Changes in placenta's protective ability during pregnancy linked to transporter proteins

May 8 2015

An important function of the human placenta is to protect the fetus from detrimental substances in maternal blood, such as glucocorticoids or toxins. Placental membrane-bound transporter proteins, known as multidrug resistance proteins, protect the fetus by returning unwanted materials to the maternal circulation. A study in *The American Journal of Pathology* reports that bacterial and viral infections differentially influence these transporter proteins in early and late pregnancy, suggesting potential mechanisms underlying infection-related pregnancy complications such as preterm birth and fetal brain damage.

"Our data show that bacterial and viral challenges can reduce the expression of the multidrug transporters in the human placenta," explained Stephen G. Matthews, PhD, Professor, Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Canada. "Because intrauterine infection/inflammation is relatively common during pregnancy, and associated with significant pregnancy disorders, the consequent reduction in the expression of drug transporters may expose the embryo/fetus to potentially harmful drugs, toxins, and hormones that cross from the maternal circulation at a time when it is most vulnerable."

The researchers analyzed placental tissues from patients undergoing surgical termination of pregnancy in the first trimester (8 to 10 weeks gestation) or from term elective cesarean deliveries in the third trimester (>37 weeks' gestation). The placental explants were exposed to either lipopolysaccharide (LPS), a component of gram-negative bacterial walls to simulate bacterial infection, or polyinosinic-polycytidyic acid [poly(I:C)] to simulate viral infection.

The researchers examined the effect of bacterial or viral antigen on two multidrug transporter proteins: P-glycoprotein (P-gp; encoded by the ABCB1 gene) and breast cancer resistance protein (BCRP; encoded by the ABCG2 gene) from the tissues taken at the different stages of pregnancy. Exposure with LPS for 24 hours decreased P-gp- and BCRP-related mRNA and protein levels in the first-trimester explants, whereas no effects were seen in the third-trimester explants. In contrast, poly(I:C) decreased ABCB1 mRNA levels in the third trimester but not the first trimester. Poly(I:C) did not change ABCG2 mRNA or BCRP levels at either time in pregnancy.

The investigators also looked at the effects of pregnancy on the receptors for LPS (toll-like receptor-4, TLR-4) and poly(I:C) (TLR-3). TLR-3/4 mRNA expression increased from the first to the third trimesters, and

the location changed from the inner layer to the outer layer of the placenta at term. This was the first time that a gestational age-dependent pattern of expression was found for TLR-3. The expression of the receptors was not changed by LPS at either time in pregnancy, whereas poly(I:C) decreased the expression of both receptors in the third trimester with no effect in the first trimester.

TLRs are essential components of the signaling network within the innate immune response, which can stimulate the release of cytokines. Consistently, both LPS and poly(I:C) elicited strong cytokine and chemokine responses (as measured by interleukin-8 and CCL2) in both first and third trimester explants.

"Until this study, the extent to which bacterial- and viral-associated infection affects placental expression of ABC transporters at different stages of gestation in humans was largely unexplored," said Dr. Matthews. "Our data suggest that infection and inflammation are capable of inducing changes in the levels of drug transporters. Our data also suggest that the placenta exhibits a differential response to infectious agents and this effect is greater for bacterial challenge compared to viral challenge. Moreover, the first-trimester placenta appears to be more sensitive to the effects of bacterial infection, potentially leading to increased exposure of the embryo/fetus to drugs and toxins at a critical time in development, whereas viral infections may disrupt fetal protection in later stages of pregnancy."

More information: "Impact of bacterial and viral challenge on multidrug resistance in first- and third-trimester human placenta," by Phetcharawan Lye, Enrrico Bloise, Mohsen Javam, William Gibb, Stephen J. Lye, Stephen G. Matthews (DOI: dx.doi.org/10.1016/j.ajpath.2015.02.013). This article appears online ahead of The *American Journal of Pathology*, Volume 185, Issue 6 (June 2015)

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