First-Trimester Prediction of Early Preeclampsia
A Possibility at Last!

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P}{\text{P}}reeclampsia, which presents after midgestation, is the most common pregnancy complication associated with serious maternal-fetal morbidity and mortality; and at present the only effective treatment is delivery of the placenta. The ability to predict in early pregnancy those women at risk for preeclampsia might decrease maternal and fetal morbidity through closer surveillance by physicians experienced or specialized in high-risk obstetrics, as well as delivery at tertiary care centers. Reliable prediction would also permit institution of preventive or treatment regimens, unavailable in 2009, although exciting possibilities are under scrutiny.1

Investigators have been evaluating tests to predict preeclampsia for >50 years without much success.2,3 These have included tests relating to placental perfusion and vascular resistance (eg, the “rollover” and cold pressor tests, as well as uterine artery Doppler evaluation); placental products (eg, proangiogenic and antiangiogenic proteins, human chorionic gonadotropin, placental protein 13, and inhibin A); renal dysfunction (eg, fractional urate clearance and microalbuminuria); and endothelial dysfunction (eg, fibronectin, P- and L-selectin, and vascular cell adhesion molecule 1). The list is enormous, and recently investigators have begun exploring the fields of proteomics and metabolomics for tests to predict preeclampsia.

A large systemic review published in 20042 and to be updated in 20093 concluded that no single test met clinical standards for a predictive test. The authors recommended further evaluation of approaches measuring maternal blood and urine levels of certain angiogenic and antiangiogenic factors and suggested that success might require the combination of several different tests. Clinically useful prediction tests, it was stated, should ideally be simple, rapid, noninvasive, inexpensive, easy to perform early in gestation, and should impose minimal discomfort or risk. The technology should be widely available and the results valid, reliable, and reproducible. Useful prediction of preeclampsia would also require a very high likelihood ratio for a positive test (>15), as well as a very low likelihood ratio for a negative result (<0.1). How do the results of Poon et al4 fare with such criteria?

Poon et al4 evaluated 7797 women with singleton pregnancies during gestational weeks 11 to 13 (when prenatal screening tests are normally performed), of whom 157 developed preeclampsia, 34 before gestational week 34, the group most prone to severe morbidity. Using logistic regression analysis, an algorithm to predict early preeclampsia that combined the logs of uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A, serum free placental growth factor, and the body mass index and presence of nulliparity or of previous preeclampsia was developed. Thus, this approach combines several predictive tests, as suggested by Conde-Agudelo et al4 in his 2004 systematic review: tests that appear simple, rapid, noninvasive, and easy to perform (at least in developed nations) and that appear to impose minimal discomfort or risk. However, it remains to be determined whether the benefits justify the expense.

At a 5% false-positive rate for normotensive deliveries, 476 women tested positive for early preeclampsia, of whom 32 actually developed early disease and 444 did not. Of the 7321 women who tested negative for early preeclampsia, 2 developed early disease and 7319 did not. Thus, the sensitivity of the prediction model for early preeclampsia at a 5% false-positive rate for normotensive deliveries was 32 of 34, or 94.1%, and the specificity was 7319 of 7319 or 94.3%. The likelihood ratio for a positive test was 16.5 and for a negative test was 0.06, easily fulfilling the World Health Organization criteria for a clinical prediction test.2,3 These are remarkably good results!

Our enthusiasm must be tempered somewhat for several reasons. First, this model must be tested by other investigators and in populations that differ from those used to develop it to give us confidence that similar results are universal and that the model may be universally employed. It would have been of interest to know the variability and reproducibility of each test, especially the use of Doppler technology. Clinical trials are required to assess the effectiveness of early prediction and to perform cost-benefit analyses. They should be structured as randomization to usual care and to early prediction followed by a more stringent protocol for follow-up in patients who screen positive for early preeclampsia.

Let us note here that the mortality and morbidity of preeclampsia is far greater in developing compared with developed nations. Although in industrialized countries ma-
ternal characteristics, medical history, and mean arterial pressure are easily obtained; pregnancy-associated plasma protein-A and placental growth factor determined by a clinical laboratory; and sonographic testing with adequately trained personnel readily available, this is not the case in the developing world. Moreover, the cost of the combined tests is obviously prohibitive in many of these countries. Thus, the need to search for alternative approaches to accurate prediction is required in such countries and should receive priority given their high rates of maternal and fetal mortality secondary to preeclampsia.

Another problem is that the tests are performed between gestational weeks 11 to 13, and many women seek prenatal care at a later date. Thus, ideal approaches should also focus on later periods of gestation. In this respect, the antiangiogenic proteins sFlt-1 and sEng and the ratio sFlt-1:placental growth factor should be considered for algorithms beginning perhaps at 17 to 20 weeks of gestation; and given their performance in studies performed as of 2008, a “package” might be constructed that could be more universally applicable.

Poon et al are to be congratulated for developing a predictive model with the likelihood ratios for positive and negative tests needed for a clinically useful approach to predict early preeclampsia. As noted, the approach is currently only applicable in developed nations, where the incidence of serious complications from preeclampsia has already been reduced substantially by the dictums of appropriate prenatal care. Although further testing must be performed, their work opens the possibility of identifying women at high risk of early disease in time to modify prenatal care to minimize maternal and fetal complications.

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### References


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