Cadmium Exposure Prevents Placental Adaptation to Inflammation During Pregnancy: Sex Differences in Fetal Responses

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The placenta facilitates nutrient delivery, waste removal, and fetal protection from xenobiotics. The placenta is not a complete barrier, and toxic substances can accumulate, including the environmental metal cadmium (Cd). Cd is ubiquitous in the environment and can move freely in water, soil, and air. Cd is detectable in maternal plasma and placentas, and exposure during pregnancy has been associated with poor pregnancy outcomes. Cd alters macrophage phenotypes in mouse placentas and has been linked to an increased susceptibility to infection in preterm infants. Therefore, we sought to determine whether prenatal Cd exposure alters susceptibility of mice to preterm birth caused by lipopolysaccharide (LPS) exposure in late gestation. C57BL6/Crl mice were mated overnight and separated in the morning, designated gestational day (GD) 0. On GD7, pregnant dams began to receive either distilled water (Ctrl), or 50 ppm cadmium chloride ($CdCl_2$) in drinking water. On GD15, dams received saline or LPS (100 µg/kg, ip) 16 or 24 hours prior to tissue collection. Enrichment of male-specific genes (*Sry, Ssty1, Ssty2*) and *β-actin* (housekeeping gene) was quantified in fetal tissues using RT-qPCR. Exposure to LPS caused sex-dependent adaptation in placenta morphometrics, with female offspring exhibiting lower placental weights and increased placental efficiency at 24 h. In male offspring, placental area was reduced by LPS at 16 and 24 h. Remarkably, cadmium pre-exposure prevented these adaptations and instead increased preterm birth to 70% compared to 17% in dams treated only with LPS. Future work will examine placental vasculature development using endothelial markers CD31 and CD34. Supported by NIH R25ES020721.