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IGFBP3 repression driven by inflammation links air pollution to placental and developmental defects

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Abstract

Air particulate matter (PM2.5 and PM10), can cross the placental barrier, triggering oxidative stress and inflammation that compromise fetal development. These insults lead to placental dysfunction and complications including preterm birth, low birth weight, and preeclampsia. In cell line and placental explant models, urban particulate matter (UPM) increased pro-inflammatory cytokines and oxidative stress pathways, impairing trophoblast invasion, angiogenesis, and nutrient transport, while also altering epigenetic modifications and endoplasmic reticulum function. Rodent studies revealed reduced litter size, placental abnormalities, and fetal growth arrest along with postnatal neurodevelopmental alterations. Human cohorts from high-exposure regions showed elevated low birth weight rates. Proteomic and transcriptomic analyses of rat placenta revealed an inflammatory signature and altered metabolic networks, while gut microbiome dysbiosis suggested links to metabolic disturbances. Importantly, transcriptomic analysis identified IGFBP3 as a major downregulated gene following UPM exposure. IGFBP3, a key regulator of IGF bioavailability, was suppressed by IL1β, establishing inflammation-driven repression as the mechanism. These findings underscore UPM's multidimensional impact on maternal–fetal health and highlight preventive strategies as urgent priorities.

Keywords Urban Particulate Matter; Trophoblast differentiation; Inflammation; Insulin-like Growth Factor Binding Protein 3 (IGFBP3); Fetal Neurodevelopment

Subject Categories Development; Evolution & Ecology; Immunology

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Introduction

Particulate matter (PM) is a harmful air pollutant and has become a global health concern. These can be classified as PM0.5, PM2.5 and PM10 (Pryor et al, 2022). The toxicity of PM relates to their composition, quantity, mass, shape, size, and surface area. PM of diameter <10 μm have the potential to enter the bloodstream, leading to premature deaths in vulnerable populations with co-morbidities like heart or lung diseases, diabetes mellitus, malnutrition, and hypertension (Li et al, 2022; Bennitt et al, 2025). Recent research has shown links between air quality and adverse pregnancy outcomes, suggesting air pollutants disrupt processes involved in placentation and maternal-neonatal health (Singh et al, 2024; Soesanti et al, 2023; Mandal et al, 2023). The placenta is a transient yet crucial organ that delivers oxygen and nutrients to the fetus while disposing of waste materials. The placenta performs vital endocrine functions during pregnancy, synthesizing hormones that support fetal development and maternal physiological adaptations. It also exhibits metabolic plasticity, enabling it to respond to environmental changes and meet the dynamic needs of both mother and fetus (Burton and Jauniaux, 2023; Ortega et al, 2022).

However, studies have shown that certain environmental pollutants can breach the placental barrier, impairing its function, consequently affecting maternal and fetal health (Bové et al, 2019; Zurub et al, 2024). Placental cells consisting of an invasive cytotrophoblast and fusogenic syncytiotrophoblast, have been shown to be affected by pollutants (Knöfler et al, 2019). A landmark study by Bongaerts et al demonstrated the presence of black carbon particulates from polluted air in cord blood, indicating that air pollutants can breach the placental barrier and reach the fetus, contributing to harmful effects (Bongaerts et al, 2022). In an urban Tanzanian cohort with personal exposure monitoring, Wylie et al observed a 0.15 kg decrease in birth weight per interquartile increase (23.0 μg/m^3) in maternal PM2.5 exposure, (95% CI: −0.30 to 0.00 kg; $p = 0.05$) (Wylie et al, 2017). Although modest in magnitude, a 100–150 g left-shift is clinically meaningful at the population level: by WHO/GAIA (World Health Organization/Global Alignment of Immunization Safety Assessment in Pregnancy) criteria, LBW is <2500 g, and such shifts increase the share of infants crossing the LBW threshold—an outcome linked to markedly higher neonatal mortality and long-term neurodevelopmental and cardiometabolic risks—especially in regions with already high LBW prevalence(Brämer, 1988). Multiple

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