Outdoor Air Pollution and Pregnancy Loss: a Review of Recent Literature

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Abstract

Purpose of Review This review summarizes recent literature about the impacts of outdoor air pollution on pregnancy loss (spontaneous abortion/miscarriage and stillbirth), identifies challenges and opportunities, and provides recommendations for actions.

Recent Findings Both short- and long-term exposures to ubiquitous air pollutants, including fine particulate matter < 2.5 and < 10 μm, may increase pregnancy loss risk. Windows of susceptibility include the entire gestational period, especially early pregnancy, and the week before event. Vulnerable subpopulations were not consistently explored, but some evidence suggests that pregnant parents from more disadvantaged populations may be more impacted even at the same exposure level.

Summary Given environmental conditions conductive to high air pollution exposures become more prevalent as the climate shifts, air pollution’s impacts on pregnancy is expected to become a growing public health concern. While awaiting larger preconception studies to further understand causal impacts, multi-disciplinary efforts to minimize exposures among pregnant women are warranted.

Keywords Air pollution · Particulate matter · Pregnancy loss · Miscarriage · Stillbirth · Spontaneous abortion

Background

Pregnancy loss is the death of an unborn baby at any time during pregnancy [1]. Pregnancy loss is generally grouped into two categories including miscarriage or spontaneous abortion, defined as a loss before 20 weeks of gestation; and stillbirth, defined as a loss at or after 20 weeks of gestation [1]. The incidence of pregnancy loss is estimated to be around 15% of all recognized pregnancies [2], and approximately 30% in prospective cohorts of couples attempting to become pregnant [3, 4]. The true incidence of pregnancy loss in the general population is difficult to ascertain but expected to be higher as a significant proportion of losses occur early, even before clinical recognition.

Globally, one in 10 women experiences a miscarriage in their lifetime, equivalent to approximately 23 million cases annually [5]. Meanwhile, approximately two million babies are stillborn each year [6]. The impact of pregnancy loss is beyond the loss of a life [2]. In addition to the considerably high financial cost associated with medical management [2], affected families experience significantly higher levels of emotional and psychological burden. Parents who experience a pregnancy loss are more likely to experience depression, anxiety, and post-traumatic stress symptoms after delivery [7, 8]. Moreover, they also have higher risk of recurrent pregnancy loss, and all-cause as well as cardiovascular mortality [2, 9].

Several potential causes of pregnancy loss have been identified in the literature. These include complications of the placenta, cervix, or uterus; chromosomal abnormalities, abnormal fetal development; trauma or injury; and selected maternal comorbidities such as infection and autoimmune disorders [2, 6]. In addition, known risk...
factors for pregnancy loss include advanced maternal age, history of pregnancy loss, maternal smoking, alcohol consumption, illicit drug use, obesity, gestational complications, and certain environmental exposures [2, 6]. Nevertheless, the cause of a significant proportion of pregnancy loss is unclear, which contributes to the lack of effective prevention strategies. As such, identifying and understanding the etiology of pregnancy loss remain among the top priorities in maternal and child health initiatives.

Based on the 2020 State of Global Air report, air pollution is the fourth leading risk factor for premature mortality globally [10]. It is responsible for approximately 12% of all deaths, equivalent to about 6.67 million deaths in 2019 [10]. While the impacts of air pollution on mortality and cardiorespiratory health have received significant attention in the past few decades [11–14], we are only beginning the effort to understand how air pollution affects pregnancy. These efforts should be continued, strengthened, and expanded given pregnancy is a vulnerable period during which small environmental perturbations may have serious short- and long-term impacts on both the mother and developing fetus [15, 16]. In addition, while health impacts attributable to household air pollution have decreased by 30% in recent years, the health burden of outdoor air pollution remains elevated [17]. This is concerning given the context of climate change and its expected role in exacerbating air pollution burden. Furthermore, health effects of air pollution are seen at levels experienced by almost the entire population, who lives in areas with air quality below the World Health Organization’s recommended standards [18].

As air pollution is now a leading contributor to the global health burden [19], research has given increasing attention to its relationship with pregnancy loss risk. To date, six systematic reviews have summarized the existing literature on the relationship between air pollution exposure and pregnancy loss risk (Supplemental Table S1) [20–25]. Zhu et al. 2015 evaluates associations between particulate matter < 2.5 μm (PM2.5) and pregnancy outcomes, but this review focuses on one pollutant and includes one study on stillbirth [25]. Siddika et al. 2016 [22] (n = 15), Bekkar et al. 2020 [20] (n = 5), Zhang et al. 2021 [24] (n = 15), and Xie et al. 2021 [23] (n = 7) also reviewed studies on the associations between air pollution and stillbirth, but these reviews do not include spontaneous abortion. Grippo et al. (2018), to date, is the most comprehensive review, which includes 35 studies on air pollution and both categories of pregnancy loss [21]. However, given multiple studies have emerged since 2018, we seek to review the recent literature regarding the impacts of outdoor air pollution on both categories of pregnancy loss.

Methods

A comprehensive literature search spanning from March 2018 to March 25, 2022 was performed using PubMed. The search included terms related to air pollution and spontaneous abortion or stillbirth. We also used various alternative search terms for pregnancy loss including miscarriage, stillborn, fetal/foetal mortality, and intrauterine mortality (Supplemental Table S2). The articles were carefully reviewed and were excluded if they were (a) not an original study, (b) qualitative studies, (c) animal studies, (d) did not include specific outdoor air pollutant, (e) did not include any pregnancy loss outcomes, or (f) were not published in English. We also searched reference lists of relevant articles for additional publications.

Due to high heterogeneity between studies in terms of study design, exposure assessment, outcome assessment, and statistical analysis, we were unable to perform a systematic meta-analysis and presented a narrative review instead. We assessed the quality of each included study using an adapted version of the Effective Public Health Practice Project Quality Assessment tool [26]. This is a validated and widely used instrument to assess quality of epidemiologic research with respect to selection bias, study design, confounding, data collection, and attrition (or missing data). A detailed description of our qualitative review strategy is presented in Supplemental Table S3. Each study was assessed by two independent reviewers. Discrepancies were reconciled after a thorough discussion and any remaining differences were resolved by a third reviewer.

Results

Study Characteristics

A total of 21 articles were included in this review (Table 1). Supplemental Table S4 presents all existing articles on air pollution and pregnancy loss before this review period. Since these articles were included in previous reviews, they are not the focus of this review. The majority of the studies included in this review were conducted in the USA (n = 6, 28.6%) [27–32] and China (n = 6, 28.6%) [33–38], followed by Iran (n = 2, 9.5%) [39, 40], South Asia (n = 2, 9.5%) [41, 42], Africa (n = 1, 4.8%) [43], Australia (n = 1, 4.8%) [44], England (n = 1, 4.8%) [45], Israel (n = 1, 4.8%) [46], and Korea (n = 1, 4.8%) [47]. Retrospective cohort (n = 6) [31, 34, 44–47] and case–control designs (n = 6) [30, 35, 38, 41–43] were most popular, followed by times series (n = 3) [33, 39, 40], prospective cohort (n = 2) [27, 37], and case-crossover designs (n = 2) [28, 32]. Two studies also used multiple
Table 1  Summary of existing studies on air pollution and pregnancy loss (since March 2018)

| Reference        | Study settings | Study design          | Participants | Pollutants | Pollutant assessment | Windows of exposure | Pregnancy loss outcome | Outcome assessment | Main findings                                                                 | Covariates and effect modifiers                                                                 |
|------------------|----------------|-----------------------|--------------|------------|----------------------|---------------------|------------------------|---------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Gaskin et al. 2019 [52] | US, 1990–2008 | Mixed method: prospective cohort, case-crossover | 6,599 of 35,025 pregnancies from 19,309 women in the Nurses' Health Study | PM$_{2.5}$, PM$_{10}$ (estimated at residential address) | Nation wide spatiotemporal models using data from the USEPA Air Quality Systems (resolution: 6 km × 6 km) | Chronic: prior year, 1-year average, 2-year average, cumulative average | Fetal loss < 20 weeks | Self-reported questionnaire | Positive associations with 1-year average PM$_{2.5}$, PM$_{2.5-10}$, and PM$_{10}$ in the case-crossover analysis | Age, smoking status, year of pregnancy, BMI, history of infertility, current multivitamin use, marital status, race, region, census tract-level median income and median home value Tested for effect modification with gestational length, region, gestational age but found no difference |
| Leiser et al. 2019 [32] | Utah, US 2007–2015 | Case-crossover | 1,398 spontaneous pregnancy loss events identified from administrative medical records | PM$_{2.5}$, NO$_{2}$, and O$_{3}$ (estimated at zip code level) | Inverse distance weighting of observations from fixed-site monitors located in the same air basin as zip code centroid | Acute: week before event | Pregnancy loss < 20 weeks | Medical records | Positive associations with 7-day average NO$_{2}$ concentrations | Daily mean temperature Tested for effect modification with Hispanic ethnicity but found no difference |
| Zang et al. 2019 [37] | Yancheng city, China 2015–2017 | Prospective cohort | 587 stillbirths and 59,281 live births identified by administrative data | PM$_{2.5}$, PM$_{10}$, SO$_{2}$, CO, NO$_{2}$, and O$_{3}$ (estimated at residential address) | Nearest fixed-site air monitor to residential address | Chronic: each trimester and entire pregnancy | Stillbirth 28–42 weeks | Medical records | Positive associations with PM$_{10}$ during all windows, PM$_{10}$ during first trimester, O$_{3}$ during first and third trimester | Adjusted for maternal age, pre-pregnancy BMI, parity, occupation, educational level, infant sex, high-risk pregnancy, chronic disease, and season of conception |
| Reference             | Study settings          | Study design                      | Participants                                                                 | Pollutants                                                                 | Pollutant assessment                                                                 | Windows of exposure                                                                 | Pregnancy loss outcome | Outcome assessment | Main findings                                                                 | Covariates and effect modifiers                                                                 |
|-----------------------|-------------------------|-----------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------|------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Zhang et al. 2019 [38]| Tianjin, China 2017–2018| Case–control                      | 364 cases and 364 livebirth controls matched on maternal age and gravidity Recruited from hospitals | PM$_{2.5}$ (estimated at residential address) | Land use regression models using 28 fixed-site monitors and geographic variables including population density, road length, industrial land area, and distance to coast (resolution: 1 km $\times$ 1 km) | Chronic: 4 weeks before conception, first 4 weeks after conception | Pregnancy loss $<$ 13 weeks | Transvaginal ultrasound | Positive associations with PM$_{2.5}$ during the second week after conception | Body mass index, parity, maternal education, family monthly income per capita, interior renovation either of home or work, occupational exposure, alcohol consumption, active smoking and passive smoking |
| Rammah et al. 2019 [30]| Harris County, TX, 2008–2013| Nested case–control               | 1599 stillbirths and 1,600 randomly selected controls matched on calendar time Identified from vital statistics | PM$_{2.5}$ constituents (estimated at county level) | One of two fixed-site monitors in the county | Chronic: Entire gestational period | Stillbirth $\geq$ 20 weeks | Vital statistics | Positive associations with Zn exposures during the gestational period | Adjusted for age, race, education, number of prenatal care visits, smoking, BMI, and apparent temperature |
| Rammah et al. 2019b [31]| Harris County, TX 2008–2013| Retrospective cohort, case–crossover | 1599 stillbirths and 356,767 livebirths identified from vital statistics | O$_3$, PM$_{2.5}$, and NO$_2$ (estimated at residential address) | Inverse distance weighting using the nearest 3 fixed-site monitoring stations to residential address | Chronic and acute: The week prior, entire gestational period | Stillbirth $\geq$ 20 weeks | Vital statistics | Positive associations with O$_3$ exposures over the entire gestational period for preterm births | Adjusted for apparent temperature, maternal age, race/ethnicity, education, smoking, pre-pregnancy body mass index, and number of prenatal care visits Tested for interaction with preterm births and race/ethnicity, and found stronger associations for preterm births and Hispanic women |
| Reference         | Study settings                     | Study design          | Participants                                                                 | Pollutants                                      | Pollutant assessment                                                                 | Windows of exposure                      | Pregnancy loss outcome | Outcome assessment      | Main findings                                                                 | Covariates and effect modifiers                        |
|-------------------|------------------------------------|-----------------------|-------------------------------------------------------------------------------|------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------|------------------------|----------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------|
| Xue et al. 2019 [42] | 33 African countries, 1998–2016   | Case-control (self-match) | 42,952 pregnancy losses matched with 107,910 successful deliveries within the same women identified by international dataset (Demographic and Health Survey) | PM$_{2.5}$ and its constituents (estimated at geographic coordinates of the survey cluster) | Chemical transport model and remote-sensing measurements (resolution: 0.1° × 0.1°) | Chronic and acute: Five days prior, entire gestational period | Miscarriage < 5 months, and stillbirth ≥ 5 months | Self-report questionnaire | Positive associations between all pregnancy loss (combined both miscarriage and stillbirth) with PM$_{2.5}$ exposures during whole pregnancy and all lags 0, 2, and 5 | Tested for effect modification by region, education, urban/rural, maternal age, insurance, employment status, anemia, and BMI. Results showed that younger maternal age or higher education level might reduce the risk of stillbirth |
| Gaskin et al. 2020 [52] | Boston, MA, USA 2004–2019 | Prospective cohort | 81 losses among 275 couples attempting pregnancy Recruit from a Fertility Center | NO$_2$, O$_3$, PM$_{2.5}$, black carbon (estimated at residential address) | Spatiotemporal models using data from satellite-derived aerosol optical depth measurement, land use indicators, and meteorology (resolution: 1 km × 1 km) | Chronic and acute: Week prior and entire gestational period | Time to pregnancy loss at any week | Clinical assessment | Cumulative NO$_2$ exposures was positively associated with pregnancy loss after 30 days since positive hCG test | Age, BMI, smoking status, race, education, current employment, and protocol Tested for interaction with days since positive hCG, primary infertility diagnosis, smoking status, and female age Significant impacts were detected for loss after 30 days since hCG test but not before |
| Reference          | Study settings         | Study design     | Participants | Pollutants          | Pollutant assessment                                                                 | Windows of exposure      | Pregnancy loss outcome | Outcome assessment     | Main findings                                                                 | Covariates and effect modifiers                                                                 |
|--------------------|------------------------|------------------|--------------|--------------------|--------------------------------------------------------------------------------------|--------------------------|------------------------|------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Smith et al. 2020  | Greater London, 2006–2010 | Retrospective cohort | 581,774 live and 3392 stillbirths identified through registries | NO$_2$, NO$_x$, O$_3$, PM$_{2.5}$, PM$_{10}$ (estimated at residential address) | Atmospheric dispersion models (resolution 20 m $\times$ 20 m) using emission data and meteorologic information | Chronic: each trimester, entire gestational period, last 3 months of pregnancy | Stillbirth $\geq$ 24 weeks | Birth/stillbirth registries | Positive associations with O$_3$ exposures during trimesters 1, 2               | Adjusted model covariates: sex, maternal age, birth registration type, tobacco expenditure (neighborhood-level), carstairs quintile (neighborhood-level), individual-level ethnicity, season of conception, year (linear term) and random intercept for census output area |
| Ranjaran et al. 2020 | Tehran, Iran (2015–2018) | Time-series | 3460 stillbirths identified from administrative data | O$_3$, CO, NO$_2$, SO$_2$, PM$_{2.5}$ (estimated at the study area level) | Average of 37 fixed-site monitoring stations in the study area | Acute: 7 days prior | Stillbirth $\geq$ 22 weeks | Administrative data | Positive associations with SO$_2$ exposures during the same day (lag 0) | Temperature, humidity, time of year, holiday, and day of week Tested for effect modification by ethnicity, deprivation, region, preterm birth status |
| Wang et al. 2020   | Shanghai, China, 2014–2019 | Case-control     | 1075 cases and 1370 controls identified from a hospital | NO$_2$ and CO (estimated at the district level) | Average of 16 fixed-site air monitors within the same district | Entire gestational period, 1–3 months before conception | Spontaneous abortion $<20$ weeks | Medical records | Positive associations with NO$_2$ exposures during the whole gestation period (LMP-date of abortion) | Adjusted for gestational age, maternal age, BMI, marital status, maternal parity, assisted reproductive technology use, temperature, and relative humidity |
| Reference          | Study settings | Study design | Participants | Pollutants | Pollutant assessment | Windows of exposure | Pregnancy loss outcome | Outcome assessment | Main findings | Covariates and effect modifiers |
|-------------------|----------------|--------------|--------------|------------|----------------------|---------------------|------------------------|---------------------|---------------|-----------------------------|
| Sarovar et al. 2020 [28] | CA, USA 1999–2009 | Case-crossover | 13,018 stillbirths identified from fetal death records Lived in a zip code whose centroid was located within 10 km of an air monitor | PM$_{2.5}$, PM$_{10-2.5}$, O$_3$, NO$_2$, SO$_2$, CO (estimated at zip code level) | Closest fixed-site air monitors for mother’s living within 10 km within an air monitor | Week prior to event | Stillbirths ≥ 20 weeks | Fetal death records | Positive associations for SO$_2$ (lag 4) -O$_3$ (lag 4) -PM$_{10-2.5}$ (lag 2) | Apparent temperature Tested for effect modification by maternal age, education, race/ethnicity, fetal sex, cause of death, gestational weeks. Strongest estimates for O$_3$ found for maternal ages 25–34 |
| Dastoorpoor et al. 2021 [39] | Ahvaz, Iran 2008–2018 | Time-series | 5063 spontaneous abortion, 1965 stillbirth identified from administrative records | CO, NO, NO$_2$, PM$_{10}$, PM$_{2.5}$, SO$_2$, and O$_3$ (at province level) | Average of four fixed-site monitoring stations in the study province | The week prior to event | Spontaneous abortion and stillbirth (definition unclear) | Medical records | Weak and inverse associations for spontaneous abortion with pollutants: NO: lags 0, 1, 2, 3, 4, 5, 6 NO$_2$: lags 0, 1, 2, 3, 4, 5, 6 CO: lags 0, 1, 2, 3, 4, 5, 6 PM$_{10}$: lag 0 Weak positive SO$_2$: lags 0, 1, 3, 4, 5, 6 Neglectable inverse association with PM$_{2.5}$ at lag 6 for stillbirth | Temperature and relative humidity, day of the week |
| Reference       | Study settings                        | Study design       | Participants                                                                 | Pollutants                  | Pollutant assessment                  | Windows of exposure | Pregnancy loss outcome | Outcome assessment | Main findings                                                                 | Covariates and effect modifiers                  |
|-----------------|---------------------------------------|--------------------|-------------------------------------------------------------------------------|-----------------------------|----------------------------------------|---------------------|------------------------|---------------------|--------------------------------------------------------------------------------|--------------------------------------------------|
| Xue et al. 2021 | India, Pakistan, and Bangladesh (1997–2018) | Case-control       | 34,197 cases and 76,282 live-birth matched within the same woman Identified from a population-based Demographic Health Survey | PM$_{2.5}$ (estimated at the GPS coordinates of survey cluster) | Geophysical models using satellite remote sensor measurements (spatial resolution: 0.1 $\times$0.1') | The entire gestational period | Miscarriage < 5 months, or still-birth ≥ 5 months | Self-report | Positive associations between PM$_{2.5}$ during the entire gestational period with both miscarriage and stillbirth | Adjusted for maternal age, non-linear terms for temperature and humidity, seasonal variation, and long-term trends. Potential effect modification by age and type of residence (urban/rural) but results were not discussed |
| Xue et al. 2021b| India, Pakistan, and Bangladesh (2000–2014) | Case-control       | 24,876 cases of pregnancy loss and 50,386 self-matched controls Identified from a population-based demo-graphic health survey | PM$_{2.5}$ (estimated at residential address level) | Global chemical transport model GEOS-Chem using satellite remote-sensing (spatial resolution: 0.1 $\times$0.1') | The entire gestational period | Miscarriage < 5 months, or still-birth ≥ 5 months | Self-report | Positive associations between PM$_{2.5}$ during the entire gestational period with both miscarriage and stillbirth | Maternal age, temperature, humidity, and temporal trends. Effect modification by maternal age, where older women (> 35 years) were more susceptible |
| Reference | Study settings | Study design | Participants | Pollutants | Pollutant assessment | Windows of exposure | Pregnancy loss outcome | Outcome assessment | Main findings | Covariates and effect modifiers |
|-----------|----------------|--------------|--------------|------------|----------------------|---------------------|------------------------|---------------------|--------------|----------------------------------|
| Wang et al. 2021 [36] | Six Chinese counties (2007–2010) | Prospective cohort (and self-match case-control) | 69 pregnancy losses among 2451 pregnancies identified from an ongoing cohort | PM$_{2.5}$ (at county of residence level) | Machine learning model using remote-sensing measurements of aerosol optical depth (resolution: 10 km × 10 km) | Entire gestational period | Pregnancy loss at any time | Self-report | Positive associations between PM$_{2.5}$ during the entire pregnancy and spontaneous loss | Temporal trend, maternal age, pregnancy intentionality, residence, education, employment status, and household income. Higher estimates for ages < 25 and intended pregnancies tested for effect modification by maternal age, pregnancy intentionality, residence, education, employment status, and household income. |
| Liang et al. 2021 [33] | Chongqing, China (2014–2018) | Time-series | 42,334 visits of spontaneous abortion identified from administrative data | CO, PM$_{10}$, PM$_{2.5}$, O$_3$, NO$_2$, SO$_2$ (estimated at the area level for the whole study region) | Averaged from 28 fixed-site area-level monitors in the region | 5 days prior | Spontaneous abortion (definition unclear) | Medical records | Positive associations with NO$_2$ during lags 0, 1, and cumulative lags 0, 05, and 05 | Time trend, day of week, temperature, and humidity. Explored interaction with age, season. Strong effects were seen in cool season and women ages 30–39 |
| Reference          | Study settings | Study design     | Participants                                                                 | Pollutants                                                                 | Pollutant assessment                                                                 | Windows of exposure                                                                 | Pregnancy loss outcome | Outcome assessment | Main findings                                                                 | Covariates and effect modifiers                                                                                                                                                                                                 |
|--------------------|----------------|------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------|-------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Jalaludin et al. 2021 [44] | Sydney, Australia (1997–2012) | Retrospective cohort | 4287 stillbirths among 97,198 singleton births between 20 and 42 weeks and ≥400 g identified from administrative data | O$_3$, PM$_{10}$, PM$_{2.5}$ (estimated at the area level for the whole study area) | Averaged across eight fixed-site monitors in the city                              | Each trimester and entire gestational period                                     | Stillbirth ≥ 20 weeks, at least 400 g | Administrative data | No association between any pollutant and stillbirth | Infant gender, maternal smoking, indigenous status, first pregnancy, antenatal care attendance, gestational diabetes, maternal diabetes, maternal hypertension, mother country of birth, mother age, and neighborhood SES. Effect modifier: maternal age, area-level SES. There is evidence of stronger effects among ages < 35 |
| Kim et al. 2021 [47] | Korea (2015–2018) | Retrospective cohort | 648 stillbirths among 789,595 high-risk pregnancies identified from administrative data | PM$_{10}$, PM$_{2.5}$, CO, NO$_2$, SO$_2$ (estimated at residential address) | Spatial prediction models using 185–261 fixed-site stations (resolution: district level) and area-averaging from 278 to 533 fixed-site monitoring stations | 6 months before event | Stillbirth (week cutoff unclear) | Medical records | No association between any of the pollutant with stillbirth | None |
| Wainstock et al. 2021 [46] | Southern Israel (2003–2017) | Retrospective cohort | 444 cases of intrauterine fetal death among singleton 87,897 deliveries without congenital malformation or chromosomal abnormalities identified from administrative data | PM$_{2.5}$ (estimated at residential address) | Mathematical model with satellite remote-sensing data (resolution: 1 km × 1 km) | Each trimester and entire pregnancy | Intrauterine fetal death ≥ 24 weeks | Medical records | Positive associations with first trimester and whole-pregnancy exposures to PM$_{2.5}$ among only Jewish women; no associations among Bedouin women | Maternal age, smoking, socioeconomic score, season |
Table 1 (continued)

| Reference          | Study settings                  | Study design            | Participants                                                                 | Pollutants                                      | Pollutant assessment | Windows of exposure | Pregnancy loss outcome | Outcome assessment | Main findings                                      | Covariates and effect modifiers                                |
|--------------------|---------------------------------|-------------------------|------------------------------------------------------------------------------|-------------------------------------------------|----------------------|----------------------|----------------------|-------------------|-------------------------------------------------|---------------------------------------------------------------|
| Liang et al. 2021b | Pearl River Delta Region, China (2014–2017) | Retrospective cohort | 3150 still-births out of 1,273,924 singleton deliveries between 20 and 42 weeks, identified from administrative data | PM$_{2.5}$, O$_3$, NO$_2$, SO$_2$ (estimated at residential district) | Fixed-site air monitors within the district of residence, or within 5 km of the district (total monitors available: 10) | Each trimester and entire pregnancy | Stillbirth 20–42 weeks | Medical records | Positive associations with PM$_{2.5}$ for all trimesters and entire pregnancy | Maternal age, baby sex, season of conception, previous pregnancy, previous delivery condition, temperature, humidity, co-pollutant interaction with baby sex, maternal age, previous pregnancy, and previous delivery. Stronger associations for male, maternal ages < 35, women without previous pregnancy or delivery |
designs to ensure robustness of findings [29, 36]. Most studies \((n=12)\) [27, 29, 31, 32, 36, 38, 41–43, 45–47] assessed exposures using the modeling approaches, while the rest used measurements from fixed-site air monitors \((n=9)\) [28, 30, 33–35, 37, 39, 40, 44]. In terms of exposure, 12 studies assessed long-term exposures across different periods of pregnancy [30, 34–38, 41, 42, 44–47], five studies assessed short-term impacts of exposures within the last week [28, 32, 33, 39, 40], three studies assessed both short- and long-term impacts [27, 31, 43], and one study investigated average exposure in the study area with no specific window [29]. In terms of study outcome, 10 studies investigated stillbirth [28, 30, 31, 34, 37, 40, 44–47], five studies assessed spontaneous abortion [29, 32, 33, 35, 38], four studies evaluated both pregnancy loss outcomes [39, 41–43], and two studies evaluated any loss without categorization based on gestational age [27, 36]. One study measured pregnancy loss prospectively using clinical assessment [27], five used questionnaires [29, 36, 41–43], and 15 relied on administrative data or medical records [28, 30–35, 37–40, 44–47]. Studies also vary in quality ranging from weak to strong, as presented in Supplemental Table S5.

**Air Pollution and Spontaneous Abortion**

Eleven studies evaluated associations between various air pollutants and spontaneous abortion/miscarriage (Table 2) [27, 29, 32, 33, 35, 36, 38, 39, 41–43]. Particulate matter, especially \(\text{PM}_{2.5}\), received the most attention, followed by nitrogen dioxide \((\text{NO}_2)\), ozone \((\text{O}_3)\), carbon monoxide \((\text{CO})\), and \((\text{particulate matter} < 10 \mu\text{m} (\text{PM}_{10})\). Sulfur dioxide \((\text{SO}_2)\), fine particles sizes 2.5 to 10 \(\mu\text{m}\) and \(\text{NO}_2\) appeared to have demonstrated deleterious impacts on spontaneous abortions in at least one study, with fine particles and \(\text{NO}_2\) showing the most consistent associations.

### Fine Particles and Constituents

Gaskin et al. (2019) estimated fine particles at residential address using spatiotemporal models and found positive associations between self-reported fetal loss (<20 weeks) and 1-year average exposure to \(\text{PM}_{2.5}\) (OR 1.09; 95% CI 1.03–1.15 per 2.0 \(\mu\text{g/m}^3\) increase), \(\text{PM}_{2.5-10}\) (OR 1.08; 95% CI 1.03–1.13 per 2.3 \(\mu\text{g/m}^3\)), and \(\text{PM}_{10}\) (OR 1.11; 95% CI 1.05–1.17 per 3.9 \(\mu\text{g/m}^3\)) in their cross-over analysis [29]. A large self-matched case–control study across 33 African countries also found positive associations between self-reported miscarriage <5 months and \(\text{PM}_{2.5}\) estimated using chemical transport models and remote sensing [43]. Each 10 \(\mu\text{g/m}^3\) increase in average \(\text{PM}_{2.5}\) exposures across the whole gestational period was associated with 12.5% (95% CI 10.9–14.2%) increased risk of miscarriage. When assessing short-term risks, \(\text{PM}_{2.5}\) exposures were

| Pollutants assessed | Spontaneous abortion \((n=11)\) | Stillbirth \((n=16)\) |
|--------------------|-------------------------------|------------------|
| CO                 | 0                             | 0                | 5                |
| \(\text{PM}_{10}\)  | 2                             | 3                | 5                |
| \(\text{PM}_{2.5}\) | 6                             | 10               | 14               |
| \(\text{PM}_{2.5-10}\) | 1                         | 1                | 1                |
| \(\text{PM}_{10}\) constituents | 0                    | 2                | 1                |
| \(\text{NO}_2\)    | 4                             | 5                | 10               |
| NO                 | 0                             | 1                | 0                |
| \(\text{NO}_x\)    | 0                             | 0                | 1                |
| \(\text{O}_3\)     | 0                             | 4                | 0                |
| \(\text{SO}_2\)    | 1                             | 2                | 2                |
| Windows of susceptibility assessed | | |
| Preconception       | 0                             | 3                | 0                |
| Trimester 1         | 1                             | 1                | 4                |
| Trimester 2         | 0                             | 0                | 3                |
| Trimester 3         | 0                             | 0                | 2                |
| Whole pregnancy     | 6                             | 6                | 10               |
| Acute exposures within last week | 3           | 5                | 12               |
| Last 3–6 months of pregnancy | 0       | 0                | 2                |
| Average during study period | 1         | 1                | 0                |

Studies that evaluated both outcomes or had no gestational cut-off were counted in both categories of loss.
also associated with 4–6% increased risk on the same day as well as 2 and 5 days later [43]. Two similar large case–control studies using the same dataset in several South Asian countries also found similar and positive associations between PM2.5 during the entire gestational period and self-reported miscarriage <5 months (OR 1.04 and 1.05 in both studies) [41, 42]. A case–control study in China also found positive associations between pregnancy loss <13 weeks (ascertained by transvaginal ultrasonography) and PM2.5 exposures within four weeks after—but not before—conception [38]. Each 10 μg/m3 increase in average PM2.5 exposure during the second week after conception and the entire 4 weeks after conception were associated with a 13% (95 CI 3–23%) and 25% (95% CI 2–46%) increased risk of clinically recognized early loss, respectively [38]. Another study from China also found positive associations between PM2.5 during the entire pregnancy and spontaneous loss [36]. Particulate matter is comprised of a mixture of components that can vary depending on sources. Thus, a couple studies investigated potential impacts of fine particle constituents (e.g., black carbon) on pregnancy loss but found no associations [27, 43]. Despite relatively consistent associations, several large studies also did not detect any significant association between PM2.5 or PM10 and spontaneous loss, although effect estimates were mostly above the null value [27, 32, 33].

Gaseous Pollutants

During the review period, four studies evaluated the impacts of O3 on spontaneous abortion, but none found positive association [27, 32, 33, 39]. On the other hand, NO2 appeared to have consistent associations across four of five relevant studies. For example, in a case-crossover analysis of almost 1400 cases in Utah, USA, Leister et al. (2019) investigated acute associations between spontaneous abortion (<20 weeks) and exposures to PM2.5, NO2, and O3 within 1 week. While the study found no associations with PM2.5 or O3, a positive association with NO2 was observed [32]. Each 10 parts per billion increase in average NO2 exposure during the 7 days prior was associated with a 16% increase in the odds of spontaneous abortion [32]. A prospective cohort study also found that an 18 parts per billion increase in cumulative NO2 exposures during the entire gestational period was associated with 34% (95% CI 13–58%) increased risk of pregnancy loss after 30 days since positive hCG test [27]. Wang et al. (2020) also evaluated associations between loss (<20 weeks) and CO2 and CO; positive associations with whole-pregnancy NO2 exposures but not CO was observed [35]. Similarly, a time-series study in China reported associations with NO2 exposure within 1 week, but not with any other pollutant [33]. Meanwhile, a time-series study in Iran showed mostly null or neglectable inverse associations with NO, NO2, SO2, and CO exposures within 1 week [39].

Air Pollution and Stillbirth

Sixteen studies evaluated the associations between air pollutants and stillbirth during the review period (Table 2) [27, 28, 30, 31, 34, 36, 37, 39–47]. Like the case for spontaneous abortion discussed above, PM2.5, NO2, and O3 received the most attention.

Fine Particles and Constituents

Of the 14 studies evaluating the associations between PM2.5 and stillbirth [28, 31, 34, 36, 37, 39–47], seven suggested positive association [34, 36, 37, 41–43, 46], six suggested null association [28, 31, 39, 40, 44, 47], and one showed inverse association [45]. Positive associations between stillbirth and whole-pregnancy average PM2.5 exposures were observed in two large case–control analyses of pregnancies from three south Asian countries [41, 42] and several large cohort studies in Southern Israel [46] and China [34, 37]. These positive associations were observed for PM2.5 exposures during all three trimesters [34, 37] and first trimester [46]. Particles with slightly bigger sizes including PM2.5-10 and PM10 were also observed to be associated with stillbirth [28, 37]. On the other hand, a number of studies from Texas and California, USA; Korea; Australia; and Iran showed no associations with particles of any sizes [28, 31, 39, 40, 44, 47]. Constituents of fine particles were also investigated in two studies [31, 43], one of which found that an interquartile range (0.007 μg/m3) increase in average zinc particle exposure during the entire gestational period was associated with an 11% increased risk for stillbirth in Harris County, Texas [31].

Gaseous Pollutants

Eight studies evaluated the impacts of O3 on stillbirth risk, with four showing positive associations [28, 31, 37, 45] and four no association [34, 39, 40, 44]. None of the five studies investigating CO impact observed any relationship [28, 37, 39, 40, 47]. One of 10 studies on NO2 showed positive association with stillbirth [27] while one suggested inverse association for first and second trimester exposures [45], and another showed neglectable inverse association for exposures during the week before the event [39]. NO and NOx were evaluated in two studies [39, 45] with one showing a weak inverse association with NOx [45]. Furthermore, two studies [28, 40] suggested positive associations with SO2 while four did not [34, 37, 39, 47].
Windows of Exposure

Studies considered both acute and chronic windows of exposure (Table 2). Acute windows of exposure generally included daily exposures during the week prior to the pregnancy loss event. Chronic windows include average exposures during preconception (usually within a few months of conception), each trimester, entire pregnancy, or the entire study period. Some studies also considered average exposures during the last 3–6 months of pregnancy. Generally, there is evidence suggesting that air pollution has both acute and chronic impacts on both pregnancy loss outcomes. For chronic exposures, nearly all studies that investigated impacts of average whole-pregnancy and first trimester exposures showed positive associations with both pregnancy loss outcomes. Acute exposures during the week prior to loss were also implicated in numerous studies.

Susceptible Subpopulations

Numerous studies identified subgroups who may be more susceptible to the impacts of air pollution, even at the same level of exposure (i.e., explored potential effect modifiers). Some commonly considered effect modifiers included maternal age, fetal sex, maternal education, race/ethnicity, gestational age, employment status, income/deprivation index, comorbidity, and smoking status (Table 2). Overall, there is some evidence suggesting that more disadvantaged populations and those with extreme maternal age may be more susceptible. However, effect modifier variables were not consistently defined across studies, which contributed to the somewhat inconsistent findings. Rammah et al. (2019) found that the impacts of O3 over the entire gestational period on stillbirth risk was the strongest among Hispanic women and for pregnancies ended before 37 weeks [31]. One study suggests that the impacts of PM2.5 were lower among women with lower maternal age and those with higher educational attainment [43]. Another study found significant impacts for women ages 25–34 but not for any other age groups [28], while others suggested women <35 years [33, 42] and <25 years [36] were more susceptible. One study found stronger associations for male fetuses and women with no previous pregnancy and delivery experience [34].

Discussion

This review summarizes the recent literature regarding the impacts of outdoor air pollution on pregnancy loss. Evidence suggests that both short- and long-term exposures to air pollution during pregnancy can increase one’s risk. While associations with fine particles appeared most consistent, there is evidence suggesting pregnancy loss risk associated with SO2, NO2, and O3. These findings are consistent with older literature before the review period. Grippo et al. (2018) conducted a comprehensive review on the impact of air pollution on pregnancy loss and found consistent evidence suggesting that PM10 (during the entire gestational period) and CO (during first trimester) were associated with spontaneous abortion [21]. The same review also suggests that PM2.5, PM10, and CO during the third trimester were also associated with stillbirth risk, while evidence for other pollutants like NO2 and SO2 were somewhat inconsistent [21]. Another review of stillbirth in relation to PM2.5 and O3 also reported consistent positive associations for these two pollutants in four of the five included studies [20]. Two more recent reviews reported positive associations between stillbirth and PM2.5 (third trimester and entire gestational period), CO (third trimester), and O3 (first trimester and 4 days prior) [23, 24]. Despite consistency in findings for many pollutants, there were still some inconsistencies. For example, we did not find evidence of association with CO in recent studies. In general, there were challenges that can explain inconsistencies.

Challenges and Opportunities

Exposure Assessment

To better estimate and understand the causal effects of air pollution on pregnancy loss, accurate assessment of air pollution exposure is crucial. This includes not only the intensity, but also the pattern, timing, and duration of exposure. A few studies estimated exposures by linking residential address of participants (at the time of delivery) to local fixed air monitors [28, 30, 33, 34, 37, 39, 40, 44]. This strategy assumes that people have the same exposure levels as measured at local fixed station(s), regardless of proximity. While highly feasible, especially for studies with large sample size, this approach cannot capture small local variations and is highly prone to misclassification that may vary by distance from the monitor(s). Some studies minimize this issue by restricting to only participants within a certain distance (e.g., 10 km) from a monitor [28]. However, this approach can potentially introduce selection bias and cannot completely address small spatial variation.

A higher proportion of recent studies uses complex mathematical or machine learning models to estimate exposures for individuals located at any location and time. Such approach allows more flexibility for estimation by incorporating factors that can influence air pollution variation such as land use, weather parameters, and photochemical and transport properties of pollutants. Even so, the output resolution of these models differed significantly across studies. Furthermore, many studies do not have residential addresses and had to rely on large geographic unit such as US zip...
code for estimation. Even for those that do have residential address, it is known that pregnant women are mobile across pregnancy [48]. Thus, while residential history or time activity patterns are valuable for accurate estimation, these data points are not available, leading to potential non-differential misclassification, which would bias results towards the null. It is also important to note that in many regions of the world where stillbirth risk is high, there is no air pollution data for population-based risk estimates. A detailed systematic review of exposure assessment of air pollution exposure in relation to reproductive outcomes (including pregnancy loss) has been published elsewhere [49].

As wearable technologies become more accessible, they can be used for personal monitoring and/or supplementing existing exposure assessment strategies. To date, although no studies on pregnancy loss utilize personal monitoring, studies on other health outcomes have successfully implemented this approach [48, 50–54]. Given pregnancy is a relatively short window of opportunity, this approach is potentially feasible and allows prospective capturing of small variation in timing, pattern, and duration of exposures, which can help explore specific windows of susceptibility. Many wearable devices do not have federal reference quality, but they can help improve exposure assessment and are becoming increasingly sophisticated.

Air pollution is a mixture of different pollutants, each of which may have both independent and joint effects with other pollutants. Many of these pollutants are also highly collinear. As such, sometimes we may be interested in the effects of (a) an aggregate mixture, (b) a sum of components within a mixture, (c) independent effects of components within a mixture, or (d) joint effects of components within a mixture [55]. To date, no study on air pollution and pregnancy loss have considered mixture effects, but multiple approaches have been used in related literatures. For example, Hierarchical Bayesian approach (e.g., Bayesian Kernel Machine Regression), dimension reduction methods (e.g., principal component analysis), clustering, and recursive partitioning have been suggested to address mixture effects [56–58]. Machine learning tools can also be used to explore the independent and joint effects air pollution data with high dimension [56]. These tools can include the use of penalized estimators such as partial least absolute shrinkage, selection operator, and ridge regression; and decision trees, which may include techniques such as random forest and Bayesian additive regression trees [56].

Outcome Assessment

A significant challenge for pregnancy loss studies involves the fact that most losses occur early, even before parents are aware that they are pregnant. During the review period, most studies were retrospective and relied on self-report or administrative data such as medical statistics, or registries to identify pregnancy loss cases. Thus, many early losses were likely excluded, potentially leading to an underestimation of risk. To date, only two studies used prospective clinical assessment of pregnancy loss (with one during the review period) [3, 27]. It is important to note that participants only included couples who were actively planning to become pregnant. These studies therefore excluded unintended pregnancies, which represent nearly half of all US pregnancies [59]. Prospective study designs are necessary for not only effective capture of early losses, but also allow better assessment of exposure and potential confounders that are not available in administrative data.

Another challenge is the inconsistent definition of pregnancy loss. For administrative data, different jurisdictions may be mandated to capture loss/mortality outcomes for births beyond different gestational age. As such while some studies defined stillbirth as death ≥ 20 weeks [28, 30, 31, 34, 44], others use different cutoffs including 22 weeks [40], 24 weeks [45, 46], 28 weeks [37], and 5 months [41–43]. For miscarriage/spontaneous abortion, the range of definition included < 20 weeks [29, 32, 35], and < 13 weeks [38], and < 5 months [41–43]. Meanwhile, the definition was unclear in a couple studies [33, 39, 47]. As these inconsistencies presents a challenge for direct comparison across studies, it may be helpful for the field to consider at least a more standardized approach to design and report studies.

Susceptible Populations

Even at the same level of exposure, specific subgroups of individuals may experience higher risks because of other intrinsic or extrinsic factors. The general literature regarding the health impacts of air pollution suggests that individuals who are pregnant, have genetic predisposition, have health complications, come from disadvantaged communities, or at the age extremes (i.e., children and the elderly) are more susceptible to the impacts of air pollution [60]. While some studies on air pollution and pregnancy loss attempted to identify these subgroups by incorporating interaction or stratified analyses, efforts and findings are still inconsistent. Some challenges include the inconsistent definition of effect modifiers across studies, and insufficient sample size/power for group-specific analyses, especially when pregnancy loss is a relatively rare outcome. Nevertheless, with limited resources, accurate identification of these susceptible populations is crucial for targeted mitigation efforts. As such, there is a critical need for large and diverse studies, especially among underserved populations, that can allow detailed analyses to identify susceptible subgroups.
Biologic Mechanisms

Although the exact biologic mechanisms remain to be elucidated, the association between air pollution and pregnancy loss is biologically plausible. Exposures to fine particles can induce the release of systemic oxidative stress [61] and inflammation markers [62, 63], which are capable of compromising placental-fetal exchange and disrupt the normal oxygen and nutrients delivery into fetal circulation [64]. Oxidative stress and inflammatory markers can also cross the maternal–fetal blood barrier to perturb fetal development [64, 65]. Fine particles have also been noted in a recent study to be capable of traversing the placental barrier to the fetal side [66]. CO exposures reduce oxygen carrying capacity of maternal hemoglobin, thus can also influence fetal development [67]. More mature literature of reproductive health impacts of smoking, which has many components found in air pollution, suggest that pollutants may trigger irreversible cellular damage, hypoxic damage, or immune mediated injury for both mother and baby [68–73].

Recommendations

Given the global concerns related to increased air pollution exposure because of climate change, reproductive impact of air pollution is expected to be a growing public health problem. While more research is needed to further understand the causal impact of specific air pollutants on pregnancy health, existing evidence suggests that air pollution exposures during the gestational period can increase the risk of pregnancy loss. Based on the Precautionary Principle adopted by the United Nations in 1992, when threats of serious or irreversible damage is present, the lack of full scientific certainty and understanding should not be the reason to postpone cost-effective measures [74]. As such, efforts to reduce air pollution exposures among pregnant women should be continued, strengthened, and expanded.

Air pollution has no geographic boundaries, an effective mitigation strategy should involve concerted efforts among policy makers, healthcare providers, researchers, industry partners, community partners, and the public. Efforts to reduce emissions for existing sources should be continued. Meanwhile, judicious permission and careful review of new sources, particularly those located in vulnerable populations, are needed. In addition, promotion and expansion of fuel efficient and clean energy should be a priority, especially in places with high pollution. More funding opportunities to support efforts to reduce exposures and foster a more equitable and sustainable environment are also warranted.

As a trusted voice, healthcare providers are uniquely positioned to become advocates in the efforts to minimize exposure. Studies show that very few healthcare provider discuss the effects of air pollution with their patients, and many feel that they are not prepared for such discussion [75, 76]. There is a clear need for efforts that prepare, empower and incentivize healthcare providers to engage in this important discussion with their patients. There are ongoing discussion for medical schools and continuing education opportunities to highlight environmental health [77, 78], and some colleges are prepared to make sure their medical education curriculum ensures physicians better understand the health effects of air pollution [79, 80]. It is also important to recognize that emerging evidence suggests that communication about environmental risks should also move beyond individual behavior education to empower communities to reduce environmental threats. As such, clear and culturally competent resources should be available to educate, mobilize, and incentivize communities to be involved in this important endeavor [81].

Meanwhile, research efforts are further needed to address a few important gaps. First, much of our current knowledge about the biologic mechanisms linking air pollution on health come from the cardiovascular and respiratory literature. Bove et al. (2019), for the first time, demonstrated that fine particles (i.e., black carbon) can cross the human placenta and accumulate on the fetal side [66]. However, further work is needed to understand the biologic mechanisms linking specific pollutants and pregnancy loss. Detailed data that can allow rigorous investigation of biologic mechanisms related to air pollution exposures during pregnancy are extremely scarce due to ethical and financial feasibility. However, the relatively short duration of pregnancy may present an opportunity for detailed prospective data collection that can also permit temporality and assessment of potential confounding.

Second, it is also important for future studies to improve exposure and outcome assessment. As discussed in “Exposure Assessment,” “Outcome Assessment,” and “Susceptible Populations,” existing studies are limited due to indirect measures of pollution exposures, lack of refined windows of measurement to explore windows of susceptibility, inconsistent outcome definition, inability to capture early loss, and lack of data to explore susceptible subpopulations. As such, prospective cohort studies with diverse participants and more direct and refined windows of air pollution measurements are critical. Despite feasibility challenges, the availability of wearable technology and the relatively short window of pregnancy may present a unique opportunity to advance the field. Additionally, efforts are needed to standardize reporting practices, explore interactions between pollutants and mixture effects, and identify windows of susceptibility and vulnerable subpopulation. As the most impacted communities, who know best regarding solutions for their communities, are often excluded from research and other efforts, it is critical to ensure that all our efforts are inclusive. As such, quality data are also needed in underserved areas.
where environmental issues are common and pregnancy loss risks are high due to structural and social problems.

**Conclusion**

Mounting evidence suggests both short- and long-term exposures to air pollution may increase the risk of pregnancy loss. As the climate shifts to conditions increasingly conducive to higher air pollution exposure, these risks will likely be a growing public health concern. While awaiting larger preconception studies to further understand the causal impacts, multi-disciplinary efforts to minimize exposures among pregnant women are warranted. These efforts should involve policy makers, public health practitioner, healthcare providers, researcher, industry partners, community partners, and the public.

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**Declarations**

**Human/Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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