Review Article

How Can Outdoor Air Pollutants Adversely Affect the Women's Fertility? Systematic Review

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Abstract

In the current century, air pollution is known as one of the most critical environmental problems and it is important to find the relations of air pollution and human health. Various air pollutants, such as volatile organic compounds (VOCs), can negatively affect women's fertility. An exhaustive electronic search was done from 2013 until July 2023 in PUBMED and The Cochrane Central Register of Controlled Trials. The following keywords were combined using Boolean hints in the databases queried: air pollution AND (fertility OR miscarriage OR embryo quality OR embryo development OR pregnancy OR implantation OR live birth). The randomized controlled trials, case-control and cohort studies analyzing the impact of air pollutants on fertility were included in the review. In this systematic review, a significant relation was found between the increase in air pollution and the reduction of fertility health, live birth rates, embryo quality, fertility, implantation rates, and miscarriage in exposed women. These results suggest low fertility health rates are associated with traffic-related air pollution. This review has concluded four components (particulate matter, nitrogen dioxide, sulfur, and carbon monoxide) of traffic pollution that can impair women's fertility. Air pollution harms women's fertility. These effects affect gamete's quality at the genetic and epigenetic level. These effects also alter fetal development. Studies have also reported an effect on fetal growth with increased miscarriages. Since air pollution is everywhere and has many sources, it seems necessary to increase the awareness of people and government officials, especially in hygiene and health, to limit air pollutants as much as possible.

Keywords: Air pollution, environmental pollutants, fertility, outdoor, women

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Introduction

Today, air pollution in cities is known as one of the most important risk factors that may affect entirely the life of population in urban areas, including women.[1] Regarding the damage to human health particulate matter (PM) and ground-level ozone(O3) are the most problematic pollutants followed by benzo(a) pyrene (BaP) (an index of polycyclic aromatic hydrocarbons (PAHs)), nitrogen dioxide, sulfur, and carbon monoxide are located. (NO2).[2] The main pollutant sources are transportation and energy, followed by industry.

A key question is how women's unavoidable exposure to pollutants during pre- and post-pregnancy causes abnormalities in eggs, embryos, and/or fetuses and can hinder safe delivery of the baby and overall health and mental functioning. Several studies have investigated the effects of pollution on human health, and some studies on the impact of air pollution as a cardiovascular disease risk factor,[3] stroke,[4] and respiratory diseases,[5] such as lung cancer,[6] childhood asthma[7], and atopic dermatitis.[8] In addition, recently, some studies have emphasized outdoor air pollution as a carcinogenic factor for humans.[9] In some studies, it have shown a relationship between air pollution and adverse perinatal outcomes including premature birth,[10] low weight at birth,[11] and miscarriage.[12] Major air pollutants seem to damage both animal and human

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gametogenesis and lead to reduced reproductive performance.[13] The main mechanisms that affect the ovary are depended on their capacity to convert the endocrine system, increase of OS and inflammation, and activate the specific targets capable of stimulating inappropriate MAPK signaling.[14] Several studies have also suggested that women living in highly industrialized/air-polluted areas have significantly lower antral follicle counts, lower fertility rates (number of live births per 1000 women), and higher rates of implantation failure compared to the control group, they have fewer fertile eggs.[15]

Infertility has been increased in recent decades, and some reports have pointed to the effects of air pollution on fertility in mammalian,[16] semen quality,[17] and success rate of IVF fertilization.[18] The review showed that previous studies have only emphasized broadly on the effect of air pollutants on fertility,[19,20] and most of the studies are related to male gametes,[21,22] probably because they can be easily obtained and analyzed, and few previous studies have been focused on oocytes and folliculogenesis. In this study, the main focus is finding clinically the effects of various air pollutants on fertility and understanding whether the female population is more susceptible to these harmful effects. Therefore, this systematic review aims to evaluate the available evidence for the effect of air pollution on women's fertility. The results of such a review can sensitize people and health officials to consider air quality.

Materials and Methods

Literature searches

The strategy of this research was a systematic review of research related to environmental air pollutants exposure and women's fertility or reproductive health. This analysis was performed according to PRISMA criteria. This research data was conducted with a comprehensive search strategy with a time limit from 2013 until July 2023 in PUBMED and the Cochrane Central Register of Controlled Trials. In this search, terms and descriptors related to air pollution and fertility were combined so that air pollution is the presence of pollutants or pollutants in the air (gases, suspended particles, or volatile organic chemicals) and they interfere with women's health or produce they interfere. In this research, approved filters were also considered for wider search and retrieval of cohort and case-control studies. These keywords were combined with Boolean operators in the investigated databases. Therefore, the search was as follows:

(((((((Air pollution [Title/Abstract]) AND (fertility [Title/Abstract])) OR (miscarriage [Title/Abstract])) OR (embryo quality [Title/Abstract])) OR (embryo development [Title/Abstract])) OR (pregnancy [Title/Abstract])) OR (implantation [Title/Abstract])) OR (live birth [Title/Abstract])

Paper screening

In this research, only articles published in English were selected. Eligibility criteria for this review included randomized trials, cohort studies, and case-control studies that analyzed the effects of air pollutants on female fertility. The studies that examined exposure to air pollutants and their effect on semen quality and also those on the effect of occupational exposure, tobacco exposure, or exposure to toxins were excluded. We also excluded non-environmental factors (e.g. alcohol, drugs) that were evaluated on fertility because they were not the main subject of the research and could distort the evaluation of outdoor air pollution on female infertility.

Data extraction

Data was extracted using standardized forms that recorded study design characteristics, participants, interventions and/or comparisons, and primary outcomes. Three independent authors (M.l), (F.E), and (F.R) assessed study eligibility, risk of bias, and extracted data. Disagreements were resolved by agreement and, by consensus with the four authors (H.GH) if necessary.

Results

The primary search retrieved 107 studies, and 63 were excluded by title/abstract screening based on the described exclusion criteria. Forty-four studies were met the criteria for review by both reviewers. In the second stage of the inclusion process, 31 of these 44 studies were excluded due to their designs that were not match the eligibility criteria, and 16 studies that were not RCT, case-control, or cohorts were excluded. Eleven studies were excluded because they did not report the interested outcomes, and four studies were excluded because the intervention was not evaluated. As it shown in Figure 1, finally, 13 studies had the inclusion criteria and were selected to be included in the study.

Outcomes

Table 1

Live birth

Three studies have analyzed the impact of air pollution on live births in the general population. The results of the Khadka study in 2021 in America showed that the exposure of pregnant mothers (more than 20 weeks) to $PM_{2.5}$ has a positive relationship with the mortality of newborn babies.[27] Balakrishnan *et al*.[24] and Wylie *et al*.[29] reported the negative effect of high levels of air pollution on live birth rates. The results of Wylie *et al*. showed that exposure to air pollution, especially fine particles of PM 2.5, NO2, and SO2, can decrease the live birth rate. Balakrishnan *et al*.[24] reported that a significant relationship was observed between birth weight loss and mother's exposure to pollutants such as PM 2.5 and CO.

Clinical pregnancy and implantation rates

In one study, it was shown that high concentrations of air pollutants have a significant detrimental effect on clinical pregnancy rates (PRs) and implantation rates.[33] Slama *et al.* evaluated the short-term effects of air pollution on 1916 women of reproductive age from the normal population during their first month of unprotected intercourse. They found a reduced

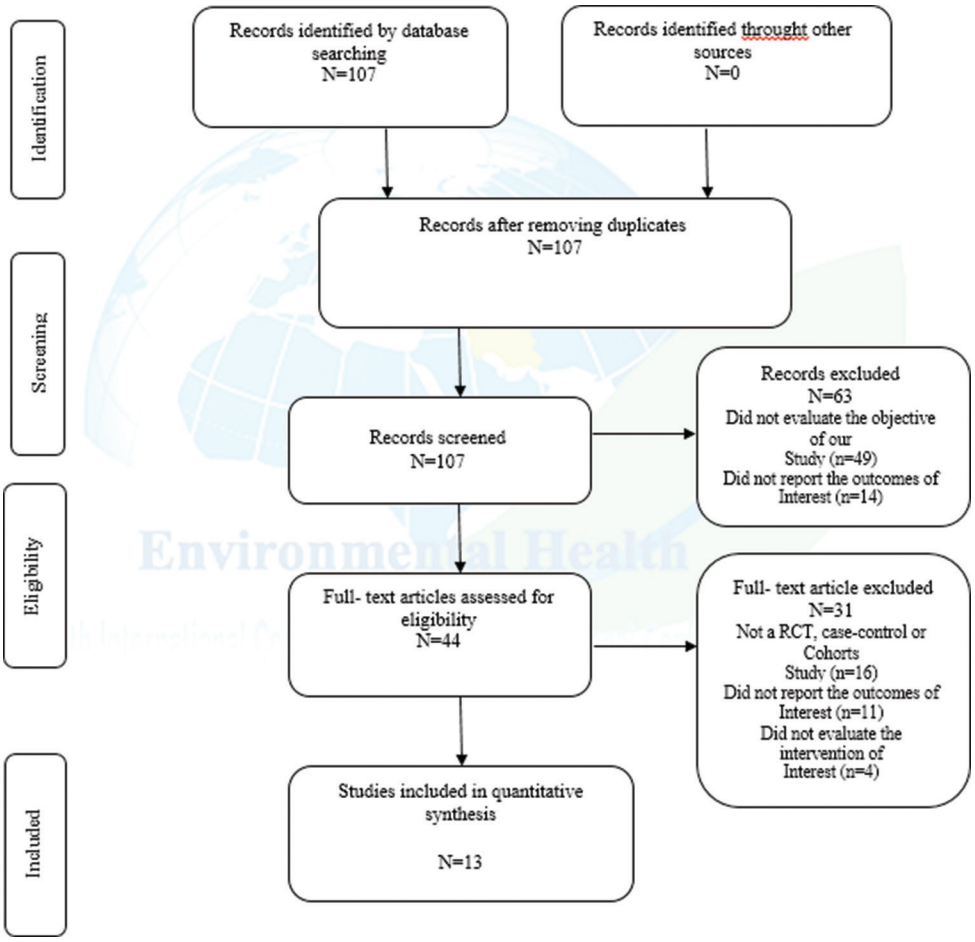

Figure 1: Flowchart describing the trial identification and selection process. RCT = randomized controlled trial

fertility ratio associated with higher concentrations of PM with an aerodynamic diameter of ≤2.5 μm (PM2.5) during this period (fertility ratio 0.78, 95% CI 0.65–0.94 per 10 μg per cubic meter increase in PM2.5 and higher NO2 concentrations (odds ratio 0.72, 95% confidence interval (CI): 0.53–0.97 per 10 μg/m3 increase in NO2), although this observation was not statistically significant. It seems that higher concentrations of sulfur dioxide (SO2) exposure are related with the reduction of PRs.[33]

Miscarriage

Two studies have analyzed the impact of air pollution on miscarriage in the general population. Quinn *et al*.[31] and Padula *et al*.[34] indicated a significant increase in the miscarriage risk of general population associated with exposure to high levels of NO2, $PM_{2.5}$, BC, CO, and pollution. Exposure to air pollution from $PM_{2.5}$, BC, and CO increases blood pressure in pregnant women less than 20 weeks, and this can cause the risk of miscarriage.

Embryo quality

Five studies have analyzed the impact of air pollution on embryo quality in the general population.[23,25,26,28,32]

Children of mothers exposed to high concentrations of PM_{10}, $PM_{2.5}$, NO_2, and SO_2 were associated with increase of birth defects such as heart disease, organ defects, and cleft palate.[23] Also, in another study, air pollutants (PM_{10}, O_3) significantly affected the increase of stress hormones and oxidative damage in fetal umbilical cord blood.[25] The results of the Ulziikhuu *et al*.[26] study also showed that the increase in air pollution caused by traffic during pregnancy is effective on the fetus's brain development. Therefore, a significant relationship exists between air pollution and defects in brain development. Two studies also showed a significant relationship between congenital disorder and respiratory infection due to a mother's exposure to pollutants such as $PM_{2.5}$.[28,32]

Fertility

The effect of air pollution on infertility or fertility rate in the general population has been analyzed in two studies. In an ecological study of Barcelona, a statistical significant relation was found in the decrease of fertility rate in general population and higher air pollution caused by traffic, especially in relation to the fraction of coarse PM (hazard ratio 0.882, 95% CI: 0.942–0.828).[1] In a prospective cohort, Mahalingaiah *et al*.[30] found that the risk of infertility in nurses was slightly increased in those living closer to a major road than those farther away (multivariable-adjusted hazard ratio 1.11, 95% CI 1.02–1.20).

Table 1: Information and results of epidemiological studies on the effect of exposure to pollutants in the general population

Author, year (ref. no.)	Study design	Population (*n*)	Pollutants/ variables analyzed	Results
Cheng Y, *et al*., 2023,[23]	An observational study	70 854 singletons with gestational age <20 weeks who were delivered at a large maternal and child healthcare center in Wuhan, China	PM10, PM2.5, NO2, and SO2	Maternal exposure to high PM10, PM2.5, NO2, and SO2 concentrations in the first trimester had a significant associated with elevated ORs of birth defects (ORs ranged from 1.13 to 1.23). For male fetuses, maternal exposed to high PM2.5 concentrations was associated with elevation of CHDs odd (OR 1.27, 95% CI 1.06 to 1.52). The ORs of birth defects were significantly increased in the cold season among women exposed to PM2.5 (OR 1.64, 95% CI 1.41 to 1.91), NO2 (OR 1.22, 95% CI 1.08 to 1.38), and SO2 (OR 1.26, 95% CI 1.07 to 1.47).
Balakrishnan, *et al*. 2023,[24]	An observational analysis	3200 non-smoking women who were pregnant, between 18 and 35 years of age, 9 weeks to less than 20 weeks of gestation	PM2.5, NO2, and SO2	An interquartile increase in mean prenatal PM2·5 exposure (74·5 μg/m^3) was associated with lower birth weight and gestational Z-scores (birth weight: -14·8 g [95% CI (CI): −28.7 to− 0·8]; gestational age Z-scores: −0·03 [−0·06 to 0·00], as did interquartile increases in black carbon (7·3 μg/m3 ; was -21·9 g [-37.7 to -6·1]; -0·05 [-0·08 to -0·01]). Carbon monoxide exposure was associated with these outcomes (1·7; -3·1 [-12·1 to 5·8]; -0·003 [-0·023 to 0·017]).
Zhu L, *et al*. 2023[25]	observational study	200 pregnant women and newborns	PM2.5, PM10, SO2, NO2, CO, O3, AQI	Mean values for AQI, PM2.5, PM10, SO2, NO2, and CO were higher in the warm season group (all $P < 0.001$). There was a positive correlation between PAHs, 8-OHdG levels in pregnant women and their infants, and approximate air pollutant concentrations (all $P < 0.05$). Based on the results of multiple linear regression analysis, it was found that air pollutants (PM10, 03) had a significant effect on the level of 8-OHdG in the umbilical cord blood of newborns, and its participation rate was high (R2=0.320). Based on the epidemiological questionnaire, a multiple linear regression model was created (R2=0.496).
Ulziikhuu B, *et al*. 2023[26]	The UGAAR randomized controlled trial	540 pregnant women	PM2.5	The intervention improved mean FSIQ (full-scale IQ) among children of mothers in the lowest (5.4 points; 95% CI: -0.8, 11.5) and higher (6.1 points; 95% CI: 0.5, 11.8) cortisol levels, but not among those whose mothers were in the middle level. Reducing air pollution during pregnancy is effective on the baby's brain develoPMent, and there is a connection between air pollution and defects in brain development.
Khadka A, Canning D. 2021[27]	Observational Cohort Analysis Using US Vital Records	10017357 live births 58913 infant deaths	PM2.5 exposure	Prenatal PM2.5 exposure was associated with infant mortality, and prenatal PM2.5 exposure was positively associated with infant mortality in all trimesters, although the relationship was strongest in the third trimester.
Barn P, *et al*. 2018[28]	Randomized controlled trial	540 participants (272 control and 268 intervention)	PM2.5	In an analysis of 429 term births, the intervention was associated with an 85 g (95% CI: 3, 167 g) increase in mean birth weight. Use of a high-efficiency particulate air (HEPA) filter air cleaner in a highly polluted environment is associated with higher birth weight only among term infants.
Wylie BJ, *et al*. 2017[29]	observational cohort study	239 pregnant women	CO, PM2.5	Low birth weight contributes to 60% of all infant deaths. Exposure to air pollution during pregnancy has been suggested as a risk factor. Exposure to CO and PM2.5 during pregnancy was relatively high and exceeded WHO air quality guidelines. Exposure to air pollution, especially fine particles, may adversely affect birth weight.
Mahalingaiah *et al*.,[30]	Prospective cohort	36,294 women	PM10; PM25-10; PM25; distance to roadway	A slightly increased risk was observed for those living closer to a major road compared to those further away, multivariate-adjusted HR=1.11 (CI: 1.02–1.20) for those reporting primary or secondary infertility., Is compatible. For women living closer to a major road, the HR for primary infertility was 1.05 (CI: 0.94–1.17), while for secondary infertility the HR was 1.21 (CI: 1.07–1.36). In addition, the HR for each 10 μg/m (3) increase in cumulative PM2.5-10 among women with primary infertility was 1.10 (CI: 0.96-1.27) and similarly in secondary infertility 1.10 (CI: 0.94-1.28).

Contd...

Table 1: Contd...

Author, year (ref. no.)	Study design	Population (*n*)	Pollutants/ variables analyzed	Results
Quinn AK, *et al*. 2016[31]	Randomized controlled trial	817 pregnant women	CO exposure	There was a significant positive association between CO exposure and diastolic blood pressure (DBP): on average, each 1 ppm increase in exposure to CO was associated with 0.43 mmHg higher DBP [0.01, 0.86]. There was also a non-significant positive trend for systolic blood pressure (SBP), which will lead to abortion.
Balakrishnan, *et al*. 2015[32]	Cohort	5 Cohort with 1200 participants in each cohort	PM2.5 and NO2	Developing models to predict exposure to PM2.5 in relation to community-level variables and also to explore interrelationships between PM2.5 concentrations and air toxics
Nieuwenhuijsen *et al*., 2014[1]	Ecological study		PM2.5; PM 10; PM coarse NO2; NOx; O 3, Absorbance PM2.5	A statistically significant reduction of fertility rates was found with increased traffic-related air pollution levels, particularly for the coarse fraction of particulate matter (IRR=0.87 95% CI 0.82, 0.94 per IQR).
Slama *et al*.,[33]	Retrospective cohort	1,916 women	PM2.5; NO_2; SO_2; O_3; carcinogenic-polycyclic aromatic hydrocarbons (c-PAH)	Acute and subacute PMs exposure revealed a tendency to higher rates of miscarriage and reduction of clinical pregnancy rate, although the results showed no statistical significant difference. PM2.5, coarse PM10, and PM10 exposures in 3D after adjusting for subacute exposure in the first sensitivity analysis showed a significant risk of miscarriage and an increased risk of no pregnancy in 3D. A second sensitivity analysis showed a significant risk of miscarriage for PM2.5 exposures in 3D and a significant risk of no pregnancy for PM2.5, coarse PM10, and PM10, especially in 3D. A correlation between nitrogen dioxide and reproductive outcomes was observed.
Padula *et al*.,[34]		1,723 women	PM10, PM 2.5, NO2, NO, CO, O3	Few odds ratios have confidence intervals not including 1.0. The odds of esophageal atresia increased for the highest to lowest traffic density ratio (aOR=2.8, 95% CI, 1.1–7.4) and PM10 exposure (aOR 4.9; 95% CI, 1.4–17.2). PM10 had relation with a reduced risk of hydrocephalus (aOR=0.3; 95% CI, 0.1-0.9) and CO was associated with lower risk of anotia/microtia (aOR=0.4; 95% CI, 0.2-0.8) and transverse limb deficiency. aOR=0.4; 95% confidence interval (CI), 0.2–0.9), again reflecting the highest versus lowest quartile comparison. There is a relationship between environmental pollutants and some structural abnormalities leading to miscarriage.

Discussion

In this systematic review, a significant relation was found between the increase in air pollution and the reduction of fertility health, live birth rates, embryo quality, fertility, implantation rates, and miscarriage in exposed women. These results suggest low fertility health rates are associated with traffic-related air pollution. This review has concluded four components of traffic pollution that can impair women's fertility.

- PM is a primary pollutant affecting air quality. It is a complex combination of solid and liquid particles suspended in the air and is various in size and composition. The diameter of the particles can be from PM2.5; "respirable" particles <2.5 μm that can penetrate the gas exchange zone of the lung up to PM10. Different "chest" particles with a diameter of fewer than 10 micrometers can penetrate inside. The results showed the significant association of specific material contamination with reduced fertility rates,[1,27,30] lower live birth rates,[24,29] and higher risk of miscarriage.[31,34]
- Nitrogen dioxide is the main source of human pollution of nitrogen oxides in the atmosphere, which is caused by the combustion of fossil fuels in stationary sources (heating, electricity generation) and motor vehicles. Under ambient conditions, nitric oxide is rapidly converted to atmospheric oxidants such as O3 to NO2.[2] It has been reported that NO2 can significantly increase the fertility rates in the general population,[34] although results for fertility rates are conflicting. Slama *et al*.,[33] confirmed negative impact on the fertility rate and found the association between the increase of PM2.5 and NO2 levels with a significant decrease in fertility, especially in the first month.
- The primary source of SO2 is the combustion of sulfur-containing fuels. In combustion, the sulfur present in the fuel is almost quantitatively converted to SO2; this metabolite reduces DNA synthesis.[23] According to the articles included in this review, a small increase in miscarriage rate in the general and infertile populations was associated with SO2. Zhu *et al*.[25] reported that SO2 exposure can affect infant health in the first trimester.
- The industrial combustion, car exhaust, and cigarettes are considered the main sources of carbon monoxide production.[2] It is from oxyhemoglobin and prevents the

absorption of oxygen by red blood cells. According to the results of the current review, there is a statistically significant relationship between CO and increased miscarriage rates.[31,34]

This study showed that air pollution-induced damage, including damage to the immune system, is most likely at critical stages of fetal development, as the pollutants transfer directly through the placenta and result in irreversible damage of dividing cells, which can potentially cause abortion. CO exposure to air pollution during pregnancy has increased circulating levels of carboxyhemoglobin and red blood cells, both indicators of fetal hypoxia.[25] Cheng *et al*.[23] suggested that in the case of poor air quality due to heavy traffic, healthy pregnancy should be promoted by education of fertile women to adopt safe lifestyle practices during pregnancy, including using high-efficiency particulate air filters (HEPA) indoors and promoting avoidance of outdoor activities.

There is relatively little information about the air pollution and its effect on female fertility, and we were able to include only thirteen articles in this systematic review. Contrary, there are more experimental data on the effects of pollutants on fertility in studies on experimental mammals that many of them from different groups have suggested lower number of offspring in rats exposed to air pollution.[35] In addition, the effects of air pollution on sperm quality were investigated in several studies that reported the harmful effect of air pollution on the morphology,[36] concentration,[37] and motility of the sperm.[38] Also, the effect of pollution from cooking with a gas stove and domestic air pollution was considered in many studies.[39-41]

In general, a significant association has been found between air pollution and fertility rates, although no prospective trials allow us to conclude causality, and it is only based on evidence from observational studies. Therefore, more prospective cohort studies are required to confirm these findings.

Conclusions

Air pollution harms women's fertility. These effects affect gamete's quality at the genetic and epigenetic level. These effects also alter fetal development. Studies have also reported an effect on fetal growth with increased miscarriages. It is difficult to identify the individual role of specific pollutants, as subjects in epidemiologic studies are usually exposed to multiple pollutants simultaneously. Since air pollution is everywhere and has many sources, it seems necessary to increase the awareness of people and government officials, especially in hygiene and health, to limit air pollutants as much as possible.

Authors' contributions

Latifi, M and Rahim, F participated in the collection of the data, performed the statistical analysis, and wrote the manuscript, equally Ahmadloo M and Pouladian N participated in the design of the study and helped to draft the manuscript. Allahbakhshian L substantial contributor to conception and design of the study, interpretation of data, revising of the manuscript critically, and has given final approval of the version to be published. All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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