Gene variation can affect fetal growth

Baylor College of Medicine
HOUSTON -- (May 18, 2010) -- Smoking during pregnancy can affect an infant's growth in two ways, said researchers at Baylor College of Medicine [1].
First, a deletion of genetic material in the fetus itself inactivates a gene (GSST1) that would normally enable the fetus to excrete intermediates of some of the most harmful chemical metabolized from cigarette smoke. These chemicals -- the polycyclic aromatic hydrocarbons (i.e., hydrophilic DNA adducts) – are among the more than 4,000 chemicals metabolized from cigarette smoke.

Second, maternal smoking causes an increase in the amount of another gene (CYP1A1) in the placenta, which is responsible for generating the harmful intermediate called hydrophilic DNA adducts (mentioned above) in the first place. Interestingly, this occurs not as a result of change in the DNA sequence but from a specific chemical modification called methylation to one of the DNA base pairs. This effect is an epigenetic event, which means it occurs because of an event that affects the expression of a gene.

The sum total of these two events is that the fetus not only has more of these harmful hydrophilic DNA adducts, but it cannot excrete them, said Dr. Kjersti Aagaard, an assistant professor of obstetrics and gynecology [2] at BCM, who led efforts to study the effects of tobacco smoke on growing fetuses.

Women continue to smoke

"We have understood for several decades that despite our public health campaigns, 20 percent of women continue smoking during pregnancy," said Aagaard, who has previously published studies describing smoking behavior and fetal growth in pregnancy. "However, of those women who smoke (or are exposed to second-hand smoke), only a small percentage experience adverse pregnancy outcomes because of smoking behavior."

Some infants (but not all) exposed to tobacco smoke during pregnancy are growth restricted and often low birthweight.

In previous studies, researchers have observed that the amount a mother smokes has an effect. In fact, as little as a half pack per week can increase the risk of an adverse pregnancy outcome.

In addition, increasing the dose increases the amount of the chemical carcinogens, such as the aromatic hydrocarbons and their metabolites, that reaches the baby. However, regardless of the amount smoked or the exposure to smoke, only some pregnancies suffer negative effects. That means that only some are susceptible to the harmful elements in cigarette smoke.

Why are some pregnancies susceptible?

Aagaard and her colleagues chose a two-pronged approach to finding out why some pregnancies are susceptible and some are not.

First, they looked for an effect of a functional gene mutation (a mutation resulting in a change in the gene message) in either the mother or fetus in relation to changes in a baby's growth. Second, they would look for the effect of smoking on the "epigenetics," which involves a chemical change that modifies how the gene is expressed.

With this two-pronged approach, they hoped to understand better how exposure to tobacco in the womb affects fetal growth patterns. Specifically, they were interested in whether the risk of growth restriction in the tobacco-exposed fetus resulted from a genetic or an epigenetic event.

They found both.

Genetic connection

In a report in the journal Obstetrics and Gynecology [3], Aagaard and colleagues from the Eunice Kennedy Shriver National Institute of Child Health, Human Development Maternal-Fetal Medicine Units Network evaluated DNA or genetic material from 502 mothers who smoked and their fetuses and compared them to DNA from fetuses and mothers who did not smoke.

They found a significant association between a fetal deletion in the gene GSTT1 and reduced birthweight in the fetuses whose mothers smoked. Smoking had no effect on fetuses who did not have this deletion, and there was no effect of this deletion on fetuses whose mothers did not smoke.

In the second study, published in the journal Metabolism [4], Aagaard and colleagues from BCM and the University of Utah built on what they knew about tobacco metabolism and GSTT1 deletions. In phase I, a gene called CYP1A1 prompts conversion of the carcinogenic compounds called polycyclic aromatic hydrocarbons into the harmful hydrophilic DNA adducts. In phase II, GSTT1 must prompt another conversion that allows these chemical to be excreted.

"You have a genetic hit for susceptibility, which is unique to the fetus. This occurs in the face of a more ubiquitous epigenetic modification following exposure to cigarette smoke," said Aagaard. "That makes the genetic hit (fetal GSTT1 deletion) have the specific effect on the fetus, but the epigenetic hit (increased expression of CYP1A1 in the placenta) happens with exposure to cigarette smoke," she said.

Because of the epigenetic hit in the first phase of tobacco metabolism, the placenta makes more harmful compounds (called DNA adducts) from the tobacco smoke. The

fetuses who have suffered the second genetic hit with the deletion of the GSTT1 gene cannot excrete these harmful compounds efficiently. This affects their growth. It takes two hits. Babies who have the GSTT1 gene can excrete the harmful compounds. The placentas of babies whose GSTTI1 gene is deleted but are not exposed to tobacco smoke do not have high levels of the harmful compounds.

Metabolic pathways

"This is one of the first demonstrations of metabolic pathways where epigenetic and genetic gene regulatory events come together to associate with risk of disease. It makes sense with what we know about many of the common disorders of pregnancy: there is both genetic susceptibility, and risk by virtue of environmental exposure," said Aagaard.

Aagaard emphasizes that her research does not mean that smoking is safe in pregnancy for anyone who is not genetically susceptible.

"It is important to keep in mind three essential tenets of our work. First, GSTT1 is a relatively common genetic mutation, with the deletion occurring in nearly 30 percent of all of the fetuses we studied. Second, regardless of the GSTT1 deletion, smoking behavior increased the amount of harmful DNA adducts and CYP1A1 expression in the placenta. If anything, given the commonality of the GSTT1 deletion, we should continue to be very concerned about any pregnant woman being exposed to any measure of tobacco smoke," she said.

Others who took part in this study include Melissa Suter, Adi Abramovici, Lori Showalter, Min Hu and Cynthia Do Shope, all of BCM, and Dr. Michael Varner of the University of Utah.

The previous study includes members of the Eunice Kennedy Shriver National Institute of Child Health Human Development Maternal-Fetal Medicine Units Network [5].

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SOURCE [6]

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