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Mini Review

Metabolic Disorders during Pregnancy Following Maternal Exposure to Ambient Nanoparticles

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Abstract

Animal and epidemiological studies have indicated that maternal exposure to particulate matter is related to adverse pregnancy outcomes including low birth weight in the offspring. Ambient nanoparticle or particulate matter, including $PM_{2.5}$ (fine particles, PM < 2.5 μm) and PM 0.1 (very fine particles, PM < 0.1 μm), ozone and transition metals, are potent oxidants capable of generating reactive oxygen species. Redox sensitive pathways may be triggered by oxidative stress and cause various biological processes, such as inflammation and other adverse outcomes. In this mini-review, we investigated the association between ambient nanoparticle exposure and metabolic disorders in maternal serum and placenta. Findings indicated that $PM_{2.5}$ exposure affected the nutrient transport capacity of the placenta by altering the ratio of some vital metabolites in the placenta to the maternal serum. These results by increasing our understanding of the ambient $PM_{2.5}$ toxic effects, emphasize the importance of protecting women from exposure to $PM_{2.5}$.

Keywords: Metabolomics; Placental Nutrient Transportation; Endocrine Disruption; Ambient Fine Particles; Maternal Exposure

Introduction

Some studies have shown that air pollution Particulate Matter (PM) is a non-negligible risk factor for Low Birth Weight (LBW), defined as a birth weight of less than 2500 g, regardless of gestational age, as a result of preterm birth or Intrauterine Growth Retardation (IUGR). For example, a cohort study found a 4 g reduction in birth weight with a 2% increased LBW risk per 10μg/m3 increase in exposure to $PM_{2.5}$ during pregnancy [1]. Generally, maternal exposure in the second trimester of pregnancy is associated with preterm labor [2,3]. Several meta-analyses have also reported a strong association between prenatal $PM_{2.5}$ exposure and LBW [4,5]. In addition, animal studies have shown that $PM_{2.5}$ exposure during pregnancy and/or gestation significantly reduces fetal birth weight [6-8]. LBW infants are often associated with long-term health problems, including cognitive impairment [9], cardiovascular disease [10], kidney disease [11], and type 2 diabetes [12]. According to the WHO (World Health Organization), it is estimated that there were more than 20 million LBW babies worldwide in 2016, representing approximately 15-20% of all births. Although both toxicological and epidemiological studies have shown adverse health effects following maternal exposure to $PM_{2.5}$ on fetal development, there is still insufficient information to provide biological pathways and their mechanisms are not comprehensively understood. Of course, one of the strong hypotheses emphasized that prenatal exposure to environmental nanoparticles results in the reduction of maternal and placental serum leptin levels, which leads to macrosomia in “male” fetuses [13,14]. After exposure and inhalation, $PM_{2.5}$ can induce inflammatory response, oxidative stress, endocrine disruption, and epigenetic changes that may affect normal fetal development [15-17]. In addition, some research has shown that some inhaled nanoparticles can cross the alveolar epithelial barrier, subsequently enter the bloodstream and be deposited in the placenta [18-20]. These particles can directly damage the function and structure of the placenta and affect foetal development [21-24]. During pregnancy, the foetus growth and development depend heavily on nutrients from the mother. These nutrients, including glucose, amino acids and fatty acids, are mainly transferred from the maternal circulation through the placenta. Therefore, a comprehensive and systematic analysis of the metabolic status in placenta and maternal serum is important to characterise the fetal growth environment. Metabolomics, which has been widely used in animal and human model studies to investigate the toxic effects of various ambient pollutants including tobacco smoke, Polycyclic Aromatic Hydrocarbons (PAHs) and heavy metals, is an emerging and powerful analytical method for profiling thousands of metabolites (small chemical molecules) in the biological samples [25-27]. Recently, using metabolomics analysis, researchers found that chronic $PM_{2.5}$ exposure significantly impaired the metabolism of lipids, amino acids and glucose in mice [28,29], providing insight into the potential $PM_{2.5}$ toxicity. In this mini-review, we investigated the association between exposure to

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ambient nanoparticles and metabolic disturbance in maternal serum and placenta.

Maternal $PM_{2.5}$ Exposure and Metabolomics Analysis

Recent findings have indicated an association between maternal $PM_{2.5}$ exposure and adverse effects on foetal development [30]. Also, researchers found the BDNF factor (Brain derived neurotrophic factor) was reduced in exposed mothers, which resulted in neuro-behavioral developmental disorders, decreased IQ and memory power in their new-borns [2,31]. The transfer of nutrients between the maternal and placental circulation plays an important role in fetal growth and development. Therefore, a better understanding of maternal and placental metabolic conditions is very important to identify the cause of growth restriction in the offspring. One of the supported mechanisms in exposure to particles is the reduction of the DNA methylation process (adding methyl to cytosine bases), which in healthy conditions, causes genome stability, cell proliferation and cell differentiation at placental surfaces [32,33]. The results of studies show that exposure to $PM_{2.5}$ significantly alters maternal serum and placental metabolism, causing disturbances in maternal serum and placental metabolism. It disrupts vitamin digestion and absorption, the placental nutrient transport capacity and causes endocrine dysfunction [28,29]. Exposure to $PM_{2.5}$ significantly alters the vitamin digestion and absorption metabolic pathway in the maternal serum and two metabolites involved (nicotinamide and Flavin Adenine Dinucleotide (FAD)) play vital roles in the oxidation-reduction reactions cellular process. FAD, the riboflavin biologically active form (vitamin B2), plays an important role in antioxidation as a co-factor for glutathione reductase activity [34,35]. Nicotinamide is the niacin (vitamin B3) major form and the precursor of NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate), which are the cellular antioxidant system key components [36,37]. It is thought that nanoparticles can have adverse health effects through the oxidative stress generation [20,38]. Recent findings have also indicated that dietary supplementation with antioxidants, such as vitamin C and vitamin E, can reduce oxidative stress and the nanoparticle's adverse effects. Exposure to $PM_{2.5}$ induces oxidative stress in the mother and leads to a significant decrease in FAD and nicotinamide levels. Maternal nanoparticle exposure may also cause fetal growth restriction by activating maternal and placental oxidative stress and significantly increasing placental MDA levels [39]. The depletion of antioxidants together with the production of Reactive Oxygen Species (ROS) may activate phospholipase A2 which can stimulate the release of free lysophosphatidic and polyunsaturated fatty acids such as arachidonic acid through the hydrolysis of phospholipids [40,41]. As a major inflammatory mediator, arachidonic acid may be released from the cell membrane and converted to prostaglandins via the cyclooxygenase pathway [42].

Also, increased platelet and inflammatory factors such as interleukin 6 in placental surfaces were along with increased risk of thrombosis in placental syncytiotrophoblast cells in exposed groups [43]. Previous research has suggested that pregnant women's exposure to urban air pollution may cause abnormal phospholipid metabolism [44]. Many studies have shown that Prostaglandins, Especially Prostaglandin E2 (PGE2), play an essential role in vasodilation, uterine contraction and the regulation of labour during pregnancy. In general, prostaglandins were significantly reduced by exposure to $PM_{2.5}$ [45]. Abnormal placental blood flow is probably due to altered PGE2, which can lead to IUGR [46]. PGE2 is a potent intracellular activator involved in vascular relaxation and angiogenesis. Also, PGE2 is involved in the cAMP signaling pathway, another pathway that is disrupted by exposure to nanoparticles [47]. Lysophosphatidic acid (LPA) is a bioactive lipid that can exert various biological functions by binding to specific LPA receptors (LPAR1 to LPAR6) along with G protein. Based on the findings, the LPA level was significantly increased by exposure to $PM_{2.5}$ in Blood circulation and maternal placenta changes [40]. Recent studies have shown that LPAR1 and LPAR6 mRNA expression is significantly increased in $PM_{2.5}$ -exposed placentas. Also, the LPA/LPAR signalling pathway ensures adequate blood flow to maintain normal fetal development by participating in vascular remodelling at the maternal-fetal interface [48]. In addition, phagocytosis of suspended particles by massive macrophages located in the chorionic plate of the placenta leads to blockage of the chorionic villi and decreased placental circulation, and on the other hand, facilitates the transfer of particles to the fetus [32].

Maternal $PM_{2.5}$ Exposure and Placenta Disturb

A placenta's critical role is to transport nutrients from the maternal circulation to maintain fetal development normally during pregnancy. Findings showed that maternal exposure to $PM_{2.5}$ can alter the expression of nutrient transporters and disrupt nutrient transport in the placenta [49]. Maternal $PM_{2.5}$ exposure significantly altered some metabolite transport ratios, including methionine. Methionine as an essential amino acid, is a key one-carbon metabolism component, which is critical for fetal growth and fetal protein mass accumulation [50]. Methionine is a sulfur-containing amino acid that is easily oxidized [51]. Some studies have indicated that PM exposure is related to methionine oxidation in mice [52]. Considering methionine antioxidant properties, an increase in the methionine transport ratio may indicate activation of the placental defense system to protect of it from excessive ROS induced by exposure to $PM_{2.5}$. Similarly, $PM_{2.5}$ exposure significantly increases the nicotinamide transport ratio, which is also an important antioxidant. Placentas have several fatty acid transport proteins, such as fatty acid transport proteins (FATPs), FATPpm, and CD36, which can transport LCPUFAs (long-chain polyunsaturated fatty acids), the same as PLIN proteins, which are responsible for fatty acids storage in lipid droplets [53]. According to the metabolomics results, exposure to $PM_{2.5}$ increases the levels of CD36, FATP1, PLIN4, PLIN5 and PLIN2 significantly. Maternal $PM_{2.5}$ exposure may also alter the placental amino acids, fatty acids and vitamins transport capacity [54,55].

Maternal $PM_{2.5}$ Exposure and Endocrine Disruption

One of the potential causes of adverse pregnancy outcomes is endocrine disruption during pregnancy. Among the disorders reported in endocrine function, abnormal increase in maternal FBS levels, impaired glucose tolerance, increased HB-A1C, abnormal OGTT and Thyroid dysfunction [56] were reported [57-63]. Ambient $PM_{2.5}$ contains a large number of Endocrine-Disrupting Chemicals (EDCs), such as PAHs and heavy metals [54,55], which can disrupt steroid lipid synthesis by directly interacting with the relevant enzymes. Maternal $PM_{2.5}$ exposure led to endocrine disruption as indicated by altered sex hormone levels detected in the mother and placenta. Particularly, Dehydroepiandrosterone (DHEA), a weak androgen and a primary precursor that can be converted to androgen and estrogen, was notably decreased following exposure to $PM_{2.5}$ in both placenta and maternal serum. Some studies have shown that DHEA levels are related to the function of ovarian reserve and pregnancy outcomes [64,65]. Following the maternal androgenic dysfunction, the exposed fetuses will experience quality disorders of spermatogenesis and genital structure, such as cryptorchidism, hypospadias, and reduction of anogenital length, which subsequently results in androgenic disorders in newborn's puberty [66].Furthermore, the levels of placental progesterone and circulating estriol are slightly reduced by exposure to $PM_{2.5}$. During pregnancy, estrogen and progesterone are mainly produced by placenta through the conversion of the maternal and fetal precursors [67]. As two vital hormones for maintaining pregnancy, they play critical roles in the development of a fetus by regulating angiogenesis and trophoblast invasion in the placenta [68].

Conclusion

In general, even low levels of exposure to ambient nanoparticles can affect the expression level of placental genes involved in the metabolism and such effects can be sex-specific. This mini-review adds to the body of evidence on the effects of environmental pollutants on placenta as a fetal programming potential pathway. These changes may be relevant to understanding how a fetus may be vulnerable to altered development in the womb.

Declaration of Interest

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