Research Week 2022

Fetal and Maternal Inflammatory Responses to Choriodecidual *Ureaplasma* Infection in *Macaca mulatta*

Sudeshna Tripathy, Yvonne T Dimagiba, Miles J Novy, Victoria HJ Roberts, Meredith A Kelleher
tripaths@ohsu.edu, dimagiba@ohsu.edu, novym@ohsu.edu, robertsv@ohsu.edu, kellehem@ohsu.edu
Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center, Beaverton, OR, USA

Keywords

Preterm birth, Intrauterine infection, *Ureaplasma parvum*, Fetal membranes, Fetal brain

Abstract

Intrauterine infection is associated with chorioamnionitis, preterm birth, and the fetal inflammatory response syndrome (FIRS). Choriodecidual infection represents an intermediate stage of ascending reproductive infection, providing a model of infection-driven fetal inflammation, without direct microbial exposure of the fetus. The current study aims to examine the inflammatory responses in the placenta and fetal brain in response to choriodecidual *Ureaplasma* infection.

Chronically catheterized pregnant rhesus monkeys with choriodecidual and intra-amniotic catheters were assigned to control (n=5) and choriodecidual infection (CDI; n=4) groups. Animals received inoculation with sterile media/saline or *Ureaplasma parvum* (Serovar 1, 10^5 CFU/mL) starting at 118±1 dGA every 5 days until C-section delivery at 136±2 dGA (Term=167d). Placenta, amnion, chorion and fetal brain tissues were collected at the time of delivery and immediately frozen. Expression of inflammatory and metalloproteinase genes, along with genes associated with brain glial cells were determined by RT-qPCR. Immunohistochemical staining of corresponding proteins in maternal and fetal tissues was also performed. Statistical significance ($p<0.05$) was assessed by Student's t-test or Mann-Whitney U-test after testing for normality (Shapiro-Wilk).

Expression of pro-inflammatory genes were upregulated with CDI, including the chemokine *Cxcl2* in the amnion ($p=0.0357$) and chorion. Membranes also showed an increase of *Il-1* isoforms which mediate the

activation of enzymes involved in prostaglandins synthesis (e.g., Ptgs2) involved in myometrial activation and labor. *Ptgs2* (p=0.0025) was upregulated in the chorion of CDI animals in tissue adjacent to the area of choriodecidual catheter placement but not in other regions of the chorion. An increase in *Cxcl2* and *Ptgs2* expression in CDI brains shows a fetal neuroinflammatory environment without direct infection of the fetus. The expression of myelin gene *Plp-1* (p=0.0028) was increased in the frontal cortex of CDI fetal brains, which may be linked to increased staining of activated microglia.

Utilizing a translational NHP model, our findings indicate that choriodecidual *Ureaplasma* infection activates maternal and fetal inflammatory responses related to the onset of the preterm labor syndrome (pro-inflammatory signaling, membrane weakening) and fetal neuroinflammation, even at this early stage of ascending uterine infection prior to microbial invasion of the amniotic cavity and fetal infection.