

Running Title: Acute Air Pollution and Pregnancy Loss

Acute Effects of Air Pollutants on Spontaneous Pregnancy Loss: A Case-Crossover Study

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ABSTRACT

Objective: To investigate the relationship between acute exposure to air pollutants and spontaneous pregnancy loss.

Design: Case-crossover study.

Setting: An academic emergency department (ED).

Patient(s): A total of 1,398 women who experienced a spontaneous pregnancy loss events from 2007-2015.

Intervention(s): None

Main Outcome Measure(s): Odds of spontaneous pregnancy loss.

Result(s): We found that a 10 ppb increase in 7-day average levels of nitrogen dioxide (NO₂) was associated with a 15% increase in the odds of spontaneous pregnancy loss (odds ratio (OR)= 1.15; 95% CI 1.00-1.32; p=0.04). A 10 µg/m³ increase in 3-day and 7-day averages of fine particulate matter (PM_{2.5}) were associated with increased risk of spontaneous pregnancy loss, but the associations did not reach statistical significance (OR_{3-day average}=1.09; 95 CI 0.99-1.20; p=0.05) (OR_{7-day average}=1.11; 95 CI 0.99-1.24; p=0.06). We found no evidence of increased risk for any other metrics of NO₂ or PM_{2.5} or any metric for ozone (O₃).

Conclusions: Unlike previous work, we found that short term exposure to elevated levels of air pollutants were associated with higher risk for spontaneous pregnancy loss.

Keywords: Air pollution, female reproductive effects, adverse pregnancy outcomes, PM₁₀-PM_{2.5}-ultrafine, NO₂

Introduction

Ambient air pollution poses a significant risk to population health, increasing risk for both morbidity and mortality at all ages [1-3]. Currently, air pollution is associated with multiple adverse obstetric outcomes, including pregnancy induced hypertensive disorders, neonates small for gestational age, preterm birth, low birth weight, and stillbirth [4-7]. During early gestation, both placental and fetal developments are established, and exposure to deleterious agents can lead to significant damage. The underlying mechanism for adverse pregnancy outcomes is hypothesized to be a result of oxidative stress, systemic inflammation, [8-10] and compromised placental growth and function [11, 12]. Despite biological and epidemiological evidence of such effects, however, a limited number of studies have investigated the relationship between air pollution and spontaneous pregnancy loss. Most [13-20], but not all [21] of the available literature has found an increased risk of spontaneous pregnancy loss and air pollutant exposure and results vary by pollutant and demographic factors. Additionally, many studies have been ecological in nature or limited by small sample size. Supplementary Table 1 shows a summary of results of published studies examining this association. The heterogeneity of results may be due to unobservable personal factors or misclassification of exposure and further investigation is needed to elucidate the effect of air pollutants on spontaneous pregnancy loss, particularly the effects during acute exposures [22].

The University of Utah Emergency Department (UUED) services a large urban area known as the Wasatch Front. This region is an area of unique topography where temperature inversions create high concentrations of air pollutants in the winter for limited periods of time, at levels deemed unhealthy by the United States Environmental Protection Agency (EPA)[23]. Physicians practicing in UUED noted anecdotal increases in incidence of spontaneous pregnancy loss during these inversion events. Given these observations, we conducted a case-crossover study to examine the risk of spontaneous pregnancy loss among women who presented to the UUED from 2007-2015 with short-term exposures to fine particulate matter (PM_{2.5}, <2.5 μm in aerodynamic diameter), nitrogen dioxide (NO₂), and ozone (O₃). Because the underlying mechanisms linking air pollution and early pregnancy loss have not been identified, we performed an exploratory analysis examining various exposure time windows and pollutant metrics.

Material and Methods

We identified cases of spontaneous pregnancy loss diagnosed in the UUED by extracting data from the University of Utah Enterprise Data Warehouse (UU EDW) using the following diagnosis codes (ICD-9-CM: 634.xx, 632.xx, 637.9; ICD-10: O03.4, O03.6, O03.9). We identified a total of 1,577 events in the UU EDW from 2007-2015. We excluded 73 events that occurred to women residing outside the state of Utah at the time of spontaneous pregnancy loss. We excluded an additional 106 events due to data quality issues. Our final sample consisted of 1,398 spontaneous pregnancy loss events that occurred prior to 20 weeks gestation. This study was approved by the Institutional Review Board of the University of Utah (IRB_00104032). Sample inclusion criteria are found in Figure 1.

Study Design

We used a case-crossover study design to analyze the acute effects of short term exposure to air pollution. The case-crossover design is characterized by each subject serving as her own control and acute exposure before an event is compared to a similar window of exposure on days not associated

with the event [24], The case-crossover design increases efficiency and eliminates control-selection bias, making it useful for examining acute changes in air pollution exposure. We considered case dates as the day of presentation to the UUED. We compared exposure levels prior to the case date to exposure levels prior to the control dates, i.e. other “referent” times, thus controlling for all short-term time-varying risk factors (such as smoking, seasonal patterns, socio-economic status, and comorbidities) and time-invariant risk factors (such as age, race/ethnicity, birth cohort, and genetic predisposition).

Referent Selection

We used a time-stratified approach for referent period selection. We selected referent days for each individual as the same day of the week as the event for the calendar month and year, which resulted in 3-4 referent periods per event day. We selected this strategy to control for any bias associated with time trends, overlap bias, increase efficiency [24], and control for season and day of the week by design.

Air Quality Measures

We obtained air pollution data from the EPA’s Air Quality System (AQS) Data Mart [25]. We determined population-weighted centroids for every residential zip code based Census 2010 block group population totals. Using topographic features, we delineated 6 air basins within the Wasatch Front as areas where lateral air movement would be reduced due to mountain ranges and basin, and assigned each monitoring station to the air basin where it was located using ArcGIS © (ver 9.3, Redlands, CA). We estimated daily PM_{2.5}, NO₂, and O₃ levels for each zip code centroid using inverse distance weighting of all observations from monitoring stations located in the same air basin as the zip code centroid. The benefit of this method is that we were able to assign values at the zip code level, rather than county-level measurements from the raw data.

We then calculated exposure measurements as the average daily concentrations of the day of the spontaneous pregnancy loss and the preceding two days of PM_{2.5}, NO₂, and O₃. We calculated the average of the 3-day averages for the case/control date and 2 days prior (i.e. lag0, lag1, and lag2) 7-day averages for the case/control date and 6 days prior (i.e. lag0, lag1 – lag6), 3-day maximum value, and 7-day maximum value. Descriptive statistics for each pollutant and metric can be found in Table 1.

Statistical Analysis

We estimated the association between pollutant concentrations and spontaneous pregnancy loss using conditional logistic regression clustered at the event level. All analyses were completed using SAS 9.4.

Results

Table 2 displays the descriptive statistics of the sample ($N_{\text{events}}=1398$). The sample was largely comprised of non-Hispanic White (53.6%) and Hispanic women (38.0%). The average age at admission was 28 years.

Figure 2 shows the results of the conditional logistic regression. We found a 15% statistically significant increase in the odds of spontaneous pregnancy loss per 10 ppb increase in 7-day average NO₂ (OR= 1.15; 95% CI 1.00-1.32; $p=0.04$). This means that, from the 25th (10.3 ppb) to 75th (24.7 ppb) percentile of 7-day average NO₂ in Utah during this time period, the risk of spontaneous pregnancy loss is increased by 11.1%. A 10 $\mu\text{g}/\text{m}^3$ increase in 3-day and 7-day averages of PM_{2.5} were associated with increased risk of spontaneous pregnancy loss, however the associations did not reach significance at the

$p < 0.05$ threshold ($OR_{3\text{-day average}} = 1.09$; 95 CI 0.99–1.20; $p = 0.05$) ($OR_{7\text{-day average}} = 1.11$; 95 CI 0.99–1.24; $p = 0.06$). A similar pattern was observed for the 3-day maximum value of PM_{2.5} ($OR = 1.07$; 95 CI 0.99–1.14; $p = 0.07$). We did not find a statistical association between other metrics of NO₂ or PM_{2.5} or any metric of O₃. We found that 7-day averages or maximums provided the best model fit for NO₂. We did not find any substantive differences in 7-day or 3-day metrics for PM_{2.5} or for O₃.

Discussion

The results of this study provide evidence that acute elevated levels of ambient air pollutants, specifically NO₂, are associated with spontaneous pregnancy loss. There are several possible biological mechanisms by which air pollution could contribute to spontaneous pregnancy loss including oxidative stress to the developing fetus, maternal endocrine disruption, and systemic maternal inflammation leading to abnormal placentation and growth abnormalities. Approximately 50% of early pregnancy spontaneous pregnancy loss are attributed to non-chromosomal abnormalities [26] and maternal exposure to combustion particles is associated with oxidative damage to DNA and lipids [27] which could be detrimental to growing fetuses. Exposure to air pollution has also been shown to inhibit embryo implantation, which is a risk factor for spontaneous pregnancy loss [28]. We found the highest risk for spontaneous pregnancy loss occurred with a high 7-day average exposure to NO₂. Previous meta-analyses have shown NO₂ exposures were related to an increased risk in cardiac defects including coarctation of the aorta ($OR = 1.17$; 95 CI 1.00–1.36) and Tetralogy of Fallot ($OR = 1.20$; 95 CI 1.02–1.42) [29], which supports a DNA damage mediated pathway of embryonic disruption. We also found an increased risk for spontaneous pregnancy loss with exposure to PM_{2.5}, though the estimates did not reach statistical significance. Because both PM_{2.5} and NO₂ are emitted from mobile sources, however, the results of our study add to a growing body of evidence that primary emissions contribute to spontaneous pregnancy loss.

Interestingly, results from previous studies have been mixed. Ha and colleagues found chronic exposures to O₃ and PM_{2.5} during pregnancy were positively associated with the risk of pregnancy loss ($HR_{O_3} = 1.12$, 95 CI 1.07–1.17; $HR_{PM_{2.5}} = 1.13$, 95 CI 1.13–1.24), but not NO₂ ($HR_{NO_2} = 1.03$; 95 CI = 0.98–1.08)[16]. In two recent ecological studies, Dastoorpoor and colleagues found a significant relationship between NO₂ and premature birth, but not spontaneous pregnancy loss [13] and Enkhmaa and colleagues found a strong correlation between NO₂ and spontaneous pregnancy loss ($r > 0.8$) [15]. The observed differences between studies may be due to underlying differences in the composition of air pollution in different geographical regions or due to methodological differences between our studies. Ha and colleagues used a prospective cohort from Michigan and Texas, and while their study did examine risk at varying time points, the exposures were measured through the entire pregnancy and thus were largely chronic in nature. In contrast, we tested for associations between spontaneous pregnancy loss and exposures to pollutants over a much shorter duration in time (3 days, 7 days) in an urban area where air pollution is highly varied based on weather patterns and temperature inversions. Because Utah has the lowest smoking rates in the US and unique topography, our study area provided for a unique place to conduct this natural experiment. While the two aforementioned ecological studies show a relationship between pregnancy outcomes and NO₂, our study benefits from self-matching and, thus allowing us to find an effect at the individual patient level.

This study has some notable limitations and strengths. We were not able to determine the exact gestational age of the fetuses in our study and therefore we could not test for differences in the effect

by period of exposure. Additionally, this study only captured women who presented to the UUED for care. Many other women may have sought outpatient care through their Obstetric or Primary Care providers. Spontaneous pregnancy loss that occurs within the first several weeks of gestation may not be documented if a woman is unaware of the pregnancy and perceives the event as a normal menstrual cycle or if the non-viable pregnancy is not detected until the patient's first ultrasound. These factors will limit the absolute number of cases documented in our study period. Additionally, we were able to document time of symptom presentation, but not time of actual embryonic or fetal demise. Because we cannot ascertain the exact time of spontaneous pregnancy loss, we performed an exploratory analysis with varying exposure time periods in order to investigate differences by exposure window. Strengths of this study include the large sample size (N=1398) and study design. The case-crossover design allows us to control for unobservable personal characteristics that do not change over the period of study including other risk factors for spontaneous pregnancy loss such as maternal age at conception, alcohol and caffeine consumption, smoking, and previous spontaneous pregnancy loss [30].

Our results provide important insights for clinicians and patients making health care decisions and further study is needed in order to establish medical recommendations. Women who have other risk factors for spontaneous pregnancy loss may be a target group for future interventions. Additionally, the health effects of air pollution disproportionately affect some sub-populations over others. For example, NO₂ exposure in the US has been shown to be higher for nonwhites, individuals living below the poverty level, and individuals with less than a high school education [31]. Our sample was comprised of approximately 38% Hispanic women. In contrast the proportion of Hispanic women of childbearing age in the study area during the study period was approximately 21% [32]. Future studies should test for differences in effect of NO₂ and other air pollutants in this and other potentially sensitive subpopulations. As more evidence emerges that sperm epigenetics are essential for not only initiation, but also maintenance of a successful pregnancy [33], the association between air pollution and spermatogenesis should also be explored. Importantly, because we found increased risk with pollutants directly related to industrial and auto emissions, the results of this study can be utilized for potential public policy changes as well as personal behavior modification when particular environmental pollutants are high.

Conclusions

Our findings suggest that pregnant women are at higher risk for spontaneous pregnancy loss during short periods of increased air pollution.

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Figure 1: Sample selection schematic of University of Utah (UU) Emergency Department (ED) patients who experienced a spontaneous pregnancy loss (2007-2015).

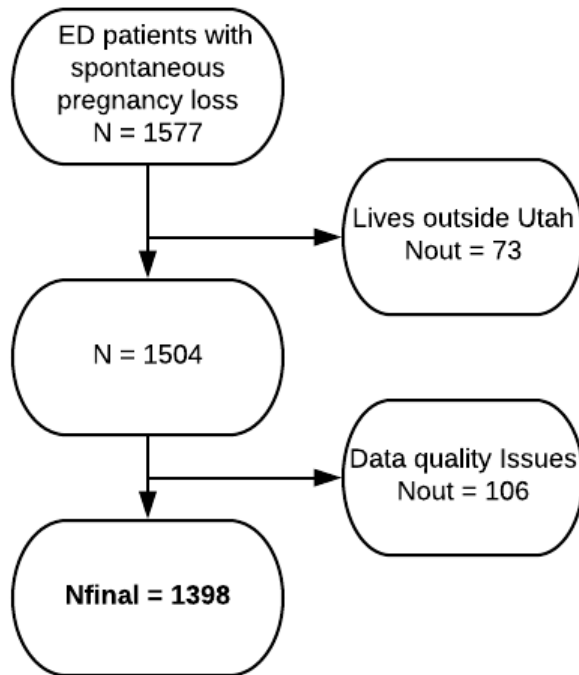


Figure 2: Forest plot of the effect of ambient air pollutants on spontaneous pregnancy loss by pollutant metric (2007-2015). Results of conditional logistic regression. Error bars indicate 95% Confidence Intervals.

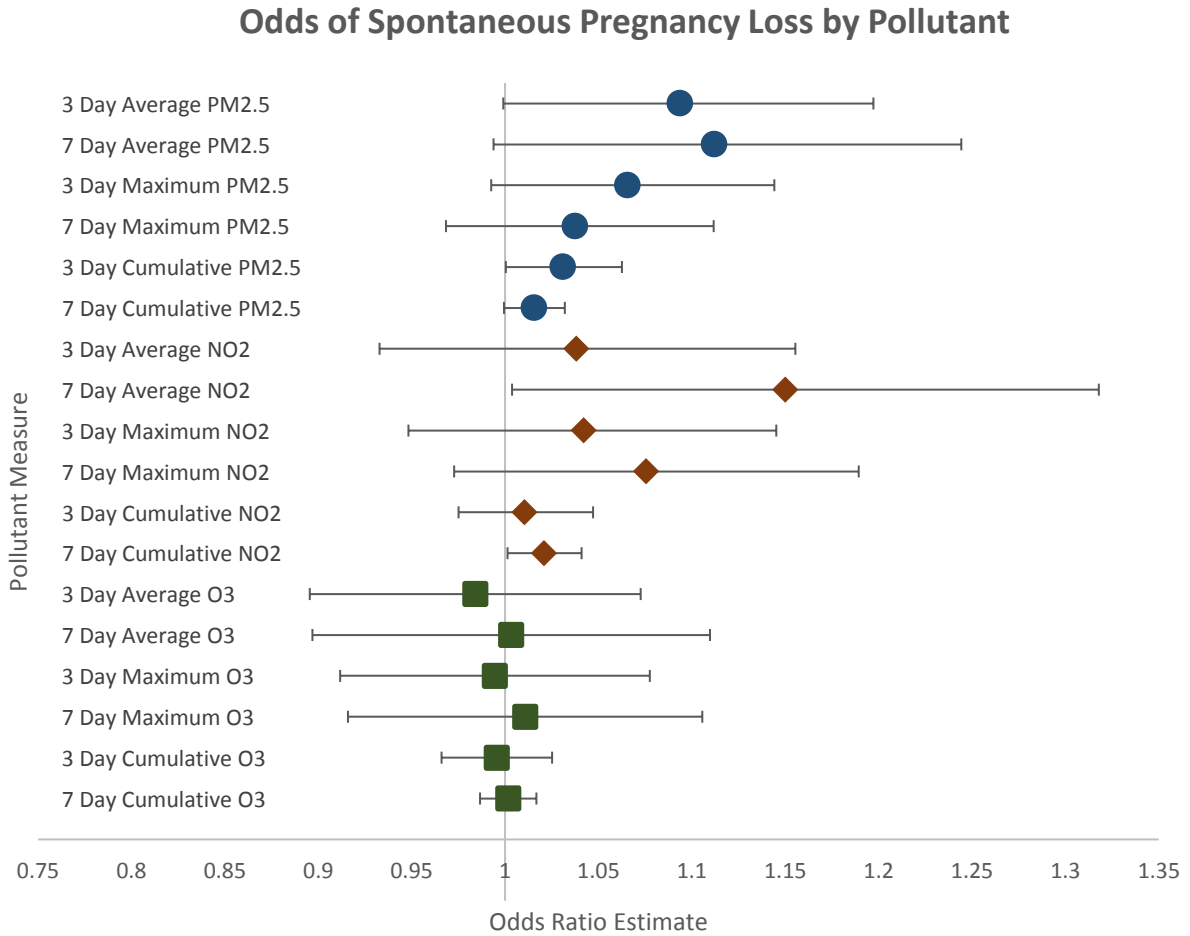


Table 1: Descriptive Statistics of Ambient Air Pollutants

Generated Metric	Min	Mean	Max
Average 3 day PM2.5 ($\mu\text{g}/\text{m}^3$)	0.0	9.0	80.0
Average 7 day PM2.5 ($\mu\text{g}/\text{m}^3$)	0.3	9.0	73.0
Maximum value 3 day PM2.5 ($\mu\text{g}/\text{m}^3$)	0.0	12.0	84.0
Maximum value 7 day PM2.5 ($\mu\text{g}/\text{m}^3$)	2.0	16.0	84.0
Average 3 day O3 (ppb)	2.0	40.0	90.0
Average 7 day O3 (ppb)	4.0	40.0	80.0
Maximum value 3 day O3 (ppb)	2.0	40.0	90.0
Maximum value 7 day O3 (ppb)	8.0	50.0	90.0
Average 3 day NO2 ($\mu\text{g}/\text{m}^3$)	0.8	18.0	67.0
Average 7 day NO2 ($\mu\text{g}/\text{m}^3$)	0.5	18.0	65.0
Maximum value 3 day NO2 ($\mu\text{g}/\text{m}^3$)	0.8	23.0	74.0
Maximum value 7 day NO2 ($\mu\text{g}/\text{m}^3$)	3.0	27.0	76.0

TABLE 2: Descriptive Statistics of Sample

No. of Events	1,398
No. of Referent Days	4,353
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Age at Admission	
Mean (years)	28
Range (years)	12-46
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Ethnicity	
White	750 (53.6%)
Hispanic	531 (38.0%)
Other or Missing	117 (8.4%)
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County	
Salt Lake	1219 (87.2%)
All others	179 (12.8%)
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