# Hopes Rise for Screening Tests for Preeclampsia

BY JEFF EVANS
*Senior Writer*

PRAGUE — New insights into the pathophysiologic changes of preeclampsia that occur in the placenta are helping researchers to develop potential early screening tests for the disease using biomarkers in maternal blood, Dr. Wolfgang Holzgreve said at the 20th European Congress of Perinatal Medicine.

The current line of research into the cause of preeclampsia originates from observations that associated the long-term presence of fetal cells and DNA in maternal blood with autoimmune diseases such as scleroderma and conditions such as polymorphic eruptions of pregnancy (Lancet 1998;352:1898-901). About 8 years ago, Dr. Holzgreve and his colleagues at the University of Basel (Switzerland) began to recognize that the association between microchimerism and maternal disease might extend to preeclampsia and play a role in its pathophysiology.

In Dr. Holzgreve's lab, researchers found many more fetal cells and DNA in the blood of women with preeclampsia than in women with normal pregnancies. Reports from his lab indicated that the elevated levels of free fetal DNA in maternal blood positively correlated with the presence and severity of preeclampsia in mothers in a dose-response–like effect (Am. J. Obstet. Gynecol. 2001;184:414-9).

Similar observations were made regarding the effect of the total amount of free maternal DNA in a pregnant woman's plasma. The total free maternal DNA seemed to be a marker for the amount of damage that preeclampsia causes to the endothelial cells that line the liver and kidneys, as well as the circulatory system, he said.

The first insult to occur in preeclampsia is an invasion of trophoblasts that causes impairment of the spiral arteries and placental changes. The investigators hypothesized that the excess fetal cells and DNA going into the maternal circulation cause leukocyte activation and an "inflammatory-like reaction" in the peripheral endothelial system (Placenta 2005;26:515-26).

Anatomists working with Dr. Holzgreve's group have calculated that about 3 billion mitoses occur in the placenta each day—no cancer in humans has such a high rate of division—and this activity produces about 3.6 g of new syncytium each day from all of the placental cell divisions. But only 0.6 g of new syncytium is incorporated into the placenta each day. Thus, about 3 g of syncytial tissue travels into the intervillous space and into the maternal circulation each day.

Normally the multinucleated cells and membrane-bound particles of syncytium undergo controlled apoptosis. But if the placenta is hypoxic from trophoblast invasion, a separate pathway of aponecrotic shedding occurs, releasing materials that are toxic to the maternal epithelial system. In vitro tests in Dr. Holzgreve's lab have shown that cultures of endothelial cells from umbilical veins break down after exposure to particles of placental syncytium.

Recent evidence has shown that the body traps the materials shed from the placenta by an extracellular filamentous network produced by neutrophils, which is the same as the defensive mechanism described for neutrophils that trap pathogenic bacteria (Science 2004;303:1532-5). These networks are present in higher abundance in preeclamptic women than in pregnant control women, Dr. Holzgreve said.

The model of excess fetal cells and free DNA also fits with the knowledge that the highest risk for preeclampsia occurs in first pregnancies (in which the mother has not been exposed to her partner's genes), in women who have a new pregnancy from a different man, and in cases of ovum donation in which all of the fetal material is foreign.

Because clinical signs and symptoms are so poor at predicting who will have preeclampsia, Dr. Holzgreve and his colleagues have tried, using the increase in free fetal DNA in the maternal circulation, to predict preeclampsia as early in pregnancy as possible. Recent studies have indicated that women with preeclampsia have significantly increased levels of free fetal DNA in their blood beginning at a gestational age of 20 weeks, which could have potential as an early test for the disease, he said.

"What needs to be done now is a big, multicenter study to see what the predictive tests are," he said. "Then the vision would be that there is first-trimester screening of nuchal translucency and second-trimester screening including free fetal DNA" in maternal blood. ■


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