Ambient air pollution and the risk of pregnancy loss: a prospective cohort study

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Objective: To estimate the association of pregnancy loss with common air pollutant exposure. Ambient air pollution exposure has been linked to adverse pregnancy outcomes, but few studies have investigated its relationship with pregnancy loss.
Design: Prospective cohort study.
Setting: Not applicable.
Patient(s): A total of 343 singleton pregnancies in a multisite prospective cohort study with detailed protocols for ovulation and pregnancy testing.
Intervention(s): None.
Main Outcome Measure(s): Timing of incident pregnancy loss (from ovulation).
Result(s): The incidence of pregnancy loss was 28% ($n = 98$). Pollutant levels at women's residences were estimated using modified Community Multiscale Air Quality models and averaged during the past 2 weeks (acute) and the whole pregnancy (chronic). Adjusted Cox proportional hazards models showed that an interquartile range increase in average whole pregnancy ozone (hazard ratio [HR] 1.12, 95% confidence interval [CI] 1.07–1.17) and particulate matter $<2.5\ \mu m$ (HR 1.13, 95% CI 1.03–1.24) concentrations were associated with faster time to pregnancy loss. Sulfate compounds also appeared to increase risk (HR 1.58, 95% CI 1.07–2.34). Last 2 weeks of exposures were not associated with loss.
Conclusion(s): In a prospective cohort of couples trying to conceive, we found evidence that exposure to air pollution throughout pregnancy was associated with loss, but delineating specific periods of heightened vulnerability await larger preconception cohort studies with daily measured air quality. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Pregnancy loss, fetal loss, spontaneous abortion, air pollution, fine particulate

It is estimated that pregnancy loss occurs in approximately 28% of pregnancies in prospective cohorts with preconception enrollment and longitudinal follow up (1, 2). Pregnancy loss can be a traumatic life event associated with a variety of psychological outcomes including post-traumatic stress disorder, grief, anxiety, depression and guilt, as well as marital conflict (3). Women who experience pregnancy loss can also develop septic miscarriage, a serious and potentially life-threatening uterine infection (4). The etiology of pregnancy loss is likely to be multifactorial and may come from both intrinsic and extrinsic characteristics including genetics, demographics, lifestyle factors, history of miscarriage, and various environmental exposures (5–7). However, the causes of most cases are unknown.

Ambient air pollution is a ubiquitous exposure that warrants special attention due to its well-established relationship with adult morbidity and mortality (8–10), and more recently, adverse pregnancy outcomes including preterm birth and low birthweight (11, 12). Numerous studies have suggested that exposures to various air pollutants, such as fine particulate matter, can induce oxidative stress (13, 14) and systemic inflammatory markers

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(15, 16), which are capable of compromising and crossing the maternal-fetal blood barrier and ultimately perturbing fetal growth and development (17).

Despite biologic plausibility, no prospective cohort studies with preconception enrollment and daily follow-up including the most vulnerable period for loss (7 weeks after conception) have investigated the relationship between air pollution and pregnancy loss. Four studies (18–21) looked at this and suggested some evidence of harmful association, but they are limited by important study design shortcomings including the lack of a prospective follow-up and dependence on nearby stationary air pollution monitors. Given that many pregnancy losses occur early before some women are aware that they are pregnant, assessment of pregnancy loss status is challenging without a detailed objective prospective assessment. In addition, no existing studies were conducted in the United States.

The objective of this study was to investigate the association between exposure to criteria air pollutants (i.e., six common pollutants that are used to regulate air quality in the United States) and the incidence of pregnancy loss in a prospective cohort of couples attempting pregnancy. This prospective design allowed for the ascertainment of losses with detailed timing information.

MATERIALS AND METHODS

Study Design and Population

The Longitudinal Investigation of Fertility and the Environment study was a prospective cohort study, conducted between 2005 and 2009, among 501 couples from 16 counties in Michigan ($n = 104$) and Texas ($n = 397$), as fully described elsewhere (1). Briefly, couples were eligible to participate if they met the following criteria: [1] they were married or in a committed relationship, [2] the female partner was aged 18–40 years and the male partner was ≥ 18 years, [3] they were able to communicate in English or Spanish, [4] they were off contraception for not more than two menstrual cycles before enrollment, [5] neither partner had clinically diagnosed infertility, and [6] the female partner had menstrual cycles between 21 and 42 days and they had received no contraceptive hormonal injections within the previous 12 months. Before enrollment, all women had a pregnancy test to ensure they were not already pregnant. Couples were followed through pregnancy or up to 1 year of actively trying to become pregnant. Of the 501 couples in the original cohort, we excluded couples who did not have an observed pregnancy ($n = 154$), did not have a singleton pregnancy ($n = 3$), or those we were unable to geocode ($n = 1$), leaving 343 couples eligible for analysis. This study was approved by the institutional review boards for all collaborating institutions, and all couples provided written informed consent before any data collection.

Exposure Assessment

We obtained hourly concentrations of common criteria air pollutants comprising carbon monoxide, nitrogen oxides, nitrogen dioxide, ozone, particulate matter with diameter ≤ 10 and ≤ 2.5 μm (PM_{10} and $PM_{2.5}$), and sulfur dioxide. These pollutants have been linked to morbidity and mortality in the nonpregnant population (8, 9). Given the lack of literature exploring specific constituents of fine particulate matter that are responsible for health effects, we also assessed five fine particulate constituents including elemental carbon, organic compounds, sulfate compounds, ammonium compounds, and nitrate compounds. All pollutants were estimated using modified Community Multiscale Air Quality models, which estimated air pollution concentrations at a 12×12 km^2 resolution using inputs from several sources including local emission data, meteorological factors, and atmospheric photochemical properties of pollutants. To reduce measurement error, modeled estimates from Community Multiscale Air Quality models were fused with actual observed levels of air pollution measured at local air monitors in the US Environmental Protection Agency Air Quality System using inverse distance weighting as previously published (22).

To estimate exposure, couples' residential addresses were geocoded using ArcGIS (ESRI) and spatially linked to the gridded outputs from Community Multiscale Air Quality models. Exposures were then assigned as the estimated average daily concentrations in the couple's residential grid. Exposures were averaged for 2 weeks before ovulation in the pregnancy cycle, the last 2 weeks of pregnancy, and whole pregnancy (estimated from the date of ovulation, as determined by the fertility monitor through loss or birth) to capture potential preconception, acute, and chronic effects.

Outcome and Covariate Assessment

The main outcome of interest is time to pregnancy loss from the date of ovulation as measured by peak LH to loss or birth. Upon enrollment, female partners were instructed to use a fertility monitor (Clearblue Easy), which was demonstrated to detect ovulation in 91% of women undergoing the gold standard of vaginal ultrasound (23), and a digital home pregnancy test (Clearblue Easy), which has demonstrated sensitivity and reliability for detecting ≥ 25 mIU/mL of hCG (24). Women were also provided daily journals to record whether they had taken a pregnancy test, the test results, and/or menses. A pregnancy loss was defined as a subsequent negative urine pregnancy test after a positive test, a clinically confirmed pregnancy loss, or onset of menstruation depending on gestational age. Couples experiencing a pregnancy loss could reenter the study, but the analysis focused on the first observed pregnancy loss. Detailed information on the presumed etiologic reason for the loss (i.e., genetic, anatomic) was not available.

At the baseline visit, information on maternal demographics and lifestyle was obtained through self-report followed by standardized anthropometric measurements including height and weight for the calculation of before pregnancy maternal body mass index (BMI). Women were also asked to complete a daily diary to record their lifestyle choices including cigarette smoking, caffeine intake, and daily multivitamin intake. Covariates included maternal age (≤ 24, 25–29, 30–34, ≥ 35 years), maternal race (White, non-White), maternal education (high school graduate or GED, some college or technical school, college graduate, or higher), before pregnancy BMI (underweight, normal weight, overweight, obese), household income (<\$30,000, \$30,000–49,999, \$50,000–69,999, $\geq$\$70,000),