Outdoor air pollution and human infertility: a systematic review

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Air pollution is a current research priority because of its adverse effects on human health, including on fertility. However, the mechanisms through which air pollution impairs fertility remain unclear. In this article, we perform a systematic review to evaluate currently available evidence on the impact of air pollution on fertility in humans. Several studies have assessed the impact of air pollutants on the general population, and have found reduced fertility rates and increased risk of miscarriage. In subfertile patients, women exposed to higher concentrations of air pollutants while undergoing IVF showed lower live birth rates and higher rates of miscarriage. After exposure to similar levels of air pollutants, comparable results have been found regardless of the mode of conception (IVF versus spontaneous conception), suggesting that infertile women are not more susceptible to the effects of pollutants than the general population. In addition, previous studies have not observed impaired embryo quality after exposure to air pollution, although evidence for this question is sparse. (Fertil Steril® 2016;106:897–904. ©2016 by American Society for Reproductive Medicine.)

Key Words: Air pollution, fertility, live birth, miscarriage

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Air pollution is one of the most important risk factors in our cities at present, and it affects the entire population living in urban areas. Since the study of air pollution and its effects became a topic of research interest, several studies have described its adverse events on the human health (1), for example, as a risk factor for cardiovascular (2–4) and respiratory diseases (5–7). The International Agency for Research on Cancer, the division of the World Health Organization that coordinates cancer research, has recently classified outdoor air pollution as being carcinogenic to humans (8). In terms of perinatal outcomes, some studies have shown a correlation between air pollution and adverse perinatal events, such as preterm delivery (9–11), low birth weight (12), and small size for gestational age (13).

Infertility has been increasing during recent decades, and one of the most important reasons for this are changes in lifestyle factors, especially a delay in the timing of motherhood (14, 15) which leads to lower ovarian reserve and poorer oocyte quality (16). Some reports (17, 18) have highlighted the effects of air pollution on mammalian fertility, semen quality (19–22), and fertilization success rates in IVF (23). More people are moving from rural to urban areas, and this displacement of the population to large cities is resulting in a dramatic increase in air pollution.

The past review in this field addressed the effect of air pollutants on fertility in a broad sense (23). That article included in the analysis the impact of these exposures in the animal model, aiming to understand the biological effect of these pollutants in the embryo development, the hatching process, the allocation and morphology of the inner cell mass (ICM), and what impact these changes had on the reproductive success. In addition, the investigators evaluated this impact on the general population as well as the subfertile population, and observed how certain outdoor air pollutants were associated with worse reproductive outcomes, although results were not consistent across the different studies. Since this latter review, two investigators have provided new data regarding the effects of air pollutants on spontaneous fertility in the general population (24, 25).

The focus of attention in clinical practice is centered in understanding the effects of different air pollutants on fertility, as well as knowing whether subfertile populations are more susceptible to these deleterious effects. The aim of the present systematic review

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is to evaluate currently available evidence on the impact of air pollution on fertility in humans.

MATERIALS AND METHODS

The study did not require approval by the Institutional Review Board because it is a systematic review. We adhered to the preferred reporting items recommended by the PRISMA statement, reporting the results of systematic reviews (26). We registered the details of our protocol for this systematic review on PROSPERO and can be accessed at CRD42016036383.

Search Strategy

We performed an exhaustive electronic search up until February 2016 in MEDLINE and The Cochrane Central Register of Controlled Trials. Our search combined terms and descriptors related to air pollution and fertility, where air pollution was considered to be the presence in the air of contaminants or pollutant substances (gases, particulate matter, or volatile organic chemicals) that interfere with human health, or that produce other harmful environmental effects (27). We modified the search strategy to comply with the requirements of each database. We added validated filters to widen the search and retrieve cohort and case-control studies. We used the following keywords, combining them with 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)*. We only included articles written in English, Spanish, French, or Italian. We screened the reference lists of all of relevant articles and overviews.

Eligibility Criteria

The review included randomized controlled trials, cohort studies, and case-control studies that analyzed the impact of air pollutants on fertility. We excluded studies that analyzed exposure to air pollutants during the course of a pregnancy or their effect on semen quality, as well as those that assessed the effect on fertility of occupational exposure, tobacco exposure, or exposure to nonenvironmental toxins (e.g., alcohol, drugs of abuse), because they were not the object of the review and could confound assessment of outdoor air pollution on female infertility.

Outcome Measures

Our primary outcome was live birth, although secondary outcomes of interest included miscarriage, clinical pregnancy, implantation rate, embryo quality, infertility, and time to pregnancy. Outcomes were defined according to the terminology recommended in the International Committee Monitoring Assisted Reproductive Technologies, World Health Organization terminologies (28), and the updated and revised nomenclature for describing early pregnancy events (29).

Data Extraction

The data were collected using standard forms in which the characteristics of the study design, participants, interventions and/or comparisons, and main results were recorded. Two independent authors (M.G.-C. and M.A.C.V.) judged study eligibility, assessed risk of bias, and extracted the data. Discrepancies were resolved through agreement, and where necessary, by reaching consensus with a third author (B.J.).

Assessment of Risk of Bias

We assessed risk of bias in each study by assessing the domains suggested in the Newcastle-Ottawa scale for evaluating the quality of nonrandomized studies (30). This instrument assesses three specific domains for each study, depending on its design: selection of participants, comparability, and outcome ascertainment.

RESULTS

A total of 368 studies were returned by the initial electronic search, and 353 were excluded by title and/or abstract screening according to the exclusion criteria described. The remaining 15 studies were considered eligible by one or both reviewers. During the second phase of the inclusion process, 2 of these 15 studies were excluded because their study design did not comply with the eligibility criteria, and 4 because they did not evaluate the intervention or the outcomes of interest. Finally, nine studies met the inclusion criteria and were included. The trial identification and selection process can be seen in Figure 1. The two reviewers achieved good agreement in the selection of trials for inclusion (weighted κ 0.63, 95% confidence interval [CI] 0.35–0.86).

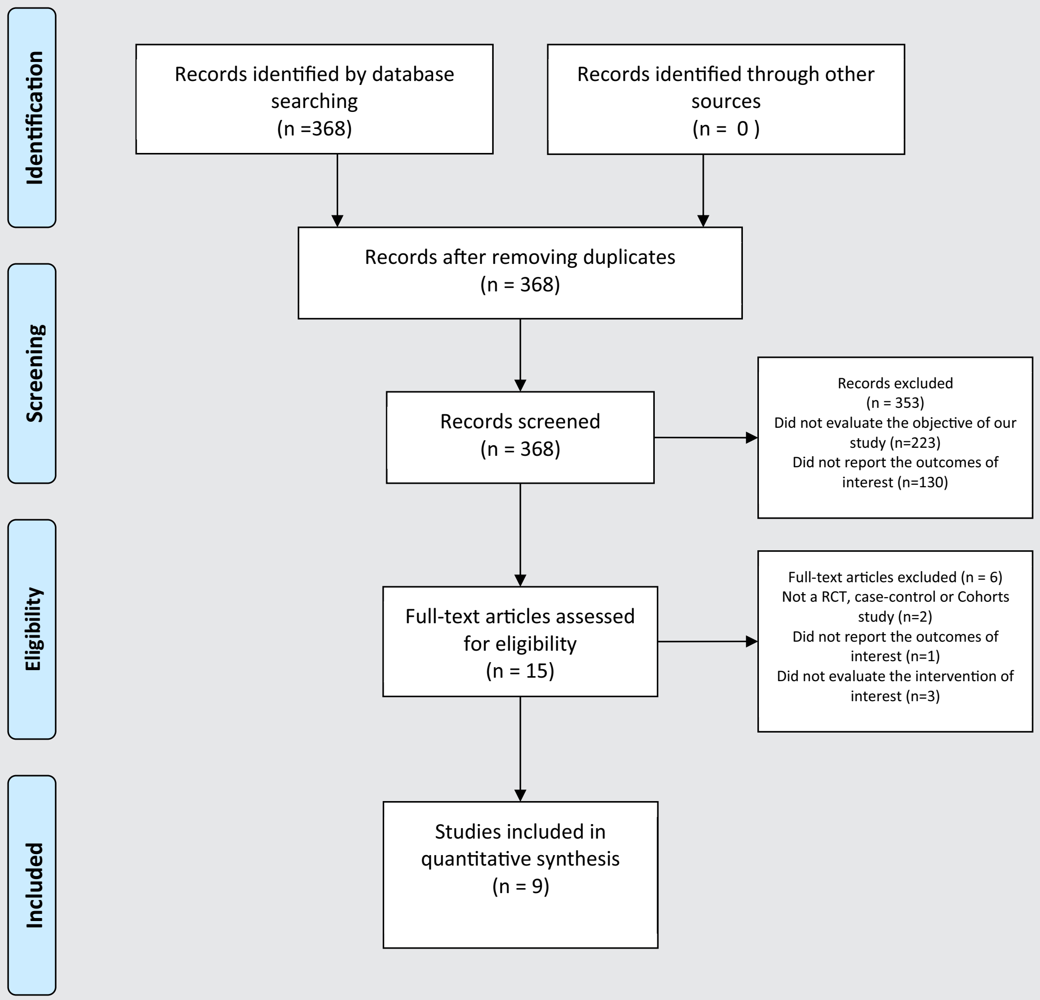
After an exhaustive analysis, the included studies were grouped according to the type of population under study. Thus, we included six epidemiological studies (24, 25, 31–34) conducted in the general population (Table 1) and three epidemiological studies (35–37) involving women undergoing IVF/ET (Table 2). We present results are according to the outcomes analyzed in the review.

Outcomes

Live birth. Three studies reported a negative impact of high levels of air pollution on live birth rates (35–37). Legro et al. (36) assessed the effect of air pollution among women undergoing IVF/ET. In that study, they found that increased concentrations of nitrogen dioxide (NO_2) had a negative impact on live birth rate at all phases of the IVF cycles, particularly as a result of in exposure from ET onward (odds ratio [OR] 0.76, 95% CI 0.66–0.86). Surprisingly, higher levels of ozone (O_3) during ovulation induction were associated with increased live birth rates, and when these higher exposures occurred after ET a significant decrease in the live birth rate was observed. However, this latter association became not significant after adjusting for NO_2 levels (Pearson's correlation coefficient, −0.44) (Table 2).

In addition, Perin et al. (37) also observed an adverse effect on live birth rate of before conception short-term exposure to high levels of particulate matter (PM) that are $<10\ \mu m$ in diameter (PM_{10}; Q_4 period), regardless of the method of conception (Table 2). However, Perin et al. (35) did not observe this detrimental effect in a retrospective study with a similar design (Table 2).

FIGURE 1



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

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Clinical pregnancy and implantation rates. Three studies have reported a significant detrimental effect of high concentrations of air pollutants on clinical pregnancy rates (PRs) and implantation rates (31, 35, 36). Slama et al. (31) analyzed the short-term effects of air pollution on PR in 1,916 women from the general population during the first month of unprotected intercourse, and observed a decrease in the fecundability ratio associated with higher concentrations of PM with an aerodynamic diameter $\leq 2.5\ \mu m$ ($PM_{2.5}$) (fecundability ratio 0.78, 95% CI 0.65–0.94 per of 10 $\mu g/m^3$ increase in $PM_{2.5}$) and higher concentrations of NO_2 (fecundability ratio 0.72, 95% CI 0.53–0.97 per of 10 $\mu g/m^3$ increase in NO_2) during this period. In addition, exposure to higher concentrations of sulfur dioxide (SO_2) appeared to be associated with a decrease in PRs, although this observation was not statistically significant (Table 1).

In a sample of women undergoing IVF/ET, Legro et al. (36) described a decrease in clinical PR associated with higher recorded levels of $PM_{2.5}$ at the IVF clinic during embryo culture (OR 0.90, 95% CI 0.82–0.99). In contrast, Perin et al. (35) did not observe a similar negative impact of high PM_{10} exposure on clinical PRs and implantation rates of women undergoing IVF/ET.

Miscarriage. Faiz et al. (32) and Mohorovic et al. (33) reported a significant increase in risk of miscarriage in the general population in association with exposure to high levels of NO_2 and SO_2, and products of coal combustion, respectively (Table 1). Green et al. (34) found no statistically significant association between maximum annual average traffic within 50 m and increased risk of miscarriage in the general population, but did observe a significant negative impact in their subanalyses of African Americans and nonsmokers in the higher percentiles of traffic exposure (Table 1).

Regarding studies conducted in women undergoing IVF/ET, there was a significant increase in the rate of miscarriage among women in the highest quartile of exposure to PM_{10} in the study by Perin et al. (35) (OR 5.05, 95% CI 1.04–25.51). The other study by Perin et al. (37) also described an increase

TABLE 1

Characteristics 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			
Mahalingaiah et al., 2016 (24)	Prospective cohort	36,294 women	PM_{10}; $PM_{25\text{-}10}$; PM_{25}; distance to roadway	Pollutant	Hazard ratios primary and secondary infertility risk		95% CI
				PM_{10}	1.06		0.99–1.13
				$PM_{25\text{-}10}$	1.10		0.99–1.22
				PM_{25}	1.05		0.93–1.20
				Distance to roadway (m)			
				0–199	1.06		1.02–1.20
				200+	1.00		(referent)
Nieuwenhuijsen et al., 2014 (25)	Ecological study		$PM_{2.5}$; PM_{10}; PM_{coarse} NO_2; NO_x; O_3, Absorbance $PM_{2.5}$	Pollutant	Risk estimate for fertility		95% CI
				NO_2	0.974		0.974–1.003
				NO_x	0.987		0.957–1.018
				$PM_{2.5}$ Absorbance	0.992		0.992–1.024
				PM_{10}	0.994		0.966–1.023
				PM_{coarse}	0.882		0.828–0.942
				$PM_{2.5}$	0.984		0.954–1.015
Slama et al., 2013 (31)	Retrospective cohort	1,916 women	$PM_{2.5}$; NO_2; SO_2; O_3; carcinogenic polycyclic aromatic hydrocarbons (c-PAH)	Pollutant	FR adjusted for potential cofounders (per 10 $\mu g/m^3$ increase in the pollutant level)		95% CI
				$PM_{2.5}$	0.78		0.65–0.94
				NO_2	0.72		0.53–0.97
				SO_2	0.94		0.85–1.04
Faiz et al., 2012 (32)	Retrospective cohort	343,077 total births	$PM_{2.5}$; NO_2; SO_2; CO	Pollutant (interquartile range) in first trimester	OR for miscarriage (adjusted for known risk factors and neighborhood socioeconomic status)		95% CI
				$PM_{2.5}$ (4 $\mu g/m^3$)	1.15		0.96–1.37
				NO_2 (10 ppb)	1.16		1.03–1.31
				SO_2 (3 ppb)	1.13		1.01–1.28
				CO (0.4 ppm)	1.14		0.98–1.32
Mohorovic et al., 2010 (33)	Prospective cohort	260 women	Products of coal combustion (SO_2; NO_2; CO_2; CO; suspended particles; other products)		Clean period	Exposure period	*P* value
				Miscarriages (number)	4	10	.0369
Green et al., 2009 (34)	Prospective cohort	4,979 women	Traffic pollutants: NO_2, O_3, $PM_{2.5}$, PM_{10}, CO_2, CH_4, CO, H_2S, NMHC (non-methane hydrocarbons), NMOC (non-methane organic compounds), SO_2, sulphur, THC (total hydrocarbons)	Traffic metric: maximum daily traffic within 50 m [percentile (range)]	OR for miscarriage (adjusted for known risk factors and socioeconomic status)		95% CI
				75–89th (1.090–15.199)	0.91		0.68–1.21
				>90th (>15.200)	1.18		0.87–1.60
				>90th and African American	3.11		1.26–7.66
				>90th and nonsmokers	1.47		1.07–2.04

Note: CI = confidence interval; FR = fecundability ratio associated with exposure (average of the study period exposure). A value below 1 indicates a decreased probability of pregnancy; OR = odds ratio; PM = particulate matter; see text for abbreviations of chemicals.

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TABLE 2

Characteristics and results of epidemiological studies on the effect of exposure to pollutants in women undergoing IVF/ET.

Author, year (ref. no.)	Study design	Population (N)	Criteria for inclusion in IVF study	Pollutants analyzed	Results			
Perin et al., 2010 (35)	Retrospective cohort	348 women	First IVF/ET cycle due to male factor infertility	PM_{10}		Live birth (%)		*P* value
					Q_1 period (PM_{10} levels $\leq$30.48 $\mu g/m^3$)	41.5		
					Q_2 period (PM_{10} levels 30.49–42.00 $\mu g/m^3$)	41.5		.968
					Q_3 period (PM_{10} levels 42.01–56.72 $\mu g/m^3$)	46.2		.721
					Q_4 period (PM_{10} levels >56.72 $\mu g/m^3$)	33.8		.224
Legro et al., 2010 (36)	Retrospective cohort	7,403 women	First IVF cycle from three centers	$PM_{2.5}$; PM_{10}; SO_2; NO_2; O_3		OR of live birth (95% CI)		
						Per 0.01 ppm increase NO_2	Per 0.02 ppm increase O_3	
					Average daily concentration (ADC) from medication start to oocyte retrieval (patient's home)	0.80 (0.71–0.91)	1.26 (1.10–1.44)	
					ADC from oocyte retrieval to ET (patient's home)	0.87 (0.79–0.96)	1.06 (0.96–1.18)	
					ADC from ET to pregnancy test—14 d (patient's home)	0.76 (0.66–0.86)	1.23 (1.07–1.41)	
					ADC from ET to the date of live birth (patient's home)	0.76 (0.56–1.02)	0.62 (0.48–0.81)	
Perin et al., 2010 (37)	Retrospective cohort	531 women	Infertile women vs. women who had conceived naturally for the first time	PM_{10}		Miscarriage (%) [OR]		*P* value
						Natural conception	IVF conception	.000
					$Q_{1–3}$ period (PM_{10} levels <56.72 $\mu g/m^3$)	13.7	14.5	
					Q_4 period (PM_{10} levels >56.72 $\mu g/m^3$)	30.2 [2.72]	28.3 [2.32]	
						Live birth (%)		
						Natural conception	IVF conception	
					$Q_{1–3}$ period (PM_{10} levels <56.72 $\mu g/m^3$)	86.3	85.5	
					Q_4 period (PM_{10} levels >56.72 $\mu g/m^3$)	69.8	71.7	

Note: CI = confidence interval; OR = odds ratio; PM = particulate matter; see text for abbreviations of chemicals.

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in OR of miscarriage in women in the highest quartile of exposure (OR 2.58, 95% CI 1.63–4.07), in the general and subfertile population, with an increase in 3% per unit increase in follicular phase PM_{10} ($P<.001$). This study also described no differences in the miscarriage rate between the general and the subfertile population within the same quartile of exposure.

Embryo quality. Perin et al. (35) also studied the effect of PM_{10} on embryo quality in women undergoing IVF/ET. This group did not observe any significant differences between subgroups of patients.

Fertility. Two studies have analyzed the impact of air pollution on sterility or fertility rates in the general population. In an ecological study in Barcelona city, Nieuwenhuijsen et al. (25) observed a statistically significant reduction in fertility rates in the general population in association with higher traffic-related air pollution, particularly in relation to the coarse fraction of PM (incidence risk ratio 0.882, 95% CI 0.828–0.942), and in a prospective cohort of nurses Mahalingaiah et al. (24) observed a small increase in risk of infertility among individuals living closer to a major road than those living further away (multivariable adjusted hazard ratio 1.11, 95% CI 1.02–1.20).

Assessment of the Risk of Study Bias

We analyzed the quality of the cohort studies (24, 25, 31–37) in the epidemiological group according to the Newcastle-Ottawa scale (30) (Supplemental Table 1). All studies showed low risk of bias in terms of participant selection and the outcomes ascertained. Only the study by Mohorovic et al. (33) failed to include the details required to evaluate selection bias. However, we observed moderate risk of bias in terms of comparability between cohorts (25, 31, 33–35). We were unable to quantify publication bias because of the methodological variability between the studies was included.

DISCUSSION

In this systematic review, we found a small significant association between elevated air pollution and diminished fertility outcomes in the exposed population, including rates of live births, fertility, and miscarriage. These results indicate that lower fertility rates may be linked to traffic-related air pollution.

Since the last published systematic review that explored fertility outcomes in relation to exposure to air pollutants (23), two new articles (24, 25) have been published in the same field of research. This new research shows that human reproduction is influenced by coarse PM and distance to the roadway.

In this review, we have identified four components of traffic pollution that could contribute to impair human fertility.

1. Particular matter (or aerosols) is one of the main pollutants that affect air quality. It is a complex mixture of solid and liquid particles that remain suspended in the air, and vary in size and composition. Particle diameter can vary from 2.5 μm (PM2.5; "respirable" particles <2.5 μm that can penetrate into the gas exchange region of the lung) to 10 μm (PM10; "thoracic" particles <10 μm in diameter that can penetrate into the lower respiratory system) (1). Particular matter has been found to be significantly associated with reduced fertility rates (24, 25, 31), reduced live birth rates (32, 35), and increased risk of miscarriage in IVF (35, 37) (Tables 1 and 2);
2. Nitrogen dioxide is the main source of anthropogenic emissions of nitrogen oxides into the atmosphere, due to the combustion of fossil fuels in stationary sources (heating, power generation) and in motor vehicles. Under ambient conditions, nitric oxide is rapidly transformed into NO_2 by atmospheric oxidants such as O_3 (1). In the general population, NO_2 has been associated with a significant increase in miscarriage rate (32–34), although results for fertility rate are inconsistent (25, 31). A significant decrease in rates of live birth was also observed among women undergoing IVF (36) (Table 2);
3. The main source of SO_2 is the combustion of fuels containing sulphur; on combustion, the sulphur in the fuel is converted almost quantitatively to SO_2 (38). This metabolite causes a decrease in DNA synthesis, and has been found to induce chromosomal aberrations in in vitro studies (39). In the articles included in this review, SO_2 was associated with a slightly elevated rate of miscarriages in the general (32–34) and the subfertile population (36) (Tables 1 and 2);
4. Carbon monoxide (CO). The main sources of CO are industrial combustion, automobile exhaust, and cigarettes (40). The effect of CO is the result of its ability to unite directly with hemoglobin in red blood cells, forming carbon monoxide–hemoglobin (carboxyhemoglobin), which is more stable than oxyhemoglobin and prevents red blood cells from absorbing oxygen. In our review, we observed a statistically significant association between CO and elevated miscarriage rates (32–34) (Table 1).

There is relatively little data on this issue, and we have only been able to include nine articles in this systematic review. In contrast, there are more experimental data available regarding the effect of pollutants on fertility in experimental mammals. Various groups have described a reduction in the number of offspring in mice exposed to air pollution (21, 41, 42). This evidence highlights the biological plausibility of the observed fertility decline in humans in relation to air pollution, which may operate through various mechanisms. [1] Veras et al. (42) point to endocrine disruption as the mechanism of action, by altering the normal function of the neuroendocrine-gonadal axis and producing hormonal imbalance. In addition, heavy metals contained in PM have been associated with ovotoxicity. This study by Veras et al. suggests that PM decreases the number of antral follicles, which can cause premature ovarian failure. [2] Effects on sperm quality: several studies have reported a deleterious effect of air pollution on sperm morphology (43), concentration (19), and motility (20); [3] Another possibility is damage, including immune-mediated injury, during critical stages of embryo development, where direct transfer of pollutants through the placenta leads to irreversible damage of dividing cells, potentially resulting in miscarriage (44, 45). In this regard, women exposed to CO in air pollution during pregnancy have been found to have increased levels of carboxyhemoglobin and circulating nucleated red blood cells, both of which are markers of fetal hypoxia (46). Other investigators have also described a disruption of the normal pattern of segregation of the first two cell lines, ICM and trophoectoderm (17); [4] Finally, changes in the vascular compartment or uterine environment in relation to air pollution before pregnancy have been reported in women who have miscarried (42).

Our systematic review has several limitations that need to be considered. There is marked heterogeneity between the studies included in terms of the type of population analyzed (general population vs. women undergoing IVF) as well as the outcomes reported. Regarding the latter, there were inconsistencies in the definitions used in each study that analyzed fertility and miscarriage rate. In addition, the cause and duration of infertility and miscarriages was not recorded in studies performed in the general population (24, 25, 31–34) or among women undergoing IVF (35–37), and thus was not considered in this analysis.

The pollutants analyzed and the reference levels for each pollutant vary between studies. Regarding measures of exposure to these air pollutants, there is also potential for misquantification of individual exposure in participants. Most studies used measurements of ambient pollutant to estimate individual exposure at participants' residential addresses, disregarding the average time spent at home or elsewhere, the type of residence, and the use of air purification systems, among other factors. However, several studies (47–49) support the use of ambient measurements as surrogates for estimating individual exposure to air pollutants. In addition, the use of registry data could mask changes in participants' residential address. Mohorovic et al. (33) estimated exposure according to proximity to a coal-fired thermal power plant, daily temperatures, rain, and other factors, which reduces the accuracy of the estimation.

Regarding IVF laboratories, several studies (50–52) have documented that the use of air filters, and of different types of filters, modified air quality in the laboratory, which could potentially affect PRs and implantation rates. However, none of the studies performed among women undergoing IVF reported information about the type of filters used in their laboratories, or about air quality in the IVF laboratory.

It is also important to mention the impact on fertility of participants' age, smoking habits, or other factors. The studies included in this review did not all consistently adjust for these confounding factors. In addition, there are no standard protocols for ovarian stimulation among women undergoing IVF, which could potentially lead to bias.

Another relevant limitation is the dearth of prospective cohort studies in this field. Most human studies use historic cohorts (24, 25, 34–37), therefore the validity of the results relies largely on the quality of the records available.

In summary, there is a significant association between air pollution and fertility rates in general and subfertile population, although there are no prospective trials that would allow us to draw a conclusions about causality, but rather just evidence from observational studies. Thus, further prospective cohort studies are needed to confirm these findings.

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SUPPLEMENTAL TABLE 1

Assessment of the quality of the studies with a cohort design according to the New-Castle Ottawa Scale (30).

Author, year (ref. no.)	Selection	Comparability	Outcome
Mahalingaiah et al., 2016 (24)	****	**	***
Niewenhuijsen et al., 2014 (25)	****	*	**
Slama et al., 2013 (31)	****	**	***
Faiz et al., 2012 (32)	****	*	***
Mohorovic et al., 2010 (33)	***	*	**
Green et al., 2009 (34)	****	**	**
Perin et al., 2010 (35)	****	*	**
Legro et al., 2010 (36)	****	**	***
Perin et al., 2010 (37)	****	*	***

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