

Developmental Timing of Maternal Inflammation Determines Fetal Survival and Neurologic Outcome: Possible Role for the Placenta

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Maternal inflammation or infection is a major risk factor for a variety of neurodevelopmental disorders, including autism, cerebral palsy, developmental delay, and schizophrenia. **Objective:** The goal of this study was to determine how the timing of exposure to inflammatory stimuli alters neurodevelopment in fetuses. **Methods:** We have injected pregnant mice with the immunogen lipopolysaccharide (LPS) at E12 or E14 and labeled dividing cells 2h later with BrdU to determine the effects of maternal inflammation on fetal neurogenesis. **Results:** At E12, maternal inflammation causes a high rate of miscarriage even at very low doses of LPS (60 µg/kg), but surviving fetuses show normal BrdU incorporation in the brain. In contrast, LPS treatment of mothers at E14 is relatively well tolerated at doses up to 200 µg/kg LPS, but the number of BrdU labeled cells in the fetal brain 3 days after treatment is reduced, indicating alterations in fetal neurogenesis. E12 LPS exposure is associated with inflammation and pathology in the placenta, as indicated by the presence of pro-inflammatory cytokines and chemokines in the placental tissue, and gross alterations in placental structure. After E14 LPS exposure, the placenta is relatively preserved and may allow for the communication of inflammatory signals into the fetus, thereby disrupting neurogenesis. **Conclusions:** There are critical periods during fetal development during which maternal inflammation has differing effects: early treatment promotes spontaneous miscarriage, while later treatment alters fetal neurogenesis. These differences could be accounted for by differences in the maternal, placental or fetal inflammatory responses, or by differences in the sensitivity of the placenta or neural progenitor cells to inflammatory mediators. We favor the hypothesis that the increased tolerated dose of LPS at E14 allows for increased inflammatory signaling in the fetal brain, and therefore has a larger impact on fetal neurogenesis. We are currently exploring this possibility and pursuing mechanistic studies of the molecules involved in disrupting neurogenesis in this model.

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