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).