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Review

Air pollution: cardiovascular and other negative effects on pregnancy: a narrative review

Leen Van den Eeden[1,2,3,*], Greet Leysens[1], Dominique Mannaerts[2,3], Yves Jacquemyn[2,3,4]

[1] *Thomas More University College, People & Health 2500 Lier, Belgium*

[2] *Antwerp Surgical Training, Anatomy and Research Centre (ASTARC), Faculty of Medicine and Health Sciences, University of Antwerp, 2610 Antwerp, Belgium*

[3] *Departement of Obstetrics and Gynaecology, Antwerp University Hospital (UZA), 2650 Edegem, Belgium*

[4] *Global Health Institute (GHI), University of Antwerp, 2610 Antwerp, Belgium*

*Correspondence: leen.vandeneeden@thomasmore.be (Leen Van den Eeden)

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Objectives: The main goal of this narrative review is to summarize the data on the relationship between air pollution and pregnancy outcome. *Mechanism*: The authors conducted a critical but concise review on published studies relating to particulate matter ($PM_{2.5}$ and PM_{10}), carbon monoxide, ozone and nitrogen oxide versus pregnancy outcome. *Findings in brief*: (Over) exposure to particulate matter is associated with a negative outcome on fertility and early pregnancy loss. There is an increased risk of congenital birth anomalies, birth weight and pregnancy-induced hypertensive disorders with exposure on $PM_{2.5}$. Exposure to ozone and NO_2 decreases the chance of live birth rate and increases the risk of congenital heart diseases, preterm birth and hypertensive disorders. *Conclusions*: Air pollution is traditionally correlated with adverse health effects. In the current review, we concisely but critically compile the most relevant studies on pregnancy-related effects. Particulate matter, carbon monoxide, ozone, and nitrogen dioxide are the key air pollutants. Exposure to these pollutants has been associated with cardiovascular disease, respiratory disease, and negative effects on pregnancy.

Keywords

Air pollution; Pregnancy; Respiratory health; Cardiovascular effects

1. Introduction

Although air pollution differs around the world, it is a global threat having a significant impact on human health and ecosystems. The World Health Organization (WHO) has proposed limits for the concentration of key air pollutants, but these are often not identical to national standards [1]. Exposure to ambient air pollution increases mortality and morbidity and shortens life expectancy. Environmental air pollution caused 4.2 million premature deaths in 2016 [1]. Pollutants derive from a wide range of sources, like agricultural activities, energy production and distribution, road transport, waste, fuel combustion, and natural phenomena [2]. The key air pollutants are particulate matter—black carbon, ozone, and nitrogen oxides—(PM), carbon monoxide (CO), sulphur dioxide (SO_2), and nitrogen dioxide (NO_2). These pollutants are responsible for an increase in life-threatening conditions, such as lung cancer, cerebrovascular accidents, cardiovascular conditions, and chronic obstructive pulmonary disease (COPD) [3].

Exposure to air pollution during pregnancy is associated with adverse birth outcomes [4]. These adverse birth outcomes include preterm birth, low birth weight and hypertensive disorders in pregnancy. Specifically increase in exposure during the first and second trimester increases the risks on pre-eclampsia [5]. Exposure to air during pregnancy pollution also has negative effects on offspring. Maternal exposure during whole pregnancy is associated with increased risks for neonatal respiratory complications, such as respiratory distress, asphyxia and transient tachypnoea [6]. Even exposure to air pollution prior to conception is associated with an increased risk for preterm birth and low birth weight [4].

Unfortunately, the relationship between reducing pollution and improving health is not straightforward. The majority of studies on pollution and health are correlational and not etiological. A recent Cochrane review studied the effectiveness of interventions in reducing environmental air pollution and improving health. Evidence regarding the improvement of health outcomes for all intervention categories has been either weak or very weak certainty [7].

In this paper, we first present a short overview of the health issues related to air pollution in the general population, allowing comments on differences in the pregnancy cases that we discuss in more detail in the following paragraph.

2. Overview of impact of most air pollutants on global health in the general population

The literature correlating health effects with air pollution is overwhelming. For the ease of the overview, we will consecutively discuss particulate matter, black carbon, ozone, and nitrogen oxides. Our discussion will cover mainly the respiratory and vascular effects, as these systems are most

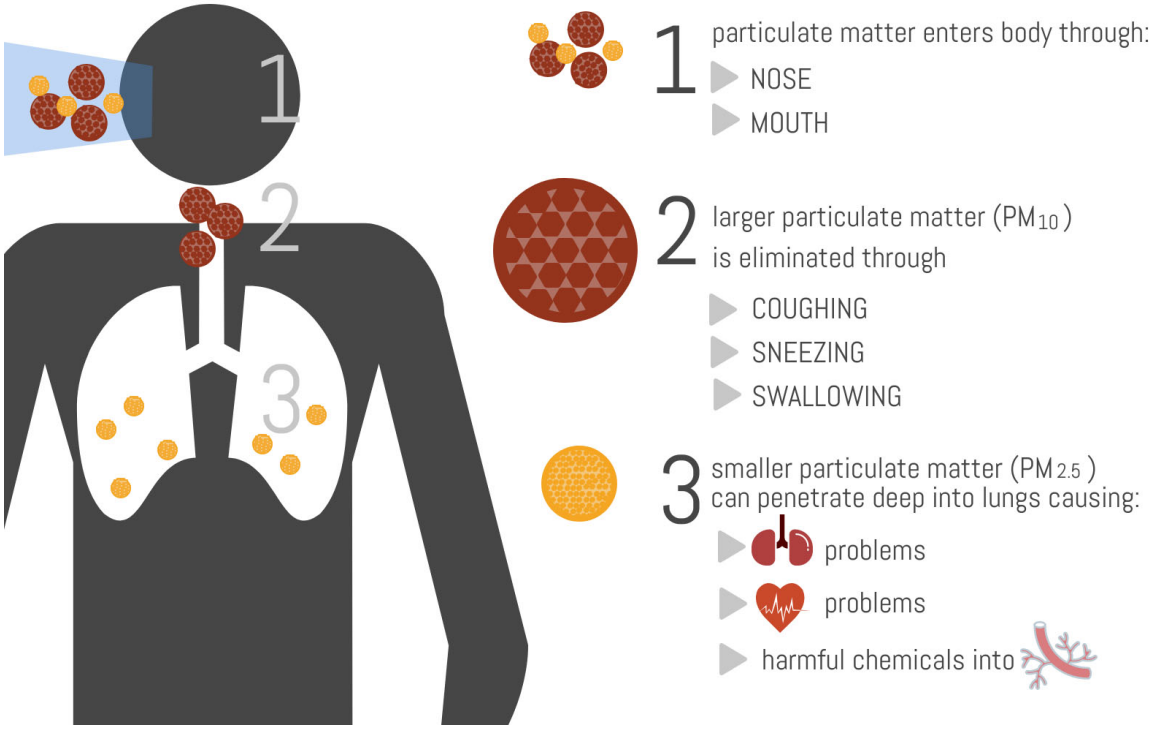

Fig. 1. Penetration of particulate matter in the respiratory system.

relevant during pregnancy to fetal growth and development. We will not discuss the endocrine-disrupting effects as these have recently been reviewed by Darbre [8].

2.1 Particulate matter

Particulate matter is the collective term to identify the mixture of solid particles and liquid droplets in air. PM derives from human (i.e., non-exhaust emission sources, brake ware emissions, exhaust emission sources, and industrial emissions) as well as non-human (i.e., windblown dust, sea salt aerosols, biological aerosols, and volcanic eruptions) sources [9]. These particles exist in different sizes and shapes. Size is linked to their potential for causing distinct health problems (Fig. 1). Most research examines particulate matter with aerodynamic diameter below 10 μm (also referred to as PM_{10}) or below 2.5 μm (also referred to as $PM_{2.5}$). Although PM_{10} can easily enter the lungs and bloodstream, $PM_{2.5}$ is more hazardous. Due to its small size, it penetrates even deeper into the lungs with ease (Fig. 1).

Exposure to PM increases plasma viscosity and serum fibrinogen concentration and leads to systemic inflammation. Inhalation of diesel exhaust triggers an acute endothelin-1 release causing vasoconstriction. Short term exposure also induces vascular injury and depletion of circulating endothelial progenitor cells [10].

Hamanaka & Mutlu [11] revealed in their review that PM is a major contributor to cardiovascular morbidity and mortality. The exact contribution is not completely understood because exposure to particulate matter is also linked with effects on other systems than the cardiovascular system. A large prospective cohort study of Yusuf *et al.* [12] in 21 countries estimated that ambient air pollution was responsible for 13.9% of cardiovascular disease cases. Exposure was higher in middle-income countries and highest in low-income countries.

Evidence suggests not only an association but a causal relationship because an improvement in air quality is associated with public health benefits [13].

There is an association between exposure to ambient air pollution and respiratory diseases like asthma, COPD, decreased pulmonary function, and lung cancer [14]. Interventions to reduce exposure to particulate matter (closure of factories, coal bans, exchange of stoves, wood-burning bans, diesel vehicle bans, or high vehicle standards) have led to improvements in respiratory health [7].

2.2 Black carbon

Black carbon (BC) is classified as a $PM_{2.5}$. The WHO describes black carbon as "carbon as measured by light absorption" [15]. In epidemiological studies, the absorbance of $PM_{2.5}$ filters is used to measure black carbon particles [16], although the proportion of BC in $PM_{2.5}$ varies largely. It is important to understand that black carbon particles have variable chemical compositions depending on their sources. Since BC is potentially the most decisive or crucial pathogenic factor of $PM_{2.5}$, the measurement of $PM_{2.5}$ as an epidemiological factor in health is highly questionable. This could explain why the health impacts of $PM_{2.5}$ vary significantly, even at equal levels of $PM_{2.5}$.

2.3 Ozone

Ozone can be divided into stratospheric ozone and ground-level ozone, which is a harmful air pollutant. Ground-level ozone derives from chemical reactions between oxides originating from nitrogen oxides and volatile organic compounds. Uptake of ozone usually occurs via inhalation. It has a low water-solubility and easily penetrates into the upper respiratory tract, where it is not effectively removed because of its low water solubility. Consequently, inhaled ozone dissolves the thin layer of epithelial lining fluid of the lower respiratory tract. Ozone reacts with proteins, lipids, and antioxidants in this epithelial layer and results in the formation of oxidation products responsible for an inflammatory cascade [17].

There is a significant association between exposure to higher ozone levels and increased morbidity. Ozone exposure has a negative effect on the respiratory system, causing decreased lung function (reflected in a reduced forced expiratory volume), lung inflammation, disturbed lung permeability, and mild bronchoconstriction [17].

Day *et al.* [18] found a positive correlation between low-level exposure to ozone and sCD62P levels, a biomarker of platelet activation linked to deep venous thrombosis and increased risk of cardiovascular disease. Despite this observation, no lung function impairment was seen, possibly due to the extremely low concentrations.

Despite the *in vitro* effects of exposure to ozone, no causal relationship was found between long-term annual ozone concentrations and mortality, as noted by Atkinson *et al.* [19]. However, there are relations demonstrated in studies using peak concentrations measured in warmer seasons. Exposure to high ozone levels affects the elasticity index of large arteries, a good marker of arterial compliance [20].

2.4 Nitrogen oxides

Nitrogen dioxide (NO_2) is one type of highly reactive nitrogen oxides (NO_x). Fuel-burning and traffic are the main sources of NO_2. Nitrogen dioxide has the capacity to easily access the respiratory tract and causes the impaired function of the respiratory system. It penetrates deep into the lungs, where it causes respiratory tract irritation: wheezing, dyspnea, coughing, bronchospasms, and even pulmonary edema when exposed to high levels [21].

Prolonged exposure causes cardiovascular problems such as ventricular hypertrophy [21].

3. Impact of air pollutant exposure on pregnancy

Several specific reviews have been published on the impact of air pollution on particular pregnancy outcomes such as fetal growth restriction, pre-eclampsia or congenital anomalies: in this text we want to offer a more general overview not limited to a single perinatal problem [20, 22].

We will discuss the respiratory cardiovascular and other effects of air pollution in pregnant women. We will compare these effects to those known in a non-pregnant population. Next, we will focus on specific gestation-related issues, namely fetal growth restriction and preterm birth. We will not elaborate on such issues as congenital malformations, as these have recently been reviewed in several studies [19, 20].

In a normal pregnancy, extensive maternal cardiovascular changes occur within the first 6 weeks after conception. There is a reduction of the maternal blood pressure, a decrease in peripheral vascular resistance, and a buildup of the cardiac output from the start of the pregnancy until mid-pregnancy, resulting in a 40% increase [23]. Also, there is a progressive increase in heart rate and stroke volume as a result of the augmentation of venous return, secondary to the expansion of the plasma volume. All these cardiovascular adaptations will return to pre-pregnancy levels 6 weeks after delivery [24].

$PM_{2.5}$, PM_{10}, NO_2, CO, and O_3 have negative effects on these maternal cardiovascular adaptations. The effect of these air pollutants on fertility, birth weight, preterm birth, and the presence of congenital anomalies was investigated (Table 1, Ref. [3, 20, 22, 23, 25–40]: Summary of the effects of air pollution on pregnancy) [25].

3.1 Particulate matter

(Over)exposure to particulate matter in a pregnant woman leads to cardiovascular maladaptation, higher risk of uteroplacental insufficiency, and hypertensive disorders and intrauterine growth restriction.

3.1.1 Particulate matter and fertility

A 2 $\mu g/m^3$ increase in exposure to $PM_{2.5}$ in the 3 months prior to the antral follicle count results in 10% fewer antral follicles [26].

Exposure to $PM_{2.5}$ and PM_{10} is also inverse associated with anti-müllerian hormone (AMH), a in indicator of ovarian reserve [27, 28].

An increase of 10 $\mu g/m^3$ in $PM_{2.5}$ concentration over the previous year has also been associated with increased fertility odds by 20% [29].

In fertility treatments, exposure to $PM_{2.5}$ during the culture of the embryos has been associated with a decreased conception rate [30].

3.1.2 Particulate matter and pregnancy loss

PM exposure has a negative impact on early pregnancy outcomes [30]. Exposure to PM_{10} >56.72 $\mu g/m^3$ increases the risk of spontaneous abortion by a factor of 5 compared to women exposed to lower amounts (≤ 56.72 $\mu g/m^3$) [30]. In a case-control study, Zhang *et al.* [31] showed significantly higher maternal exposure to $PM_{2.5}$ in women diagnosed with a clinically recognized early pregnancy loss in relation to women with a normal pregnancy (control). This difference in exposure was seen during the 4-week period after conception. The most vulnerable window for exposure was found to be the second week [31].

Table 1. Summary of the effects of air pollution on pregnancy.

	$PM_{2.5}$-PM_{10}	Ozone	Nitrogen oxides	References
Fertility	Negative associations on antral follicle count, AMH (++) Decreased fertility odds (+) Negative association on conception rate (during IVF) (++)	Negative association with live birth rate (during IVF) (+)	Negative associations on live birth rate (during IVF), conception rate (during IVF) (++)	[26–30]
Pregnancy loss	Negative associations on early pregnancy outcome (++)	No consensus in literature	Increases risk of spontaneous pregnancy loss (+)	[30, 31, 35, 39]
Birth anomalies	Increases risk of congenital anomalies (cardiovascular, orofacial & musculoskeletal defects) (+++)	Increases risks of congenital heart disease (++)	Increases risk of coarction aortae (+)	[3, 32, 36, 37]
Preterm birth/low birth weight	Negative association with pregnancy duration and birth weight (+++)	Significant association on risk of preterm birth (++)	Negative association with pregnancy duration (++) and birth weight (+)	[22, 23, 25, 33, 40]
Hypertensive disorders of pregnancy	Significant association between pregnancy-induced hypertensive disorders and higher levels of $PM_{2.5}$ (+++)	Increases risk of hypertensive disorders (++)	Increased risk of hypertensive disorders (++)	[20, 34, 38]

Legend: Estimated effect size (+ → +++).

3.1.3 Particulate matter and birth anomalies

Exposure to $PM_{2.5}$ during pregnancy is associated with an increased risk of congenital anomalies, especially cardiovascular, orofacial defects, and musculoskeletal defects (craniosynostosis). Cardiac anomalies were more sensitive to $PM_{2.5}$ exposure than orofacial and musculoskeletal anomalies [32].

3.1.4 Particulate matter and preterm birth/low birth weight

A review by Klepac *et al.* [25] found that exposure to PM in pregnancy was significantly associated with the risk of preterm birth.

Zhu *et al.* [33] showed a significant association between the risk of low birth weight and a 10 $\mu g/m^3$ increase of $PM_{2.5}$. The risk of $PM_{2.5}$ during pregnancy was associated with preterm birth and small for gestational age.

3.1.5 Particulate matter and hypertensive disorders in pregnancy

A meta-analysis by Perdersen *et al.* [20] found a significant association between pregnancy-induced hypertensive disorders and exposure to higher levels of $PM_{2.5}$. Similar findings were reported by Sun *et al.* [34], demonstrating the effects of exposure and the risk of pre-eclampsia. The first and third trimester were found to be the most critical windows.

3.2 Ozone

3.2.1 Ozone and fertility

Exposure to ozone between embryo transfer and pregnancy tests in fertility studies showed a 38% decrease in the chance of live birth rate [30].

3.2.2 Ozone and pregnancy loss

Although some studies report an increased risk of pregnancy loss with higher levels, the association of exposure to higher ozone levels and pregnancy loss is not clear [35].

3.2.3 Ozone and birth anomalies

An inverse association between exposure to ozone and congenital heart defects was described in the literature [36, 37]. The first trimester seems the most critical window.

3.2.4 Ozone and preterm birth/low birth weight

A review by Klepac *et al.* [25] showed a significant association between exposure to O_3 and the risk of preterm birth. The effect was higher in the second trimester of pregnancy. Especially in warm seasons, exposure to ozone is associated with an increased risk of preterm birth. Ozone is also identified to have synergistic effects when combined with higher levels of other pollutants [22, 33].

3.2.5 Ozone and hypertensive disorders in pregnancy

Exposure to ozone during pregnancy is related to an increased probability of hypertensive disorders. The most critical window is likely to be early pregnancy [38].

3.3 Nitrogen oxides

3.3.1 NO_2 and fertility

A review on the effect of NO_2 exposure in women undergoing in vitro fertilization (IVF) treatment discovered lower implantation rates with higher exposure (24% lesser chance per 0.01 ppm increase of NO_2, especially in the time frame from embryo transfer to pregnancy test), as well as lower live birth rates [30].

3.3.2 NO_2 and pregnancy loss

Leiser *et al.* [39] showed a 16% increase of the odds of spontaneous pregnancy loss, per 10 ppb increase in 7-day average NO_2.

3.3.3 NO_2 and birth anomalies

Maternal exposure to NO_x/NO_2 has not led to an increased risk of cardiovascular anomalies, other than the coarctation of the aorta [3, 37].

3.3.4 NO_2 and preterm birth/low birth weight

Second and third-trimester exposure to NO_2 is associated with an increased risk of preterm birth; a 10 $\mu g/m^3$ increase in NO_2 exposure during the second and third trimesters of pregnancy was associated with an adjusted odds ratio of 1.01 and 1.07, respectively [40, 41].

It is not clear from literature data if NO_2 exposure has an influence on birth weight, but others have found a negative association.

3.3.5 NO_2 and hypertensive disorders in pregnancy

Pedersen *et al.* [20] estimate the increased risks of pregnancy-induced hypertension between 1% and 85% with each 10 $\mu g/m^3$ increase in NO_2.

4. Discussion

In the present review we attempted to give a concise overview of the current data, based on published studies, of the effects of different pollutants on pregnant mothers and their fetuses.

Although the relationship between cleaner air and better outcome of health feels very natural, a recent Cochrane review failed to demonstrate any significant effect between air-cleaning activities and health.

This counterintuitive conclusion could partly be caused by differences between measurement methodology differing greatly between studies. Some of the techniques were not available in the research group or, at the moment of the study, were not even invented.

Since some of the effects of air pollution can be linked to the interaction with chemical or molecular reactions inside the human body, genetic predisposition potentially influences the expression levels/post-translational modifications and/or epigenetics of these specific cellular proteins leading to completely different reaction patterns. As we are not all similarly sensitive to the effects of alcohol consumption, it could be hypothesized that some people are genetically more or less sensitive to specific air pollutants, making large-scale epidemiological studies very difficult to interpret and care should be taken to draw conclusions just looking at epidemiological data without understanding the biological basis.

For some factors, it is not very clear whether there is a linear relationship between the concentration of the pollutant and the health effects. It could logically be hypothesized that pollutants only play an effect from a specific threshold level upwards.

The idea of personal sensitivity and genetic/epigenetic effect warrants new and more detailed studies to unravel the mechanisms responsible for these adverse effects and to finally understand the individual risks leading to better guidelines and recommendations.

In addition, in future published studies, we propose to clearly define and specify the precise methodology used and correct levels of the different pollutants for the different outcome parameters making future reviews more reliable.

There are multiple conflicting factors involved in studying the effect of pollution on pregnancy outcomes. Often people that live in areas with high pollution, are of lower socio-economic class, have access to less and lower quality medical care, are overweight, more likely to smoke, have exposure to pealing and lead paint in their homes. All of which could increase pregnancy and neonatal complications and often go uncontrolled for in studies. Future studies should seek to isolate the effect of pollutants on pregnancy outcome, the final analysis should correct for covariates such as socio-economic class, access to medical care, obesity, smoking habits and household exposure to lead and other domestic pollutants. Although, a relationship between pollution exposure and pregnancy complications seems self-evidence, further rigorous studies are required.

5. Conclusions

The best and most widely studied pollutants are $PM_{2.5}$.

$PM_{2.5}$, however, is made up of varying compositions of different substances, including BC.

This makes comparing $PM_{2.5}$ levels unreliable. We propose to study BC instead because exposure to $PM_{2.5}$ has a negative effect on fertility. It induces an increased plasma viscosity and fibrinogen level in the mother, leading to systemic inflammation. Elevated levels of $PM_{2.5}$ are also responsible for cardiovascular maladaptation.

Forthcoming studies should analyze and discuss the dose relationship between the pollutants and aim to establish a threshold above which problems can be expected.

Author contributions

LVdE performed the research. GL designed the figures, DM and YJ provided advice and critical reading of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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