Although the birth experience has never been as safe for mothers and children as today, the puzzling pregnancy-related disease called ‘preeclampsia’ still occurs in 2–10% of all pregnancies. Despite some therapeutic progress, it is still one of the leading causes of maternal and fetal mortality in the developed and developing world. Preeclampsia, which usually occurs late in the second or, more frequently, in the third trimester of pregnancy, is characterized by the occurrence of pregnancy-induced hypertension, edema, and proteinuria in a woman with no prior incidence of these sequelae (1). The association of hemolysis, increased liver enzymes, and low platelets (the so-called HELLP syndrome) puts not only the child, but also the mother, at severe risk. Preeclampsia preferentially affects the firstborn of a particular partner (2). The etiology of the disease is still unknown, although research suggests that the trophoblast is unable to effectively invade the decidua or to modify the spiral artery walls (3).

A serious clinical shortcoming is clearly represented by the fact that no reliable test exists to identify those women at risk for developing the disorder early enough in their pregnancies to permit preventive treatment (4). Current treatment is thus restricted to symptomatic management with drugs such as antihypertensives, benzodiazepines, or magnesium following full onset of the disease. Rapid delivery of the fetus often is the only way to resolve the disorder.

The observation made more than a century ago by Schmorl (5) that trophoblastic cells could be detected in the lungs of patients who had succumbed to eclampsia may now provide a new diagnostic tool for the early detection of preeclampsia. We have observed that fetal-maternal cell traffic is significantly increased in preeclampsia (6). In the February issue of this Journal, Lo et al. (7) show that the abundance of fetal DNA in maternal serum is also similarly increased in preeclampsia.

In our studies, conducted as part of our participation in the National Institute of Child Health and Development Fetal Cell Isolation Study (the “NIFTY” trial) to test the diagnostic efficacy of fetal cells enriched from the peripheral blood of pregnant women for the detection of fetal aneuploidies (8), we noted, originally by chance, that the number of erythroblasts was increased in pregnancies affected by preeclampsia (9). To ascertain whether these cells were of fetal or maternal origin, we performed a case-control study examining only pregnancies bearing male offspring, using X and Y chromosome fluorescence in situ hybridization to determine the number of male cells (6). This study indicated that a significant proportion of the erythroblasts was indeed of fetal origin and that there was a linear relationship between the increase in maternal and fetal erythropoiesis. Although these original results raised the hope for a new mode of diagnosis, the approach is not applicable for routine use because the enrichment procedure and subsequent analysis will not permit the rapid evaluation of a large population of pregnant women, many of whom will not be at risk for developing preeclampsia.

This drawback has been overcome to a large extent by the investigation carried out by Lo et al. (10), who expanded on their previous observation that fetal DNA is detectable in maternal serum or plasma and performed the experiment that begged to be done.

By using a sensitive real-time quantitative PCR approach to accurately determine the number of Y chromosome template copies, and by examining only women carrying male fetuses, they assessed the relative amounts present in 20 normal and 20 preeclamptic pregnancies. The results of their study closely parallel our observations, in that Lo et al. (7) also observed a significant increase (at least fivefold) in the amount of fetal DNA in preeclampsia.

Although these cumulative results indicate the presence of increased amounts of fetal genetic material in the maternal circulation in preeclampsia, thereby providing the basis for a new etiologic hypothesis and an improved diagnostic test, several questions and issues still remain to be resolved. For example, whether the serum-based approach used by Lo et al. (7) or the cell-based technique used by our group will ultimately be more successful still needs to be investigated systematically. The detection of fetal DNA in serum or plasma has one obvious advantage in that because the complicated, time-consuming, and expensive cell separation steps (11) would no longer be necessary, easy shipment of samples might be possible, and the procedure could eventually be automated. Lo et al. (12) have, however, noted previously that when using the TaqMan qPCR system to determine the amount of fetal DNA in serum during various stages of pregnancy, that two complimentary PCR reactions may need to be used, where in the first reaction the amount of fetal (male) DNA is quantified with primers for the SRY gene, and the total amount of DNA is determined using primers for the ubiquitously present β-globin gene. Because Lo et al. (12) in their previous publication noted significant fluctuations in the amount of total DNA from the various serum samples, this important control, where the ratio permits the authors to determine the relative amount of fetal DNA, may also have to be checked in studies on preeclamptic women. Other questions, such as the optimal fetal target sequence to be examined (obviously the Y chromosome is rather restricted), also remain to be resolved, and ultimately the key question of what role this deluge of fetal material plays in the development or progression of the disorder hopefully can be answered. One of the most pressing tasks will be to find out whether the detection of fetal DNA, be it in maternal serum or after the isolation of fetal cells from peripheral blood of women in early pregnancy, could be predictive of preeclampsia.
and/or HELLP syndrome in asymptomatic women. Such an early screening test would identify women at risk before the disease sets in. Whether we are now substantially closer to this long-awaited goal needs to be shown by appropriate screening studies for the prediction of preeclampsia, raising hope that in the near future we will be able to better deal with this dangerous pregnancy-related disease.

References

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