3860 Placental zones altered in rats exposed to micro and nanoplastics via inhalation throughout pregnancy

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Background and Purpose: Micro- and nanoplastics (MNPs) are ubiquitous environmental contaminants. The increased use and physical degradation of bulk for plastic material leads to the production of micro- and nanoplastics particles, defined as less than 5 mm or 100 nm in diameter, respectively. Human exposure to MNPs often occurs through inhalation, which is supported by the detection of MNPs in human lungs. Recent studies have demonstrated evidence of microplastics in human placenta. Furthermore, our lab has shown that MNPs access the placenta with 24h of maternal pulmonary exposure. The placenta can experience structural changes resulting from particulate inhalation that may also correlate to abnormal fetal development. Therefore, the purpose of this study was to determine if maternal MNP inhalation directly impacted the three different zones of the placenta and whether such impact would result in decreased provision of barrier support of the fetus. The placental zones consist of the decidua, which creates a barrier from the maternal zone and protects the embryo from attacks deriving from maternal immune cells. The junctional, the second placental zone, stores glycogen and facilitates the support of energetic and hormonal provisions of the fetus. The last zone of the placenta, the labyrinth zone, functions through the maternal and fetal circulatory exchanges of nutrients and waste materials. The metrial gland, while not a formal placental zone, is adjacent to the decidua and exists as an aggregate of mixed cell populations which function to optimize placental blood flow. **Methods:** Herein, we exposed the rats to polyamide 12 (PA12, ~10 mg/m^3) particles in our whole-body inhalation chamber starting on Gestational Day (GD) 6 and sacrificing on GD 12, 16, and 20 to assess placental development. We hypothesized that MNP inhalation throughout gestation would increase the size of the decidual zone because of maternal inflammation after MNP exposure leading to an influx of immune cells and edema. **Results:** No significant differences were detected in placental zones at GD 20 after PA12 exposure throughout gestation. At GD 12, the area of the total placenta (30%) and the area of the decidua (32%) for the exposed groups were significantly larger than control (total area: 14.5x10^6 ± 0.9 vs. 11.1x10^6 ± 0.9µm^2; decidua area: 8.9x10^6 ± 0.6 vs 6.7x10^6 ± 0.7, respectively). At GD 12 the exposed placentas also demonstrated a 21% increase in metrial gland area (p= 0.09) and a 37% decrease in junctional zone area (p = 0.06) although these were not to significance. When considering sex as a factor, MNP exposure affected decidual development differently for male (+5%, p = 0.82) and female placentas (-14%, p = 0.21) at GD 20. Analysis of GD 16 placenta are still underway. **Conclusions:** Future studies will assess additional sex-specific differences between the placental morphologies at GD 12 and GD 16 after MNP exposure. Overall, MNP inhalation throughout pregnancy raises a query between xenobiotic exposure, possible material translocation, and organ development/morphology. Additional studies are required to understand how the placenta responds to environmental contaminants and what these outcomes may suggest for fetal development.

3861 Prenatal Exposure to Cadmium Alters Macrophage Subpopulations in Mouse Placentas

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Background and Purpose: Cadmium (Cd), a ubiquitous environmental toxicant, accumulates in the placenta and has been associated with preterm birth and fetal growth restriction in rodents and humans. Cd exposure causes oxidative stress in the placenta and is associated with an accumulation of pro-inflammatory macrophages in the tissue. Macrophage subpopulations can be identified based on cell surface markers, which vary with tissue location and function. In humans, we have observed that healthy, term placentas with higher Cd accumulation have altered profiles of macrophage subpopulations. In this study, we assessed whether prenatal exposure of mice to $CdCl_2$ alters macrophage populations in placentas. **Methods:** Wild-type male and female C57BL/6Crl mice were mated overnight which marked gestational day (GD) 0. Beginning on GD7, dams (n=9-10/group) received either distilled water or $CdCl_2$ (0, 5, or 50 µg/ml) in the drinking water *ad libitum* through GD17, when tissues were collected. Placentas were either fixed in formalin and sectioned to 5 µm before immunohistochemical staining with antibodies against the F4/80 and Iba-1 macrophage markers. Positively-stained macrophages within the mouse labyrinth and junctional zones were counted. Circulating Cd concentrations were quantified using inductively coupled plasma-mass spectrometry. **Results:** Compared to vehicle controls, dams exposed to 50 µg/ml $CdCl_2$ gained less weight by GD17. Circulating Cd concentrations were similar to vehicle controls in dams treated with 5 µg/ml $CdCl_2$ (0.27 vs. 0.50 ng Cd/ml) and elevated in dams receiving 50 µg/ml $CdCl_2$ (3.66 ng Cd/ml). Notably, these concentrations of $CdCl_2$ did not alter fetal or placental weight or size, cause gross histopathological changes, or impact the number of reabsorptions. Compared to vehicle controls, immunohistochemical staining for the pan-macrophage marker F4/80 revealed greater numbers of macrophages in the labyrinth (36%) and junctional zones (184%) of placentas from fetuses exposed to 50 µg/ml $CdCl_2$. A similar increase in the number of F4/80$^+$ cells (145%) was observed in the junctional zone of mice treated with 5 µg/ml $CdCl_2$. In contrast, the number of macrophages staining positive for the phagocytosis marker Iba1 was reduced in the placental labyrinth of fetuses prenatally exposed to both 5 µg/ml $CdCl_2$ (14%) and 50 µg/ml $CdCl_2$ (29%). **Conclusions:** Exposure to 5 and 50 µg/ml $CdCl_2$ during gestation resulted in serum concentrations of Cd similar to that of pregnant humans. Furthermore, exposure of mice to 5 or 50 µg/ml $CdCl_2$ during pregnancy alters the enrichment of placental macrophage subpopulations in the absence of overt fetoplacental pathology. Supported by R01ES029275, T32ES007148, F31ES032319, P30ES005022, and Grover Fellowship.

3862 Maternal Nano-Titanium Dioxide Inhalation Exposure Increases Female Placental Cyclooxygenase and Xanthine Oxidoreductase Production

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Background and Purpose: Maternal nano-titanium dioxide (nano-TiO_2) inhalation exposure during gestation decreases fetal female pup mass, placental mass, and placental hemodynamics. Fetal sex impacts fetal growth, along with placental function and efficiency. Males have increased fetal growth, whereas females have increased placental adaptability and oxidation-reduction capacity. Reactive oxygen species imbalance and toxicant exposure both negatively impact fetal development in a sexually dimorphic manner. Oxidants, such as hydrogen peroxide (H_2O_2), and antioxidants, such as catalase, have been shown to influence cyclooxygenase activity, specifically prostacyclin (PGI_2) and thromboxane (TXA_2). Therefore, we hypothesized that *maternal nano-TiO_2 inhalation exposure during gestation alters placental production of prostacyclin and thromboxane mediated by enhanced hydrogen peroxide production in a sexually dimorphic manner.* **Methods:** Pregnant Sprague-Dawley rats were exposed to nano-TiO_2 aerosols (12.17 ± 1.69 mg/m^3) or HEPA-filtered air (sham-control) from gestational day (GD) 10-19. Dams were euthanized on GD 20 and fetal serum and placental tissue were collected based on fetal sex. Placental zones (junctional (JZ) and labyrinth (LZ)) were assessed for xanthine oxidoreductase (XOR) activity, H_2O_2, catalase activity, TXB_2, and 6-keto-$PGF_{1\alpha}$. **Results:** Fetal female LZ from nano-TiO_2 exposed dams had significantly increased XOR activity compared to fetal male LZ from nano-TiO_2 exposed dams (4.83 ± 0.44 vs 3.41 ± 0.40 mU/mg protein). Catalase activity in fetal female LZ from nano-TiO_2 exposed dams was significantly decreased compared to fetal female LZ from sham-control dams (159.31 ± 55.43 vs 346.05 ± 41.99 µU/mg of protein). Catalase activity for the fetal male LZ from nano-TiO_2 exposed dams was not different compared to fetal male LZ from sham-control dams. Fetal female LZ from nano-TiO_2 exposed dams had increased abundance of 6-keto-$PGF_{1\alpha}$ compared to fetal female LZ from sham-control dams (394.05 ± 124.10 vs 93.17 ± 24.45 pg/mg protein). TXB_2 was significantly increased in fetal female LZ from nano-TiO_2 exposed dams compared to their male counterparts (1186.48 ± 189.92 vs 598.39 ± 135.69 pg/mg protein). LZ TXB_2 levels were not different for male LZ from nano-TiO_2 exposed dams or the sham-control dams. **Conclusions:** These results indicate that gestational maternal nano-TiO_2 inhalation exposure has a greater impact on the female, specifically in the LZ. These changes in oxidants and PGI_2/TXA_2 may underlie the decreased fetal growth seen in previous studies and could impact health outcomes into the adult life of these females. Funding: K01 10029010 (ECB), WV-CTSI U54 GM104942-05 (ECB), R01 ES015022 (TRN), T32 AG 52375 (JAG), T32 ES032920 (JAG), WV-INBRE P20 GM103434, NORA 9390G1X (AE)

3863 Nanomaterial Inhalation During Gestation Results in Endocrine, Hepatic and Reproductive Dysfunction Due to Xanthine Oxidoreductase Elevation

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Background and Purpose: Maternal inhalation exposure to nano titanium dioxide (TiO2) during gestation impacts litter size, pup and placental mass, circulating estrogen concentration, and uterine microvascular reactivity. In addition, we have recently shown that maternal inhalation of nano-TiO2 results in placental redox imbalance during late gestation. However, the mechanism linking these dysfunctions and exposure has yet to be explored. Therefore, we hypothesized that elevated xanthine oxidoreductase (XOR), a critical source of oxidants in numerous inflammatory processes, is at least partially responsible for the increased oxidant production observed post-exposure. The objective of this study was to assess if treatment with a XOR inhibitor, febuxostat (Uloric®), prevents the poor reproductive

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