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High Blood Pressure During Pregnancy May Set Stage for Thyroid Problems Later

Scientists have found that a history of preeclampsia -- dangerously high blood pressure and a suite of other symptoms that complicate some pregnancies -- can dramatically increase the likelihood that a woman will experience low thyroid function later in life.

The research, by Howard Hughes Medical Institute investigator Ananth Karumanchi and colleagues, was reported online November 17, 2009, in the *British Medical Journal*.

Preeclampsia, a precipitous rise in the mother's blood pressure accompanied by impaired kidney function with leakage of abnormal amounts of protein into the urine, develops after the 20th week of pregnancy. It's a serious condition -- occurring in five to eight percent of pregnancies -- that can cause seizures, coma and, rarely, death of the mother, fetus or both. Delivering the baby as soon as it has a good chance of survival resolves the immediate situation. But premature delivery can cause problems for the infant, and preeclampsia has lingering health consequences for the mother as well.

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- S. Ananth Karumanchi

"When I was in medical school 20 years ago, we were taught that adverse effects of preeclampsia were restricted to pregnancy, and that once the pregnancy was complete and the preeclampsia went away, then the mother was fine," said Karumanchi, who has studied the condition since 2001. "That's turning out to be untrue."

It's been known for some time that a history of preeclampsia raises a woman's risk for high cholesterol, high blood pressure, heart disease and stroke later in life. Karumanchi's new research shows that preeclampsia can also reduce production of thyroid hormones, which can cause a variety of signs and symptoms including low energy, weight gain, and dyslipidemia. The study also identifies a common underlying mechanism that contributes to both conditions.

In earlier work, Karumanchi showed that excess levels of a protein called sFlt-1 contributes to preeclampsia by inhibiting VEGF, a chemical signaling molecule that stimulates blood vessel growth and repair. Other VEGF inhibitors are used in cancer treatment, where their ability to suppress the growth of vessels supplying tumors is a boon, but the downside is that patients treated with these molecules develop symptoms similar to those seen in women with preeclampsia.

"A couple of years ago I noticed reports that some cancer patients taking VEGF inhibitors for long periods of time were also developing low thyroid function. The VEGF inhibitors were blocking the vasculature in the thyroid tissue," said Karumanchi, an associate professor of medicine and obstetrics and gynecology at Beth Israel Deaconess Medical Center in Boston. "So I thought, if this is happening in cancer patients receiving VEGF inhibitors, and if preeclampsia is characterized by high circulating levels of VEGF inhibitor sFlt-1, couldn't this same thyroid damage be happening in patients with preeclampsia?"

He teamed up with two epidemiologists, Richard Levine of the National Institute of Child Health and Human Development and Lars Vatten of the Norwegian University of Science and Technology, to investigate that question using data from previous studies.

In the Calcium for Preeclampsia Prevention (CPEP) study, which was directed by Levine and conducted from 1992-1995, blood was collected from pregnant women both before 21 weeks of gestation and after delivery. For the current study, researchers analyzed archived blood samples from 282 women in the CPEP study (141 who developed preeclampsia; 141 who did not) for sFlt-1 and several measures of thyroid function and found that women with preeclampsia were more likely to have abnormal thyroid function tests and that this abnormality correlated with the high sFlt1 levels.

"What we're proposing is that this protein sFlt-1 that is made during preeclampsia damages the thyroid vascular tissue, leading to some degree of thyroid damage to the mother in pregnancy," said Karumanchi. To find out the clinical consequences of this thyroid dysfunction, the researchers turned to Vatten's data from the Nord Trondelag Health Study, which they then linked to records from the Medical Birth Registry of Norway. This gave the scientists information on 7,121 women who had their first birth registered between 1967 and the women's participation in the study, which was conducted between 1995 and 1997. The new analysis showed that women

with a history of preeclampsia were at greater risk for low thyroid function many years afterward.

"From a public health standpoint, our findings have important implications," Karumanchi said. "Thyroid problems are relatively common in women, usually affecting one in 15 over a 20 year period following pregnancy. But for a woman with a history of recurrent preeclampsia, the probability rises to almost one in five. Because low thyroid function is associated with other problems such as uncontrolled weight gain, fatigue and elevated cholesterol, and because it's easily treated with thyroxine supplementation, it's important that the internists who follow these women long-term watch out for hypothyroidism, as well as cardiovascular complications."

An open question that Karumanchi hopes to address in future research is how the maternal thyroid dysfunction during preeclampsia affects the developing fetus.

In addition to Levine and Vatten, Karumanchi's coauthors on the paper are Gary Horowitz and Anthony Hollenberg of Beth Israel; Cong Qian of Glotech Inc., Rockville, Md.; Pal Romundstad, Alf Hellevik and Bjorn Asvold of the Norwegian University of Science and Technology and Kai Yu of the National Institutes of Health.