Abstract

There is a growing evidence on the hazards of ambient air pollution on fetal development. Several review articles have been published on the adverse fetal outcomes including low birth weight, preterm birth, small-for-gestational age, and congenital anomalies. Recent studies have linked ambient air pollution to gestational hypertension, and preeclampsia which may be related to the detrimental effect of ambient air pollution on placental growth and function.

Short-term and long-term exposure to particulate air pollution may cause systemic inflammatory response which may trigger preterm delivery in pregnant women. Environmental toxic chemicals that alter intrauterine environment disregulates fetal epigenome causing epigenetic mediated changes in gene expression that may be linked to later childhood and adulthood diseases. Exposure to ambient air pollution during the whole pregnancy especially in third-trimester may cause intrauterine vitamin D deficiency which is critical for the normal development of the lung, and immune system in fetus. However, more research is needed to understand the cause and effect interaction between air pollution and fetal development.

Keywords

Air pollution, birth outcome, congenital malformation, placental insufficiency, intrauterine vitamin D deficiency.

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Introduction

Fetal period is the most critical period of human life because of rapid cellular proliferation, differentiation and growth. Survival and optimum growth and development of the fetus require complex interactions between the mother, fetus and the placenta which is a programmed, dynamic process. During fetal growth and development each of the organ systems and placenta has different stages and rates of growth and development with changing metabolic capabilities creating biological sensitive periods (critical windows) of susceptibility to toxic environmental exposures.

Pregnant women may be exposed to toxic pollutants through variety of sources and routes. Inhalation of pollutants from indoor and outdoor air is the most common route of exposure. Outdoor air contains a mixture of many potential toxins. Major pollutants routinely measured in ambient air include carbon monoxide (CO), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), suspended particulate matter (PM), ozone (O₃), and lead. Particulate matter is an air pollution term for a mixture of solid particles and liquid droplets found in the air, which originate from vehicle exhaust, road dust, smokestacks, forest fires, windblown soil, volcanic emissions, and sea spray and can be composed of many types of materials and toxic chemicals including semi-volatile and volatile compounds. Their biological toxicity differs based on its chemical composition. Pollutant particles in the air are classified according to their size ranging: coarse (PM 2.5-10 μm or PM₁₀), fine (PM < 2.5 μm or PM₂.₅), and ultrafine (PM < 0.1 μm or PM₀.₁) particles. Size directly determines a particle’s potential for causing health problems, with the smaller particles, those 10 micrometers in diameter or less (PM₁₀ and PM₂.₅), being more dangerous. Because of their small size, PM₂.₅ and PM₀.₁ are inhaled deeply into the lungs, with some depositing in the alveoli and entering the pulmonary circulation, and presumably the systemic circulation and can trigger inflammation in the lung, blood vessels or the heart, and perhaps other organs [1, 2].

Birth outcomes

In the past few decades there is a growing body of evidence on the hazards of ambient air pollution on fetal development. Several review articles have been published on the adverse fetal outcomes including low birth weight (LBW), preterm birth, small-for-gestational age (SGA), and congenital cardiac anomalies. The conclusions of the previous reviews had conflicting results due to heterogeneity of the studies. This was considered to be due to some key methodological issues in researching the effect of air pollution on birth outcomes; such as differences in period of the exposure (first, second, third trimester or entire pregnancy), using different exposure assessment measurements (air pollutant concentrations from fixed-site air pollutant monitoring stations, nearest monitoring station, spatiotemporal modeling, distance-weighted average, country-wide average), limited consideration of confounding factors (low socioeconomic factors tend to have higher air pollution levels, maternal behaviors affecting personal exposure), differences in number and type of pollutants considered [3, 4].

A recent review analyzed the results of 41 studies on maternal exposure to various ambient air pollutants and adverse pregnancy outcomes such as LBW, preterm birth, and SGA. Analysis of these studies revealed that the exposure to SO₂ was associated with preterm births, exposure to PM less than 2.5 μM diameter was associated with LBW, SGA and preterm births, coarse PM less than 10 μM diameter was associated with SGA births. Evidence was found inconclusive for nitrous oxide (N₂O), NO₂, O₃, and CO exposures during pregnancy [5].

Congenital malformations

In a meta-analyses on ambient air pollution and congenital anomalies, ten original epidemiologic studies were analyzed to obtain summary risk estimates for the association between congenital anomaly groups and ambient air pollutant levels. Continuous exposure to NO₂ and SO₂ at 3-8 weeks of gestation were related to increases in risk of coarctation of the aorta and tetralogy of Fallot, and PM₁₀ exposure to an increase in risk of atrial septal defects [6]. In a study from England, cleft lift with or without cleft palate showed an association of borderline statistical significance (OR per 10 ppb: 1.10 95% CI, 0.99-1.21) with O₃ exposure. Risk of omphalocele increased significantly (OR: 2.17; 95% CI, 1.0-4.71) in relation to PM₁₀ levels (90th vs 10th percentile) [7].

Placental insufficiency

Adequate placentation and placental functioning are critical for normal pregnancy. Maternal exposure to ambient air pollution may affect placental growth and function. In an animal study, gestational
exposure to urban air pollution (majority composed of \(\text{PM}_{2.5}\)) was associated with reduced volumes, calibers, and surface areas of maternal blood spaces and with greater fetal capillary surfaces and diffusive conductance in mice indicating that urban air pollution affects placental functional morphology [8].

Vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) are angiogenic growth factors that are important for placental vascular development and used as markers of placental growth and function. Soluble fms-like tyrosine kinase 1 (sFlt-1) binds to these proteins and inhibits their activity. In a recent population based cohort study, maternal \(\text{PM}_{10}\) and \(\text{NO}_2\) exposure were associated with higher fetal sFlt-1 and lower PIGF levels in fetal cord blood suggesting that air pollution may alter angiogenesis which may contribute to impaired placental function [9]. Prenatal \(\text{PM}_{10}\) exposure was also found to be associated with placental mitochondrial alterations, which may both reflect and intensify oxidative stress production [10].

**Gestational hypertension, and preeclampsia**

Recent studies have linked ambient air pollution to gestational hypertension, and preeclampsia. Maternal \(\text{PM}_{10}\) exposure was associated with an increased risk of pregnancy-induced hypertension (OR: 1.72; 95% CI, 1.12-2.63, per 10-\(\mu\)g/m\(^3\) increase) in 7,006 women participating in a prospective cohort study in the Netherlands [11]. Another epidemiologic study showed that exposure to local traffic-generated air pollution during pregnancy increases the risk of preeclampsia and preterm birth. In this study the risk of preeclampsia increased 33% (OR: 1.33, 95% CI, 1.18-1.49) and 42% (OR: 1.42, 95% CI, 1.26-1.59) for the highest nitric oxides (\(\text{NO}_x\)) and \(\text{PM}_{2.5}\) exposure quartiles, respectively. The risk of preterm birth increased 128% (OR: 2.28, 95% CI, 2.15-2.42) and 81% (OR: 1.81, 95% CI, 1.71-1.92) for women in the highest \(\text{NO}_x\) and \(\text{PM}_{2.5}\) exposure quartiles, respectively [12]. A latest study found an association between the first trimester \(\text{PM}_{10}\) and \(\text{O}_3\) air pollution exposures and increased blood pressure in the later stages of pregnancy [13]. Increased risk of gestational hypertension and preeclampsia among the mothers exposed to air pollution may explain the relationships between air pollution and adverse birth outcomes such as fetal growth restriction, LBW rate and preterm birth.

**Systemic inflammatory response**

Inflammation may be one other possible pathway through which air pollution may increase the risk of adverse birth outcomes. Some particles penetrate deeper into the lung, are able to interact with immune cells and even exhibit systemic effects entering the bloodstream. Studies suggest an association between short-term and long-term exposure to particulate air pollution and systemic inflammatory response as measured by C-reactive protein (CRP) levels. Positive associations of CRP with air pollution in various populations including people with coronary heart diseases, healthy adults and elderly have been published previously [14-18].

Systemic inflammatory response may trigger preterm delivery in pregnant women [19]. A previous study show an association between maternal plasma CRP concentrations in early pregnancy (before 21 weeks of gestation) and the risk of preterm delivery; and found 2.6- to 2.9-fold increases in risk of preterm delivery with early pregnancy inflammation (CRP > 8 ng/mL) [20]. A recent study investigated associations between particulate matter (PM_{10}, and PM_{2.5}) and \(\text{O}_3\) and CRP level in nonsmoking women during early pregnancy. An observed 4.6 \(\mu\)g/m\(^3\) increase in PM\(_{2.5}\) was associated with an odds ratios of 1.47 for high CRP levels (95% CI: 1.05–2.06) in early pregnancy, suggesting that air pollutants may contribute to inflammation and thereby possibly to adverse pregnancy outcomes [21].

Maternal exposure to air pollution in the last trimester of pregnancy leads changes in cord blood cytokine levels. After higher maternal exposure to \(\text{PM}_{10}\) during the last three days of the pregnancy significantly associated with reduced interleukin-10, and increased interleukin-1\(\beta\) levels in cord blood. These findings suggest that maternal exposure to ambient air pollution modulate infant’s developing immune system which may influence subsequent occurrence of allergic diseases, respiratory morbidity and lung development [22].

**Epigenetic changes**

Epigenetic programming of fetal and placental tissues is not only critical for survival, growth and development of the fetus but also important for “programming” of subsequent health. The hypothesis is that, environmental factors altering intrauterine environment during critical windows of development leads permanent changes in fetal structure, physiology and metabolism which initially
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promote survival but later predispose individual to chronic disease in adulthood [23, 24].

Environmental toxic chemicals that alter intrauterine environment disregulates fetal epigenome causing epigenetic-mediated changes in gene expression that may be linked to later childhood and adulthood diseases. DNA methylation is the most extensively investigated epigenetic mechanisms and plays an important role in gene regulation. Exposure to ambient PM$_{2.5}$ during first trimester was found to be significantly associated with a relative decrease of 2.13% in mean placental global DNA methylation for each 5 µg/m$^3$ increase (95% CI: -3.71, -0.54%, $p = 0.009$). In an animal model, disturbance of maintenance DNA methylation in placental tissue is associated with abnormal embryonic development [25].

**In utero vitamin D deficiency**

Exposure to high levels of air pollution has been suggested as a contributor to vitamin D deficiency in adults, and children [26, 27]. Children who live in regions with higher levels of ambient air pollution have been shown to be at increased risk of developing vitamin D-deficiency rickets compared with those residing in less polluted areas. The amount of solar radiation in the ultraviolet B range which is required for the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D$_3$) reaching ground level has been found to be inversely related to the level of ambient air pollution [27].

A recent study have shown that maternal exposure to ambient air pollution comparable to current World Health Organization standards during pregnancy might also contribute to low vitamin D levels in newborns. According to data on 375 mother-infant pairs, maternal exposure to ambient urban levels of NO$_x$ and particulate matter less than 10 µm diameter (PM$_{10}$) during the whole pregnancy was found to be associated to a low cord blood 25-hydroxyvitamin D [25(OH)D] status in newborns. The association between gestational exposure to air pollutants and vitamin D deficiency in newborns was strongest for third-trimester exposures. Upon making adjustments, log-transformed 25(OH)D was decreased by 0.15 U (P = 0.05) resulting in a 10-µg/m$^3$ increase in NO$_x$, and 25(OH)D was decreased by 0.41 U (P = 0.04) resulting in a 10 µg/m$^3$ increase in PM$_{10}$ pregnancy levels [28].

Recent data have demonstrated that low cord blood vitamin D levels may have an influence on the development of wheezing in offspring. Camargo et al. [29] reported a strong inverse association between maternal intake of vitamin D during pregnancy and the risk of recurrent wheezing in offspring. They also examined whether umbilical cord blood vitamin D levels were associated with risk for respiratory infections, wheezing, or asthma in infants. They found that cord-blood 25(OH)D levels were inversely associated with risk of wheezing by 15 months, 3 years, and 5 years of age. Infants at age 3 months who had cord blood levels of 25(OH)D below 25 nmol/L were twice as likely to develop respiratory infections as infants than those who had levels of 75 nmol/L or higher even after adjustment for more than 12 potential confounders. However in this study there was no association between cord blood 25(OH)D levels and incident asthma by the age of 5 years [30].

Vitamin D is critical for the normal development of the lung. Maternal vitamin D deficiency caused reduced lung volumes and reduced number of alveoli in the offspring mice in a mouse model [31]. Rats born to mothers deprived of dietary vitamin D had significantly decreased lung compliance at day 50 compared with rats born to mothers whose diet was supplemented with vitamin D [32]. Vitamin D also regulates surfactant production [33].

In utero vitamin D deficiency in mice result in a significant reduction in invariant NKT (iNKT) cell numbers that could not be corrected by later intervention with vitamin D or 1,25-dihydroxy vitamin D (1,25(OH)$_2$D). Early exposure of neonatal mice to vitamin D is required for mice to develop optimal numbers of iNKT cells. Vitamin D deficiency results in epigenetic changes in iNKT cells that cannot be rescued by later exposure to air pollution and vitamin D or 1,25(OH)$_2$D [34].

**Conclusions**

In conclusion, ambient air pollution during pregnancy affect pregnancy outcome and developing fetus. Biologic mechanisms of how air pollution leads adverse pregnancy outcomes are not well known. Although several mechanisms are suspected to underlie adverse birth outcomes, more research is needed to understand the pathogenesis as well as clinical findings.

**Declaration of interest**

The Author declares that there is no conflict of interest.
References

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