Chapter 3

Air Quality and Maternal Health: Exploring the Connection to Preeclampsia

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Abstract

Preeclampsia is an obstetric disease characterized by hypertension, proteinuria, and various end-organ damages that begin after the 20th week of pregnancy. Its incidence varies between 2% and 8% of pregnancies worldwide and is responsible for 10% to 15% of maternal deaths. Despite its high incidence, the etiology of preeclampsia is still unknown. Although many maternal, placental, and fetal factors have been suggested for its etiology, it has been reported that environmental factors may also play an important role in the development of preeclampsia. Air pollution, an environmental factor, has also been considered as one of the predisposing factors for preeclampsia, and many air pollutants in the atmosphere have been associated with preeclampsia. It is thought that these air pollutants can induce systemic inflammation and oxidative stress, as well as causing vascular endothelial damage and paving the way for endothelial dysfunction that leads to the development of preeclampsia. Pregnancy represents a special and sensitive period of life for women, as it brings extensive physiological and metabolic changes, as well as changes in the cardiovascular and respiratory systems that may lead to increased susceptibility to damage from environmental factors. Pregnant women are particularly sensitive to air pollution because it disrupts the balance between Treg and Th17 cell immunity, which are particularly important for normal placental development and maintenance of pregnancy, and is involved in the pathogenesis of preeclampsia, resulting in increased

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sensitivity to pollutants. Studies on the effects of air pollution on preeclampsia are relatively recent, but increasing epidemiological evidence has shown that preeclampsia is associated with maternal exposure to air pollution during pregnancy.

Preeclampsia is a multisystemic obstetric disease defined by varying levels of placentalimalperfusion, characterized by proteinuria andihypertension that usually occur after the 20th week of gestation (Chappell, 2021). The extended effects of preeclampsia on maternal health have been extensively reported. Studies have shown a greater chance of intrauterine growth restriction and premature birth for the newborn, as well as a higher risk of diabetes, chronic renal disease, and cardiovascular disease for the mother (Mateus, 2019; Turbeville, 2020). Preeclampsia accounts for 10% to 15% of maternal mortality globally and affects between 2% and 8% of pregnancies (Duley, 2009).

Despite its high incidence, the etiology of preeclampsia remains unknown. Many maternal, placental, and fetal factors have been suggested in its etiology, but environmental elements might also have a significant part in its development. As a component of the environment, pollution in the air has been considered a predisposing factor for preeclampsia. Numerous air pollutants in the atmosphere have been linked to preeclampsia. These contaminants have the ability to cause oxidative damage and systemic inflammation, as well as cause vascular endothelial damage, which is thought to predispose to endothelial dysfunction leading to the development of preeclampsia (Gao, 2022; Shah, 2013).

A woman's life undergoes unique and delicate changes during pregnancy, including modifications to her metabolism and circulatory and respiratory systems, all of which can make her more vulnerable to environmental harm. Because air pollution upsets the balance between Th17 and Treg cell immunity, which is essential for healthy placental growth and pregnancy maintenance, pregnant women are more vulnerable to it. This imbalance is involved in the pathogenesis of preeclampsia, and high sensitivity to pollutants develops (Gao, 2022). Therefore, oxidative stress caused by particulate matter (PM) and atmospheric gases during pregnancy may alter the vascular function of the placenta, affecting the development of preeclampsia in the adverse intrauterine environment, consequently impacting fetal development and growth.

Although research on the relationship between air pollution and preeclampsia is still in its infancy, a rising body of epidemiological data has

linked preeclampsia with contact to air pollutants during pregnancy (Cao, 2021; Cao, 2020; Dadvand, 2013; Gao, 2022; Gogna, 2022; Nobles, 2015; Yang, 2019). Although the presence and density of air contaminants vary depending on the climatic and industrial environment, NO2, CO, O3, Pb, SO2, PM2.5, and PM10 are the most commonly examined pollutants (Figure 1).

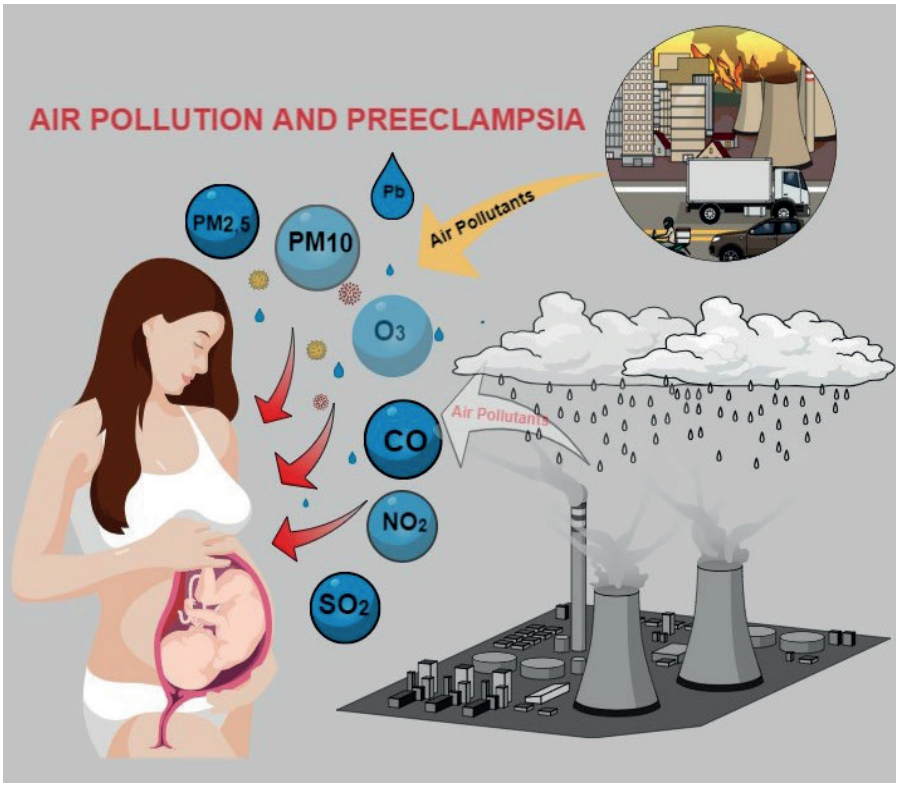

Figure 1. Air Pollution and Preeclampsia

Nitrogen Dioxide (NO2) and Preeclampsia

Nitrogen dioxide (NO2) is a reddish-brown, poisonous gas with a sharp odor similar to chlorine. It possesses strong oxidizing properties, causing significant oxidation reactions with air and water vapor, leading to the formation of corrosive nitric acid and toxic organic nitrates. This process contributes to acid rain, which can result in the death of trees, fish, and animals. Additionally, NO2 plays a key role in atmospheric reactions that lead to the formation of ground-level ozone and smog. In general, as a traffic-related pollutant, NO2 concentration is higher in cities than suburban regions.

Beyond environmental harm, NO2 poses significant health risks through inhalation. Exposure to NO2 can cause respiratory issues such as shortness of breath, inflammationxand irritation of the respiratoryxtract, and a decline in lung function. Recent studies on prenatal exposure have shown that NO2 increases the risk of preeclampsia (Goin, 2021). One study suggested that this effect might be linked to adverse impacts on trophoblast invasion and placental vascularization, as well as increases in anti-angiogenic factors like oxidative stress in addition to solublexfms-like tyrosinexkinase-1 (sFlt-1) in response to pollution in the air which is a factor in the pathophysiology of preeclampsia (Bearblock, 2021). Inxvitro and inxvivo studies on the placenta indicate that more extensive research on NO2's effects is needed.

Health Impact of Particulate Matter (PM) and Preeclampsia

Respirable PM in the atmosphere with a particle with an aerodynamic equivalentidiameter of less than 2.5 μm is called fine PM, or PM2.5. PM2.5 which is a kind of suspended particulate in the atmosphere has garnered significant attention in air pollution research due to its complex composition, which contains bacteria, viruses, water-soluble ionic salts, heavy metals, and a variety of organic contaminants (Mukherjee, 2018). PM2.5 can easily carry toxic substances into the body through respiration, potentially reaching the alveoli and bloodstream due to its tiny size, high specific surface area, and extended airborne residency duration.

Those who are exposed to air pollution have a higher risk of developing hypertension, according to several research (Honda, 2018). Preeclampsia risk has been linked to exposure to PM2.5 and PM10 (PM having a diameter of less than 10 μm) in the first trimester (Bai, 2020). The scarcity of studies regarding the relation between preeclampsia subtypes and air pollution highlights the need for up-to-date research in this field (Bearblock, 2021).

The health impact of PM increases as particle size decreases. PM with anxaerodynamic diameter of $\leq$2.5μm (PM2.5) can reach the alveoli and accumulate in the lungs, while PM10 with an aerodynamicxdiameter of $\leq$10 μm is larger and mostly accumulates in the upper bronchi. Ambient pollution in the air has been reported to rise the danger ofiihypertensive problems during pregnancy. Axmeta-analysis revealed that beeing exposed to PM2.5 and PM10 significantly increases the risks ofipreeclampsia (Pedersen, 2014).

In vitro studies have demonstrated that PM2.5 can cause trophoblasts to undergo apoptosis, reduced motility, exchange of reactive oxygen species (ROS), inflammation, and altered hormone production (Cevallos, 2017; Familari, 2019; Nääv, 2020; Qin, 2017; Wang, 2017). PM2.5, which is

approximately 1/30th the diameter of a human hair, can be transported thousands of kilometers before settling. While PM10 also contains dust from natural sources, such as volcanoes and natural fires, it is a significant source of destruction and fires caused by earthquakes. PM2.5 is mostly composed of carbon, aluminum, lead, sulfur, bacteria, and other materials (Ibrahimou, 2014).

Due to its small diameter, it is easy for PM2.5 to penetrate the respiratory barrier, enter the circulation, and enter the respiratory tract (Billet, 2007). Numerous organs and systems may experience immediate or long-term harm as a result of the complex biological reactions that PM2.5's constituents might set off. These reactions include oxidative stress, genotoxic damage, and immunological and inflammatory responses (Feng, 2016; Kreyling, 2016). Diabetes, pregnancy-related illnesses, and chronic obstructive lung disease can all arise from this. (He, 2017; Melody, 2020; Xing, 2016).

According to some research, atmospheric PM2.5 can enter the mother's circulation and pass via the placenta, oxidative stress and inflammation that can lead to placental malfunction and even preeclampsia (Brunst, 2018; Dadvand, 2013; Li, 2019; Slama, 2008). Preeclampsia risk is positively correlated with PM2.5 exposure during pregnancy, according to mounting data (Assibey-Mensah, 2020; Dadvand, 2014; Lee, 2013; Mandakh, 2020; Rudra, 2011; Wu, 2009). According to some research, there may be a higher chance of preeclampsia if pregnant women are exposed to PM2.5 during particular times (Lee, 2013; Mandakh, 2020).

Because PM2.5 has such a small particle size, there is always a risk of exposure, which has proven extremely dangerous for public health. By WHO criteria, the yearly average of 10 $\mu g/m^3$ for PM2.5 puts 92% of people globally at risk of exposure (Ghosh, 2021; Hystad, 2020). Pregnant women are particularly vulnerable to the harmful effects of PM2.5 because of the abrupt physiological shifts that pregnancy brings about (Varshavsky, 2020).

Carbon Monoxide and Preeclampsia

Carbon monoxide (CO) is an inorganic compound composed of one carbon and one oxygen atom, with the chemical formula CO. In this molecule, a triple bond exists between the carbon and oxygen atoms. CO is widely used in industry for generating various types of gases such as generator gas, water gas, power gas, and air gas, as well as serving as a fuel. CO is a odorless, colorless, and flavorless vapor that is referred to as the "silent killer." CO is mostly produced by the partial combustion of carbon-containing molecules, which can occur from a variety of biological

and environmental sources. In the industrial realm, CO plays a key role in the synthesis of several substances, such as medicines, fragrances, and fuels.

When CO concentration increases in inhaled air, it enters the bloodstream and binds more readily to hemoglobin than oxygen (O2), thereby hindering oxygen transport. CO binds to the iron atom at the center of hemoglobin, which can lead to death by asphyxiation. The relationship between CO and preeclampsia is intriguing. While harmful at high levels, recent research suggests that CO might reduce the risk of preeclampsia within certain limits. Researchers have found that CO promotes trophoblast invasion, decreases the decidual inflammatory response, increases uteroplacental blood flow, reduces hypoxia-induced apoptosis, and upregulates placental antioxidant systems. Both endogenous and exogenous CO have been reported to promote angiogenesis and suppress the release of solubleifms-like tyrosineikinase-1 (sFlt-1).

Several research have shown that CO plays a crucial role in various physiological and pathophysiological processes. Endogenous CO is a metabolite involved in the catalytic reaction and degradation of the oxygenase enzyme. CO has been shown to reduce placental apoptosis and placental perfusion pressure. Furthermore, it has been suggested that pregnant women with preeclampsia have lower tidal breath CO concentrations. Therefore, the heme oxygenase-CO pathway may be involved in the pathogenesis of preeclampsia. More research is required to investigate the potential mechanisms by which CO reduces the risk of preeclampsia (Gomez, 2020; Olgun, 2020).

Sulfur Dioxide and Preeclampsia

Sulfur dioxide (SO2) is a pungent, colorless, non-flammable, poisonous gas with the chemical formula SO2. With a gas density relative to air of 2.26, it is approximately 126% heavier than air, meaning that in case of leakage, it may accumulate near the ground and spread horizontally. The main sources of SO2 are thermal power plants and industrial boilers, with the highest concentrations found near major industrial sources.

SO2 causes the airways to narrow, impairing the lungs' defense mechanisms and potentially leading to heart diseases. Under the influence of certain chemicals and sunlight, SO2 transforms into acid rain, making it a leading pollutant in urban areas. Acid rain, smog, and reduced visibility are all consequences of high SO2 levels. Intense accumulation of SO2 can cause serious damage from both poisoning and acid rain, necessitating the

constant installation of gas detection systems in areas where SO2 gas is likely to accumulate.

It has been established that SO2 is a toxin that may raise the possibility of negative pregnancy results, including miscarriage, stillbirth, and preterm birth, during all three trimesters. Maternal exposure to SO2 has also been linked to an increased danger of preeclampsia (Raez-Villanueva, 2019; Shen, 2019; Wang et, 2018b; Zhang, 2018). Although current epidemiological studies have proven the harm of SO2 exposure to pregnant women, the mechanisms underlying these processes are still being worked out.

Environmental pollutants, including SO2, cause trophoblast dysfunction in pregnant women. Oxidative damage, characterized by high levels of ROS or other indicators of oxidative stress and decreased levels of antioxidative enzymes, is a major cause of this dysfunction (Raez-Villanueva, 2019; Shen, 2019; Wang, 2018b; Zhang, 2018).

Few research have looked at how SO2 exposure affects trophoblasts. According to one research, breathing in SO2 breaks down into its derivatives, bisulfite and sulfite, in a 1:3 M/M ratio. This can have an impact on pregnant women's placental trophoblasts (Wang, 2014). Another study used the first-trimester trophoblast cell line Swan. 71 to examine if SO2 compounds may cause trophoblast malfunction and their internal processes. According to reports, SO2 compounds cause cell apoptosis, severely lower cellular viability, stop the cell cycle in the S/G2/M phase, and impede trophoblast motility. The lowering of ROS/IL-6/STAT3 levels by SO2 derivatives is thought to be the cause of these effects (Lihao Hu, 2021). Understanding the impact of SO2 and its compounds on reproductive toxicology depends critically on these discoveries.

Ozone Gas and Preeclampsia

Ozone (O3) is a colorless gas composed of three oxygen atoms. It exists primarily in the upper layers of the atmosphere, where it is an allotrope of oxygen, also known as trioxygen. Under normal conditions, the concentration of O3 in the lower atmosphere is approximately 0.04 ppm. However, this concentration increases significantly in areas with smog. Ozone is responsible for the blue color of the sky and has a vital part in shielding Earth from the Sun's damaging ultraviolet (UV) radiation. It is formed by UV rays in the upper atmosphere and by the electric current generated by lightning in the lower atmosphere, where it helps cleanse the air. Ozone is also used as a disinfectant in the health and food sectors (Yang, 2019).

Due to chronic climate change, the ozone gas exposure limit determined by the World Health Organization (WHO) exceeds 100 μg/m3 (for eight hours of continuous exposure), raising concerns about its health risks. Ozone pollution has become a significant threat to human health, with high O3 levels and increasing anthropogenic O3 precursor emissions in recent years. In 2017, ozone pollution in China surpassed PM2.5 (44.5%), reaching 50.4% for the first time, making O3 the primary pollutant.

A growing body of literature links O3 exposure during pregnancy to an increased risk of hypertension. According to a Florida cohort research with 655,529 people, being exposed to O3 might lead to an increased danger of hypertensive disorders of pregnancy (HDP). However, studies present mixed results; a US study reported no association between early pregnancy O3 exposure and increased danger of preeclampsia or gestationalxhypertension, while Even first-trimester O3 exposure was linked to an elevated risk of preeclampsia, according to a Swedish cohort research. These discrepancies could be due to differences in O3 pollution levels across various countries and regions.

Being exposed to O3 has been specifically linked to a higher risk of gestational hypertension in individuals between the ages of 26 and 34, and preeclampsia in individuals aged 35 and older. Some studies have shown that O3 exposure in pregnant individuals aged 35 and older increases the risk of preeclampsia by 30%. This increased risk can be explained by the greater sensitivity to air pollution in advanced maternal age. Similarly, toxicokinetics, the way the body processes and eliminates toxic substances, may also vary with age. Young mothers may have a better capacity to detoxify and eliminate toxic compounds from the body (Ning, 2020).

The potential health impacts of ozone exposure during pregnancy highlight the need for ongoing research and monitoring, especially considering the varying levels of exposure and individual susceptibility factors.

Lead (Pb) and Reproductive Health

Lead (Pb) is a heavy metal with significant adverse effects on women's reproductive health. Pb is among the heavy metals with the highest environmental impact and potential harm. Women are at risk of unintentional exposure to Pb, particularly through cosmetic products, paints, batteries, and some cooking utensils. Exposure to lead has been linked to hypertension in several studies. Lead (Pb) can harm the brain and central nervous system, as well as interfere with the biological activity of enzymes and cause behavioral problems (Lu, 2018)

Reproductive health issues due to Pb exposure are not limited to women. Higher blood lead levels in men have been associated with low sperm count and poor sperm motility. During pregnancy, Pb exposure has been linked to preeclampsia, although the exact mechanisms remain unclear due to inconsistent results. Several theories have been proposed to explain the possible mechanisms:

Mobilization of Maternal Bone Lead: Maternal blood lead levels (BLL) are elevated due to the mobilization of bone lead by pregnancy-related physiological changes. The pathophysiology of preeclampsia is largely dependent on the discharge of endothelin, a vasoconstrictor implicated in inflammation, which is increased by this process.

Impact on Plasma Adrenaline and Noradrenaline Levels: An experimental animal study found that continuous consumption of drinkingİwater tainted with lead can cause a significant increase in adrenaline and noradrenaline plasma levels. This increase in bloodihypertension, partially accountable for of the preeclampsia pathogenesis, can be induced by high Pb exposure.

Changes in miRNA Profiles: Elevated maternal BLL may cause localized modifications to miRNAiprofiles. Since Pb can pass over the placenta freely, lead exposure while pregnant increases intrauterine Pb levels. High lead levels in umbilical cord blood cause changes in fetal miRNA profiles, resulting in a bgger risk of preeclampsia and undesired fetal results such as premature birth or stillbirth.

Given these potential mechanisms, it is crucial to understand the risks associated with Pb exposure during pregnancy. Continued research is needed to fully elucidate the pathways through which Pb affects maternal and fetal health, particularly concerning preeclampsia.

Sources of Lead Exposure and Health Implications

Lead exposure can occur through various environmental and occupational sources. In many regions, lead-based paints and plumbing are significant contributors to Pb exposure. Additionally, certain industrial activities, such as battery manufacturing and recycling, can lead to elevated Pb levels in the environment. Cosmetic products, particularly those imported from countries with less stringent regulations, may also contain lead.

The health implications of lead exposure are far-reaching. Chronic Pb exposure can lead to cognitive deficits, learning disabilities, and behavioral problems in children. In adults, Pb exposure has been linked to cardiovascular

diseases, kidney dysfunction, and reproductive issues. Pregnant women are particularly vulnerable, as Pb can cross the placenta and affect fetal development (Lu, 2018).

Preventive Measures and Recommendations

Preventing lead exposure requires a multifaceted approach. Key measures include:

Regulatory Enforcement: Strengthening regulations on lead content in consumer products, including cosmetics, paints, and cooking utensils, is essential.

Public Awareness: Educating the public about the sources and risks of lead exposure can help reduce unintentional exposure.

Occupational Safety: Implementing strict safety protocols in industries that use lead can protect workers from exposure.

Environmental Cleanup: Identifying and remediating lead-contaminated sites can reduce environmental Pb levels.

For pregnant women, regular screening for blood lead levels, particularly in high-risk areas, can help identify and manage exposure early. Healthcare providers should recognize the possible hazards of lead exposure at pregnancy and provide appropriate guidance and interventions.

Lead is a pervasive environmental toxin with significant implications for reproductive health. While the exact mechanisms by which Pb contributes to conditions such as preeclampsia are still being investigated, the evidence suggests multiple pathways of harm. Addressing lead exposure through regulatory measures, public education, and targeted interventions is crucial to protect maternal and fetal health. Further research is essential to fully understand the impact of Pb and to develop effective strategies for prevention and treatment.

Mechanisms of Air Pollution and Hypertension

Air pollution primarily affects hypertension through three mechanisms (Van den Eeden, 2018):

Interaction with the Sympathetic Nervous System: Through their interaction with the sympathetic nervous system, pollutants raise blood pressure by sending signals that control vascular tension and blood volume.

Oxidative Stress: Pollutants produce markers of oxidative stress in the circulation, influencing hemodynamic processes and endothelial cells to change blood pressure.

Vasoconstriction Dysfunction: Blood pressure is directly impacted by vasoconstriction dysfunction, which is brought on by pollutants.

Pregnancy is a time frame when females are particularly sensitive to toxic pollutants in the air. Exposure to pollutants at this period may be very important for the development of preeclampsia (Shih, 2017).

Air Pollutants and Preeclampsia

Because air pollutants can cause vascular endothelial damage, oxidative stress, and systemic inflammation, they have been linked to preeclampsia (Mozaffarian, 2015). Since hypertension is easily diagnosed and treated, and successful treatment is associated with reduced morbidity and mortality (James, 2014), controlling hypertension-related diseases such as preeclampsia is a cornerstone of preventive cardiovascular care. Environmental risk factors like air pollution are increasingly recognized as important determinants of preeclampsia risk.

Air pollution is also a significant risk element for adverse cardiovascular health outcomes (Brook, 2010). Evidence from animal studies (Sun, 2009) and epidemiological studies indicates that air pollution can impair cardiovascular function by causing chronic systemic inflammation and increasing oxidative stress. These effects may lead to endothelial dysfunction, changes in arterial diameter, or alterations in vascular tone and heart rate, all of which can result in increased blood pressure and hypertension/ preeclampsia (Kramer, 2010).

Preeclampsia and Long-term Health Risks

Preeclampsia is not only an obstetric problem but also poses a risk for the mother to develop many complications after pregnancy. Women who have had preeclampsia face an bigger hazard of cardiovascular problems afterwards (Irgens, 2001; Mongraw-Chaffin, 2010; Ahmed, 2014; Kestenbaum, 2003). A meta-analysis of 43 studies found an increased risk of cerebrovascular disease, stroke, hypertension, and preeclampsia with exposure to air pollution (Brown, 2013). Additionally, women with preeclampsia may have an increased danger of hypothyroidism, thromboembolism, kidney disease, diabetes, and amnesia in the long term (Williams, 2011). Preeclamptic pregnancies also pose risks to the fetus, including preterm birth, neonatal thrombocytopenia, and restricted fetal angiogenesis (Backest, 2011).

Environmental and Genetic Interactions

Improving clinical definitions of preeclampsia involves understanding the connections between the placenta and the mother's genetic and environmental variables (Valenzuela, 2012; Williams, 2011). Common environmental pollutants have received little attention. Environmental pollutants can affect trophoblasts that help form the placenta. The initial step of preeclampsia development, inadequate placentation, may be caused by inhibition or adverse effects on trophoblast migration (Goldman-Wohl, 2002). Exposure to specific environmental pollutants may have a deleterious effect on trophoblasts which leads to the genesis of preeclampsia, according to both research on animals and in vitro findings (Bechi, 2013; Fowler, 2012).

Air Pollution and Pregnancy Complications

Air pollution is a major environmental health problem, particularly for pregnant women. The World Health Organizationestimates that exposure to PM2.5 reduces life expectancy by 8.6 months in Europe. Epidemiological studies have shown that ambient air pollution, including PM2.5, PM10, CO, NO2, Pb, O3, and SO2, is linked to pregnancy complications including preeclampsia, gestationalxdiabetes mellitus, HDP, and gestational hypertension (Abdo, 2019; Mendola, 2016; Nobles, 2019; Savitz, 2015). A meta-analysis covering 10 articles showed that NO2increases the risk of preeclampsia throughout pregnancy, while CO and O3 increase the risk in the first trimester (Pedersen, 2014).

Challenges and Future Directions

Despite increased awareness of the preeclampsia hazards, clinicians face challenges due to the lack of effective treatments once diagnosed. Conventional antihypertensives are relatively ineffective in most cases, and disease management focuses on prolonging pregnancy with restrictive bed rest and anticonvulsants. Delivery of the baby and placenta is the only complete cure. Identifying new treatments for preeclampsia is crucial. Recent advances in understanding the mechanisms involved in preeclampsia development have proposed various new therapeutic approaches. Sustainable air pollution control is essential to reduce the disease burden of preeclampsia.

Conclusion

Air pollution poses significant risks to maternal and fetal health, particularly concerning preeclampsia. The mechanisms through which pollutants affect blood pressure and contribute to preeclampsia involve interactions with the sympathetic nervous system, oxidative stress, and vasoconstriction dysfunction. While hypertension-related diseases like preeclampsia are treatable, prevention through controlling environmental risk factors is paramount. Continued research and sustainable air pollution control measures are vital to improving maternal and fetal health outcomes and reducing the burden of preeclampsia.

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