Obstetricians and Gynecologists does not recommend screening to predict preeclampsia beyond obtaining an appropriate medical history to evaluate for risk factors (9). Any marginal benefit of adding biophysical tests, including uterine artery Doppler velocimetry and maternal serum analytes, to screening based on risk factors first must be demonstrated to justify the additional costs. Cost-effectiveness studies of screening strategies should quantify the adverse effects of identifying women as high risk of preeclampsia, including parental anxiety, increased frequency of prenatal appointments, and additional surveillance testing. For a first-trimester risk assessment for preeclampsia to be useful in clinical practice, future screening tests will need to have sensitivities and PPVs high enough to accurately identify women

who will develop preeclampsia, and interventions will need to be available that improve clinical outcome in women who test positive.

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