Exposure to Nanomaterials during Gestation Affects Cardiovascular Health for at Least 12 Months

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Nanosized titanium dioxide (nTiO$_2$), is a naturally occurring oxide of titanium and is intentionally manufactured for use in a wide range of applications including industrial and personal care products. In laboratory studies, nTiO$_2$ has been used as a surrogate for ultrafine air pollution particulate. We have shown that exposure to nTiO$_2$ during pregnancy affects the cardiovascular health of the dam, fetus, and young adult offspring. It is unclear whether cardiovascular dysfunction in the progeny persists into middle age. Timed-pregnant Sprague-Dawley rats (Charles River) were exposed to nTiO$_2$ aerosols [9.65 ± 0.07 mg/m$^3$, primary particle size 21 nm, agglomerate size 128.45 ± 1.83 nm (SMPS, TSI), calculated daily deposition 47.27 ± 1.88 µg] for 4 hours over 6.00 ± 1.31 days of the remaining gestation via inhalation (HPGA, IESTechno). A subset of animals was exposed to filtered air as controls. Animals delivered in-house, offspring were monitored weekly, and were sacrificed at 12 months. Pressure myography (LSI, Burlington, VT) was conducted to evaluate microvascular reactivity in coronary arterioles to assess endothelium-dependent (EDR) [acetylcholine (10$^{-9}$ - 10$^{-4}$ M)]. Gestational nTiO$_2$ exposure significantly impaired EDR relaxation (43.80 ± 5.49 %) compared with controls, a finding maintained from previous studies of young adult offspring. Following arteriolar isolation, hearts were collected, fixed in 10% formalin, sectioned, and reviewed for histopathological analysis. Samples from exposed offspring present histopathological alterations characterized by multifocal myocardial inflammation, degeneration, necrosis, loss and/or fibrosis compared with control tissue. These findings were consistent with repeated low-grade ischemia. Anecdotally, a neurological tick and seizure activity were observed in 5 female animals exposed in utero to nTiO$_2$. Brains from these animals were collected, fixed for 24 hours, sectioned, and reviewed. Early observations indicate histopathological changes within the pituitary. Overall, gestational exposure to nTiO$_2$ produced coronary microvascular dysfunction, accompanied by histological changes in the heart that persist to middle age. These results may provide experimental evidence for a better understanding of the developmental onset of cardiovascular disease after gestational exposure to aerosolized xenobiotic particulates. Supported by NIH-R00-ES024783; P30-ES005022; T32-ES007148.