Circulating Soluble Endoglin Predicts Preeclampsia

BY MARY ANN MOON
Contributing Writer

An early and steep rise in circulating levels of soluble endoglin appears to predict preeclampsia, reported Dr. Richard J. Levine of the National Institute of Child Health and Human Development, Bethesda, Md., and his associates.

Pregnant women's circulating levels of soluble endoglin, an antiangiogenic protein, appears to rise markedly 2-3 months before the onset of preeclampsia. This rise is accompanied by a similar rise in the ratio of another antiangiogenic protein—soluble fms-like tyrosine kinase 1—to placental growth factor (the sFlt-1:PlGF ratio). "Taken together with experimental evidence in rodents, these data suggest that circulating soluble endoglin and sFlt-1, each of which causes endothelial dysfunction by a different mechanism, may both contribute to the syndrome of preeclampsia," Dr. Levine and his associates said.

"Prospective longitudinal studies are needed to assess whether these biomarkers can predict the imminent onset of clinical disease."

In an accompanying editorial comment, Dr. Marshall D. Lindheimer and Dr. Jason G. Umans said these findings puts the measurement of antiangiogenic proteins "at the forefront of tests that are potentially useful for predicting preeclampsia." The findings also point the way to both preventing and treating the disorder, they said.

To examine gestational patterns in levels of these proteins, Dr. Levine and his associates performed a nested case-control study using data and frozen serum samples from a subset of 3,630 women who had participated in the Calcium for Preeclampsia Prevention (CPEP) trial. The CPEP study, conducted in 1992-1995, was a randomized trial that assessed the disorder in healthy nulliparous women with singleton pregnancies.

Of these subjects, 2,469 were normotensive throughout pregnancy and delivered normal-sized infants; these women served as controls in the current study. Another 225 subjects were normotensive but gave birth to small-for-gestational-age (SGA) infants, 651 had gestational hypertension, 213 had preeclampsia at or after 37 weeks (term preeclampsia), and 72 had preeclampsia before 37 weeks' gestation (preterm preeclampsia). For the case-control study, serum specimens that had been obtained during pregnancy were evaluated for 120 subjects randomly selected from the first four categories and from all 72 subjects in the last category.

Serum levels of soluble endoglin rose during the last 2 months of normal pregnancies, but rose earlier and much more steeply in women who later developed preeclampsia, "reaching a peak at the onset of clinical disease," the researchers said (N. Engl. J. Med. 2006;355:992-1005).

Beginning at 17-20 weeks' gestation, mean serum soluble endoglin levels were significantly higher in women who later developed preterm preeclampsia (10.2 ng/mL) than in controls (5.8 ng/mL). They then showed a steep rise at 33-36 weeks. Similarly, starting at 25-28 weeks' gestation, levels were significantly higher in women who later developed term preeclampsia (8.5 ng/mL) than in controls (5.9 ng/mL). Levels also rose steeply at 33-36 weeks.

After the onset of clinical disease, mean serum levels of soluble endoglin were markedly higher in women with preterm preeclampsia (46.4 ng/mL) than in matched controls (9.8 ng/mL) and were similarly higher in women with term preeclampsia (31.0 ng/mL) than in matched controls (13.3 ng/mL).

"Elevations in soluble endoglin were particularly pronounced—therefore, potentially most useful for prediction—among women in whom preterm preeclampsia developed or women in whom preeclampsia developed who had an SGA infant," they said.

Increased levels of soluble endoglin were usually accompanied by increased sFlt-1:PlGF ratios. In addition, women with both biomarkers in the highest quartile at 21-32 weeks' gestation had an increased risk of preterm preeclampsia, and those with levels in the highest quartile at 33-42 weeks had an increased risk of term preeclampsia.

"The data can be interpreted to imply that soluble endoglin levels and the sFlt-1:PlGF ratio both contribute to the pathogenesis of preeclampsia. Indeed, a composite measure incorporating all three molecules—the ratio of (sFlt-1 plus soluble endoglin):PlGF—was more strongly predictive of preeclampsia than were individual biomarkers," the authors said. ■