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 μm (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® 2018;109:148–53. ©2017 by American Society for Reproductive Medicine.)
Key Words: Pregnancy loss, fetal loss, spontaneous abortion, air pollution, fine particulate

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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, ≥$70,000),

parity conditional on gravidity (nulligravid, gravid/nulliparous, parous), average early pregnancy caffeine intake, and early pregnancy multivitamin intake. Maternal and paternal serum cotinine concentration (continuous) was also measured. Last, season of conception and study site were also considered as covariates to account for temporal variation in risk as well as area-related differences between sites.

Statistical Analysis

The χ^2 or Kruskal-Wallis tests were used to evaluate the differences in characteristics between women who had a pregnancy loss and those who did not. Unadjusted and adjusted Cox proportional hazards models (25) were used to model time to loss to estimate the hazards ratio (HR) and 95% confidence intervals (CIs) for pregnancy loss for an interquartile range (IQR: from the 25th to 75th percentile) increase in pollutant concentration. Due to evidence that air pollution may reduce fecundability (26), restricting our study cohort to couples who achieved pregnancy may introduce bias by excluding women with higher exposure (i.e., bias the results toward the null). Although a preliminary assessment of exposure during the first 10 days of follow-up suggested no substantive differences in exposure between couples who attained pregnancy and those who did not, to account for this potential selection issue, we used the original cohort to calculate the conditional probability of achieving pregnancy. Each couple who became pregnant in the present analysis received a weight inversely proportional to the estimated probability of not being censored (i.e., became pregnant). The weights were computed using a logistic regression model with baseline covariates, stabilized and used in the final models evaluating the associations between air pollution and pregnancy loss (27, 28). We considered an interaction effect between after gestational age (1–4 weeks vs. >4 weeks) and air pollution. but no significant interaction was detected. Last, to account for multiple comparisons, post hoc adjustment for *P* values were performed using the Benjamini–Hochberg false discovery rate controlling method (29), which is the preferential method in deciding about falsely rejected hypotheses.

RESULTS

There were 97 pregnancy losses (28%) in this analysis. Compared with their counterparts, women who experienced a loss were older, had less education, had more incomes, had higher BMIs, had more prenatal caffeine intake, were less adherent to multivitamin intake during early pregnancy, had higher serum cotinine levels, and were more likely to have an estimated date of conception in the fall (Table 1). Mean air pollution levels were low to moderate and were below the national standards (Supplemental Table 1, available online). The correlation matrix between pollutants shows that most pollutants were positively correlated with Spearman's correlation coefficients ranging from 0.18–0.79; however, ozone was inversely correlated with other criteria air pollutants with correlation coefficients ranging from -0.24 to -0.49 (Supplemental Table 2, available online).

Average chronic whole pregnancy exposures to ozone and $PM_{2.5}$ were positively associated with the risk of pregnancy loss. An IQR increase (from the 25th to 75th percentile) in ozone and $PM_{2.5}$ exposures were, respectively, associated with a 12% (HR 1.12, 95% CI 1.07–1.17), and 13% (HR 1.13, 95% CI 1.13–1.24) increased risk of pregnancy loss (Table 2). The association with $PM_{2.5}$ seemed to have been driven by sulfate compounds (HR 1.58, 95% CI 1.07–2.34 for an IQR increase) (Table 2). When whole pregnancy

TABLE 1

Characteristics of cohort participants by pregnancy loss status (n = 343 couples).

Characteristics	Loss (n = 97) n	Loss (n = 97) %	No loss (n = 246) n	No loss (n = 246) %	*P* value
Maternal age (y)					.11
≤24	5	5.2	20	8.1	
25–29	42	43.3	116	47.2	
30–34	31	32.0	85	34.6	
≥35	19	19.6	25	10.2	
Maternal race					.95
White	81	83.5	203	82.5	
Non-White	15	15.5	41	16.7	
Maternal education					.63
High school graduate/ GED	6	6.2	9	3.7	
Some college or technical school	11	11.3	37	15.0	
College graduate or higher	79	81.4	197	80.1	
Annual income ($)					.24
<30,000	50	51.6	137	55.7	
30,000–49,999	6	6.2	28	11.4	
50,000–69,999	12	12.4	32	13.0	
≥70,000	25	25.8	44	17.9	
Parity conditional on gravidity					.92
Nulligravous	37	38.1	96	39.0	
Gravous, nulliparous	6	6.2	20	8.1	
Parous	53	54.6	128	52.0	
Maternal BMI before pregnancy (kg/m^2)					.36
Underweight, <18.5	2	2.1	4	1.6	
Normal weight, 18.5–24.9	42	43.3	123	50.0	
Overweight, 25–29.9	23	23.7	65	26.4	
Obese, ≥30	30	30.9	54	22.0	
Average early pregnancy caffeine intake (daily cups)					<.0001
<2	78	80.4	232	94.3	
≥2	19	19.6	14	5.7	
Season of conception					.18
Spring	22	22.7	73	29.7	
Summer	22	22.7	64	26.0	
Fall	31	32.0	52	21.1	
Winter	22	22.7	57	23.2	
Early pregnancy multivitamin intake[a]	0.74 ± 0.03		0.84 ± 0.01		<.0001
Early pregnancy maternal serum cotinine (ng/mL)	14.8 ± 5.6		9.7 ± 3.2		.39
Paternal serum cotinine (ng/mL)	44.9 ± 11.0		46.9 ± 8.7		.01

Note: Data presented as n (percent) or mean ± standard deviation, unless indicated otherwise. BMI = body mass index.

[a] The proportion of days during early pregnancy reported taking vitamin.

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TABLE 2

Associations between chronic whole pregnancy average air pollutant exposures and time to pregnancy loss.

Pollutants	HR (95% CI)[a] Unadjusted[b]	Adjusted[b,c]	Adjusted and truncated[b,c,d]
Criteria pollutants			
CO	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
NO_2	1.04 (1.00, 1.08)	1.03 (0.98, 1.08)	1.03 (0.98, 1.08)
NO_x	0.95 (0.92, 0.98)	0.98 (0.95, 1.02)	1.01 (0.98, 1.04)
O_3	1.09 (1.06, 1.12)	1.12 (1.07, 1.17)	1.13 (1.08, 1.18)
PM_{10}	0.98 (0.96, 1.01)	1.02 (0.99, 1.06)	1.02 (0.99, 1.06)
$PM_{2.5}$	1.34 (1.24, 1.44)	1.13 (1.03, 1.24)	1.13 (1.03, 1.24)
SO_2	1.21 (0.97, 1.50)	1.01 (0.77, 1.34)	1.01 (0.76, 1.33)
Particulate constituents			
Elemental carbon	0.36 (0.11, 1.14)	0.79 (0.16, 3.86)	0.94 (0.23, 3.84)
Ammonium ions	1.43 (0.83, 2.47)	1.59 (0.72, 3.52)	1.68 (0.76, 3.72)
Nitrate compounds	0.93 (0.76, 1.14)	0.82 (0.59, 1.13)	0.80 (0.57, 1.13)
Organic compounds	1.19 (0.90, 1.57)	0.76 (0.54, 1.08)	1.28 (0.97, 1.69)
Sulfate compounds	1.22 (0.89, 1.67)	1.58 (1.07, 2.34)	1.68 (1.11, 2.53)

Note: BMI = body mass index; CI = confidence interval; CO = carbon monoxide; HR = hazards ratio; NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; O_3 = ozone; PM_{10} = particulate matter <10 μm; $PM_{2.5}$ = particulate matter <2.5 μm; SO_2 = sulfur dioxide.

[a] HRs were obtained for an interquartile range increase in exposures; all models were adjusted for inverse probability of being pregnant in the original cohort.

[b] Models for particulate constituents were adjusted for total $PM_{2.5}$ exposure.

[c] Models were adjusted for season, study site, maternal age, maternal race, parity condition on gravidity, maternal education, income, early pregnancy caffeine intake, maternal BMI, early pregnancy adherence to multivitamin intake, maternal blood cotinine level, and paternal blood cotinine level.

[d] Whole pregnancy exposures for ongoing pregnancies were truncated at 18 weeks to ensure similar length of gestation.

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exposures were truncated to 18 weeks for all ongoing pregnancies to ensure comparable length of exposures (all losses in our sample occurred before 18 weeks), the results remained unchanged (Table 2). We also adjusted for history of prior loss and of thyroid disease in a sensitivity analysis and the results were essentially unchanged (not shown). Acute exposures during the gestational week of the loss and for the prior week appeared to be unrelated to risk with the sole exception of elemental carbon (Supplemental Table 3, available online). Preconception exposures also appeared to be unrelated to risk (not shown).

DISCUSSION

In this prospective cohort of couples attempting pregnancy, who resided in geographic areas with low-to-moderate background levels of air pollution, we found evidence that chronic exposures to certain air pollutants including ozone and $PM_{2.5}$ throughout pregnancy are associated with pregnancy loss. In contrast, no association was observed for exposure to air pollutants before conception or in the 2 weeks preceding a loss. These findings suggest that chronic exposure may be more detrimental than acute exposures during sensitive windows. According to the formula (formula 4) for finding population attributable fraction presented by Rockhill (30), the 12% and 13% excess risk associated with an IQR increase in chronic whole pregnancy ozone and $PM_{2.5}$, respectively, is equivalent to about 9% excess pregnancy losses. In other words, about 9 of the 98 observed losses may have been prevented if exposures were at the bottom 25th percentile for ozone or $PM_{2.5}$. Our findings are strengthened by use of a novel exposure model that accounts for emissions, weather, and atmospheric chemical interactions among pollutants, attention to relevant covariates, and robust sensitivity analyses.

Our findings for $PM_{2.5}$ are generally consistent with the findings of the few existing studies on air pollution and pregnancy loss. Specifically, an ecologic study from 2009-2011 in Mongolia (19), using air pollution levels measured by local air monitors suggested that $PM_{2.5}$ during the study period was positively associated with fetal death before 20 weeks of gestation. In contrast, across 15 hospitals in Tianjin, China, fetal loss within 14 weeks was associated with higher exposure to sulfur dioxide (OR 19.76, 95 % CI 2.34–166.71 per IQR increase) and total suspended particles (OR 2.04, 95 % CI 1.01–4.13) measured at the nearest local monitor in the first month of pregnancy (20). In Tehran, Iran (21), whole pregnancy exposures to nitrogen dioxide (OR 1.04, 95% CI 1.02–1.05 per ppb increase) and ozone (OR 1.09, 95% CI 1.06–1.13) were associated with increased risk of spontaneous abortion before 14 weeks gestation. Contrary to the findings of the Chinese and Iranian studies (20, 21), our analysis suggested no association with sulfur dioxide or nitrogen dioxide and the associations we observed with particulate matter and ozone are less strong. We speculate that these discrepancies may be due to [1] the lower background concentrations of air pollutants in the United States compared with those in China/Iran (31), and [2] potential misclassification due to the use of fixed local monitor stations, which cannot account for small spatial variation in air pollution concentrations resulting in false-negative findings. The Chinese study (20) also suggested that the susceptible window of exposure may be the first month of pregnancy in contrast to our finding for continual exposure throughout pregnancy. In geographic areas where exposures to air pollution is relatively low (i.e., our study sites), prolonged exposure may be more important for early loss. We previously found that chronic, whole pregnancy, exposure and acute exposure to ozone in the week before delivery was associated with

stillbirth (≥23 weeks gestation) (32), suggesting that there may be a more consistent effect of ozone on pregnancy loss across gestation. Consistent with our findings, an Italian study (18) with relatively lower background air pollution found no association with nitrogen dioxide, but did observe that a 10-unit increase in exposures to particulate matter and ozone concentration was associated with 19.7% and 33.6% increased risk of spontaneous abortion, respectively.

Although the biological mechanisms responsible for the association between air pollution and pregnancy loss remains to be elucidated, our findings are biologically plausible. As previously mentioned, exposures to various air pollutants, such as fine particulate matter, can induce oxidative stress (13, 14) and systemic inflammatory markers (15, 16), which are capable of compromising as well as crossing the maternal-fetal blood barrier and ultimately perturbing fetal growth and development (17). In utero exposure to particulate matter has been found to increase oxidative makers in cord blood plasma (33) and oxidative stress early in gestation can interfere with placental development (34). Studies have also shown that exposure to air pollution can interfere with implantation (26) and induce chromosomal or structural anomalies (35), all of which are relevant for early loss.

Previous studies largely relied on pregnancies reaching clinical care and follow-up, and thereby miss the majority of losses occurring before entry into care. Generally speaking, these studies have not accounted for selection bias due to pregnancy loss (36). Our findings provide added perspective that specific pollutants may increase risk of early loss during a window typically not measured at the population level.

This study has some limitations that are important for the interpretation of findings. First, although we used a spatially and temporally flexible model to estimate exposure around the residences, we had no information on individual exposures or daily activity patterns during pregnancy. This lack of data may have caused exposure misclassification if couples happened to move or work away from home (37). However, given that losses occur early in gestation and most people who move during pregnancy relocate within a short distance (37), this lack of data may not have profoundly affected our results (38). In addition, the decreased variation in exposures likely biased our results toward the null, which can explain the lack of associations with some pollutants but cannot explain the positive associations. We also did not have information on indoor pollution level, but we adjusted for serum cotinine levels, which took away some the variation related to smoking, a major source of indoor exposure.

Our findings cannot be readily extrapolated to other adverse pregnancy outcomes, such as gestational age or birth size, without in-depth investigation. As an initial inquiry into this exposure, we sought to focus on pregnancy loss that can be exceedingly hard to capture given the preponderance of losses at early gestational ages and often before pregnant women are recruited into cohort studies. Our findings do support continued investigation of air pollution and pregnancy outcomes beyond the scope of our article for a more complete understanding of its implications for a spectrum of reproductive outcomes. Last, the lack of data on specific cause of loss did not allow us to perform a more detailed investigation. This in part reflects the distribution of time to loss, which is skewed (as expected) to earlier gestational ages. On the same note, we chose to assess pregnancy loss without further categorization (39) given no clear established standard endocrine criteria for defining loss (40).

Despite limitations, our study is the first prospective obstetric cohort that was designed to accurately assess early pregnancy loss when many women are otherwise unaware of their pregnancy. This study design also allowed us to account for potential issues associated with excluding women who were unable to conceive due to high air pollution exposure. The modified Community Multiscale Air Quality models allowed us to combine estimated data to observed concentrations at local air monitors to reduce measurement errors resulted from mathematical models. Finally, this is the first study to simultaneously investigate the specific components of $PM_{2.5}$ that could drive the observed association.

In conclusion this prospective cohort of couples attempting pregnancy in areas with low-to-moderate background pollution levels, we found chronic exposures to $PM_{2.5}$ and ozone throughout the entire pregnancy are associated with pregnancy loss. Although more research is needed to replicate these findings and to understand the biologic mechanisms underlying this relationship, this study represents an important step in identifying potentially modifiable risks for pregnancy loss. Meanwhile, our findings suggest that pregnant women may benefit from adapting their behavior during air quality alerts, such as avoiding outdoor activities when the air quality is poor, similar to the recommendation for other vulnerable groups such as people with asthma or other respiratory disease.

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