Scientists identify maternal and fetal genes that increase preterm birth risk

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Researchers at the National Institutes of Health have identified DNA variants in mothers and fetuses that appear to increase the risk for preterm labor and delivery. The DNA variants were in genes involved in the regulation of inflammation and of the extracellular matrix, the mesh-like material that holds cells within tissues.

"A substantial body of scientific evidence indicates that inflammatory hormones may play a significant role in the labor process," said Alan E. Guttmacher, M.D., acting director of the NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). "The current findings add evidence that individual genetic variation in that response may account for why preterm labor occurs in some pregnancies and not in others."

Like sensitivity to allergens such as house dust or pollen, the severity of the immune response appears to vary from individual to individual, accounting for why some pregnancies end in early labor and delivery. The findings may one day lead to new strategies to identify those at risk for preterm birth, and to ways to reduce the occurrence of preterm birth among those at risk.

The findings were presented today at the 30th Annual Society for Maternal-Fetal Medicine meeting by Dr. Roberto Romero, M.D, chief of the perinatology research branch and program head for perinatal research and obstetrics at the NICHD. At the meeting, Dr. Romero and his team received the March of Dimes Excellence Award for innovative

research on preterm birth for this study.

Premature birth affects 13 million infants worldwide each year.According to the National Center for Health Statistics, roughly one half million preterm births occur in the United States each year. Infants born preterm are at risk for infant death, life-threatening infections, blindness, breathing problems, learning and developmental disabilities, and cerebral palsy.

The finding is the most recent in a body of research by Dr. Romero and his colleagues. On the basis of earlier studies, the scientists had determined that an estimated 1 of every 3 preterm infants is born to a mother who has a silent infection of the amniotic fluid. A silent infection is one which does not show any outward signs or symptoms.

Dr. Romero described pregnancy as a unique state in which two genetically distinct organisms—mother and fetus—must coexist. Each fights infection by using hormones that stimulate the immune system. Hormones which play a role in immunity also play a role in labor. When released by either the mother, or the fetus, these hormones set in motion a cascade of events that can cause labor to begin.

"Our hypothesis is that the mother and/or the fetus signal the onset of preterm labor when the environment inside the uterus is unfavorable and threatens the survival of the maternal-fetal pair," Dr. Romero said.

Similar to sensitivity to allergens such as dust mites or pollen, the intensity of the immune response varies greatly, depending on genetic factors, the scientists theorize. Presumably, this genetic variability in the immune response accounts for why some pregnancies progress to full term, while others end early,

"When there is an infection in the uterus, the onset of premature labor

appears to have survival value," Dr. Romero said. "In the presence of infection, premature labor would allow the mother to rid herself of the infected tissue and preserve her ability to have future pregnancies. If premature labor occurs too early, babies may not survive." If premature labor due to infection occurs late in pregnancy, it may be life-saving for both mother and fetus.

Along with genes controlling the inflammatory response, the physician-scientists also found that DNA variants in genes active in the extracellular matrix were also linked to premature labor. The extracellular matrix is the mesh-like material that holds cells within tissues. The maternal and fetal genes that Dr. Romero and his colleagues identified regulate the amount of extracellular matrix in the uterus. The extracellular matrix of the uterine cervix and of the membranes containing the embryonic fluid are broken down at the beginning of labor.

To conduct the study, the scientists evaluated 190 genes and more than 700 DNA variants in samples from 229 women and 179 premature infants, and a large number of women who delivered at term. The study was conducted on a population of women in Chile. All of the women in the study were of Hispanic origin (of largely white and Native American backgrounds.). The study is one of the few to look at the genetic factors governing birth in an exclusively Hispanic population.

Infants who carried the DNA variant in the gene for the Interleukin 6 receptor were more likely to be born premature than those who did not. Interleukin 6 is produced by cells in response to infection and is involved in inflammation. In previous studies, Dr. Romero and his team found that high levels of Interleukin 6 in the amniotic fluid and in the fetal blood are associated with the beginning of premature labor.

Dr. Romero noted that molecules responsible for inflammation such as

Interleukins 1 and 6 predate the human species and even mammals. He added that Interleukin 1-like molecules are even present in primitive organisms, such as sponges (which do not undergo labor). The primary function of these molecules is to fight infection. However, in most mammals, these molecules are not only used by the immune system to fight infection, but also play a role in triggering the onset of labor.

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