HHS Public Access

Author manuscript

Rev Environ Health. Author manuscript; available in PMC 2020 April 27.

Published in final edited form as:

Rev Environ Health. 2018 September 25; 33(3): 247–264. doi:10.1515/reveh-2017-0033.

Air pollution exposure during pregnancy and spontaneous abortion and stillbirth

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Abstract

The developing fetus is particularly susceptible to environmental pollutants, and evidence has shown adverse effects of air pollutants on pregnancy and birth outcomes. Pregnancy loss, including spontaneous abortion (miscarriage) and stillbirth, is the most severe adverse pregnancy outcome. This review focuses on air pollution exposure during pregnancy in relation to spontaneous abortion and stillbirth. A total of 43 studies are included in this review, including 35 human studies and eight animal studies. Overall, these studies suggest that exposure to air pollutants such as particulate matter (PM), carbon monoxide (CO) and cooking smoke may be associated with higher risk for stillbirth and spontaneous abortion. PM_{10} exposure during an entire pregnancy was associated with increased risk of spontaneous abortion, and exposure to $PM_{2.5}$ and PM_{10} in the third trimester might increase the risk of stillbirth. CO exposure during the first trimester of pregnancy was associated with an increased risk of spontaneous abortion and exposure during the third trimester was associated with an increased risk of stillbirth. Cooking smoke was found to increase the risk of stillbirths, and the evidence was consistent. Insufficient and conflicting evidence was found for various other pollutants, such as NO_2 and SO_2. Studies did not show clear evidence for associations between pregnancy loss and others pollutants such as heavy

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Conflict of interest: Authors state no conflict of interest.

Informed consent: Informed consent is not applicable.

Ethical approval: The conducted research is not related to either human or animal use.

metals, organochlorine compounds, PAH and total dust count. Further research is warranted to better understand the relationship between air pollution exposure and pregnancy loss.

Keywords

cooking smoke; fetal death; intrauterine mortality; miscarriage; particulate matter

Introduction

In 2012, the World Health Organization (WHO) estimated that ambient (outdoor) air pollution was the cause of 3.7 million premature deaths, and household (indoor) air pollution was the cause of 3.8 million premature deaths worldwide. Air pollution has been associated with the increased risk of respiratory disease (1), cardiovascular disease (2), cerebrovascular disease (3) and lung cancer (4) in adults. In particular, $PM_{2.5}$ (particulate matter with aerodynamic diameter less than 2.5 μm), a heterogeneous mixture of solid and liquid particles, is a harmful risk factor in ambient air pollution and can elicit a wide range of biological responses (5). Due to its small size and large surface area, $PM_{2.5}$ can enter the human respiratory tract and participate in blood circulation. Inflammation and oxidative stress could also be pathways by which exposure to air pollution may result in adverse pregnancy outcomes, as well as particles capable of passing through the blood-brain barrier and placental barrier (6). Research on air pollution exposure and the developing fetus are emerging but still undetermined.

The developing fetus is thought to be particularly susceptible to environmental pollutants, including air pollution. Evidence has shown adverse effects of air pollutants on maternal health and pregnancy outcomes including preterm birth, low birth weight, intrauterine growth restriction and congenital anomalies (7, 8). Pregnancy loss includes spontaneous abortion (miscarriage), usually defined as the loss of the fetus before 20 weeks of pregnancy, and stillbirth, usually defined as the loss of the fetus after 20 weeks of pregnancy. Pregnancy loss is the most severe adverse pregnancy outcome, but understanding around the cause of fetal death is limited. Detrimental effects of environmental pollution on spontaneous abortion and stillbirth have been previously suggested with exposure to magnetic fields (9, 10), parental smoking and environmental tobacco smoke (11, 12). However, the relationship between air pollution and pregnancy loss has not been well studied.

Spontaneous abortion, or miscarriage, is considered the most common and severe complication of early pregnancy, with an incidence of 17–22% of all recognized pregnancies (13). The true rate of pregnancy loss is difficult to determine, and some authors have suggested 20–40% of all losses may occur before clinical detection (14, 15). In 2009, the WHO reported that 2.6 million stillbirths occurred worldwide, and more than 7200 stillbirths occur every day (16). Several potential causes of stillbirth have been reported as umbilical cord accidents, congenital anomalies, placental abruption and smoking during pregnancy (17). In the last 10 years, literature has been emerging on the topic of air pollution and pregnancy loss, however, the evidence has not been reviewed systematically. Two recent reviews evaluated the effect of exposure to ambient air pollution and adverse pregnancy

outcomes. Zhu et al. evaluated the effect of exposure to $PM_{2.5}$ on pregnancy outcomes, but included only one study on stillbirth and none on spontaneous abortion (5). Siddika et al. evaluated the effect of exposure to ambient air pollution and stillbirth, but included no studies on spontaneous abortion (18). The purpose of this review was to collect and analyze the growing literature to better understand the effects of air pollution on spontaneous abortion and stillbirth.

Methods

A literature search was performed until March 2018 in PUBMED. The search combined terms related to air pollution exposure and spontaneous abortion or stillbirth outcomes. All study types were included in this review, including: ecological, time-series, case-control, cohort and experimental. Animal studies were included to focus on possible biological mechanisms relevant to human studies. Occupational studies were included to focus on highly exposed populations. This review excluded any study with the major environmental exposure of environmental tobacco smoke.

Our primary outcome of interest was spontaneous abortion and stillbirth. Synonyms for these keywords (i.e. miscarriage, intrauterine death, etc.) were also used in the search. Specific definitions of the outcomes were not used when determining which articles to include as each study may define abortion or stillbirth differently. The following keywords were used to search for outcomes related to spontaneous abortion or stillbirth: spontaneous abortion, miscarriage, stillbirth, intrauterine fetal death, intrauterine mortality and missed abortion.

Air pollutants are a mixture of many contaminants, therefore we searched for various air pollutants in this review. These exposures included air pollution, particulate matter (PM), particles, sulfur dioxide (SO_2), carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), total dust count (TDC), respirable dust concentration (RDC), suspended dust concentration (SDC), total suspended particles (TSP), household air pollution (HAP), indoor air pollution (IAP), cooking smoke, hydrogen sulfide (H_2S), diesel exhaust particles, polycyclic aromatic hydrocarbons (PAH), smoke, biomass, carbon disulfide (CS_2), solid fuel, benzene, volatile organic compounds (VOC), lead dust and lead fumes. All articles searched were carefully reviewed for inclusion. Those articles were excluded if they did not pertain to the air pollution exposure or the outcome being investigated. Reference lists of all relevant articles were screened for any articles that may have been overlooked.

A total of 43 studies that met the inclusion criteria are included in this review. Eight of the articles were animal studies (Table 1). Seventeen studies focused on spontaneous abortion (Table 2), four of which focused on occupational exposures and spontaneous abortion (Table 3), and 22 studies focused on stillbirth (Table 4). Four studies investigated both spontaneous abortion and stillbirth as the outcome (27, 29, 30, 32).

Results and discussion

The studies included in this review varied by population, geographic location, study design and exposure assessment. Study designs included were ecological, time series, cross-

sectional, case-control and cohort study. For exposure measurements, 13 studies used self-reporting measures, such as a questionnaire or interview, 21 studies used routine monitoring stations and two studies used biological measurements (32, 35). The exposure period was not consistent across all studies. Most studies focused on exposure throughout the entire pregnancy, however, some were able to look at specific time periods during pregnancy. The outcome definition was also different across the studies.

Particulate matter

Particulate matter and spontaneous abortion—Out of the seven studies that focus on PM exposure throughout the entire pregnancy and spontaneous abortion, four provide strong evidence that there is an association between exposure to PM throughout the entire pregnancy and increased risk of spontaneous abortion (28, 36, 37, 39). A prospective cohort found a significant increased hazard ratio of 1.13 per interquartile range increase for $PM_{2.5}$ and spontaneous abortion throughout the entire pregnancy (39). Two retrospective cohorts found significant increased AORs of 5.05 and 2.59 with spontaneous abortion for w >56.72 $\mu g/m^3$ PM_{10} vs. ≤56.72 $\mu g/m^3$ PM_{10} (36, 37). Both studies had recruited around 400 participants from fertility clinics. One time series study reported a 20% increased risk of spontaneous abortion per 10 $\mu g/m^3$ increase in PM_{10} exposure [adjusted risk ratio (ARR) = 1.20, 95% confidence intervals (CI) 1.08–1.34] (28). A case-control study failed to confirm the association with PM_{10}, but suggested that TSP exposure in the first 14 weeks of pregnancy during the heating period (December to May) has a doubled risk of spontaneous abortion [adjusted odds ratio (AOR) = 2.04, 95% CI: 1.01–4.13] (31). Although evidence on PM_{10} and spontaneous abortion is strong, the limited data on $PM_{2.5}$ exposure warrants more research in this area.

Particulate matter and stillbirth—Overall, the results between particulate matter and stillbirth are controversial. Six cohort studies were conducted, with three large studies finding significant associations between PM exposure in the third trimester and stillbirths (54, 58, 60). The cohort study from the United States found a 42% increased stillbirth risk with exposure to high levels of $PM_{2.5}$ (>12 $\mu g/m^3$) in the third trimester (AOR = 1.42, 95% CI: 1.06–1.91) (54), and the cohort study from Korea found an 8% increased stillbirth risk per 10 $\mu g/m^3$ increase in PM_{10} exposure in the third trimester (AOR = 1.08, 95% CI: 1.02–1.14) (58). No association was found between exposure in the first and second trimester and stillbirths in both studies (54, 58). A prospective cohort from China found an 8% increased stillbirth risk per 10 $\mu g/m^3$ increase in PM_{10} exposure in the third trimester (AOR = 1.08, 95% CI: 1.04–1.11) and a 12% increased stillbirth risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure in the third trimester (AOR = 1.12, 95% CI: 1.07–1.19) (60). The study also found a 60% increased stillbirth risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure throughout the entire pregnancy (AOR = 1.60, 95% CI: 1.34, 1.91). The other two cohort studies, a case-control, and two time-series study showed null results (27, 38, 46, 52, 57). Two other studies, a cross-sectional and a cohort, found insignificantly increased risk for stillbirth from increased PM_{10} and $PM_{2.5}$ exposure throughout the pregnancy (38, 47), while a case-control study from California found a 6% increased stillbirth risk per interquartile range increased in $PM_{2.5}$ exposure among all stillbirths (AOR = 1.06, 95% CI: 1.01, 1.11) (51). Many of the previous studies found a strong association between high particulate matter exposure and

stillbirths. As stillbirths were often described as fetal deaths occurring ≥20 weeks of gestation and the third trimester is assumed to start from 27th week of gestation, it is difficult to determine whether these findings can be attributed to an acute exposure to pollutants in the third trimester or rather relatively chronic exposure during the first and second trimester. Regardless of this issue, the results from the previous studies are not consistent and further studies are necessary to elucidate the association between particulate matter exposure and stillbirths.

Cooking smoke

Cooking smoke and spontaneous abortion—The only available epidemiological evidence on the association between exposure to cooking smoke and spontaneous abortion is from a case-control study conducted in Sri Lanka (34). This study reported that compared to women who carried a viable fetus, those who had miscarriages (defined as partial or full expulsion of fetus ≤28 weeks of pregnancy) during the second trimester were 283% more likely to be exposed to cooking smoke (from burning firewood) during their pregnancy. While this study provides suggestive evidence on the association between cooking smoke and spontaneous abortions, these results should be interpreted with caution as they are based on a low case-yield. Smoke from burning biomass fuels contains many pollutants including particulate matter, carbon monoxide and polycyclic aromatic hydrocarbons. Additional evidence from future studies is necessary to determine how this mixture of pollutants can influence the risk of spontaneous abortions.

Cooking smoke and stillbirth—Overall, one time-series, three cross-sectionals, a case-control and two cohort studies measured the association between cooking smoke and stillbirth, with all but one providing strong evidence for the positive association between cooking smoke and stillbirth (45, 48–50, 53, 55, 59). A prospective cohort that took place in India, Pakistan, Kenya, Zambia and Guatemala found a 66% increase in macerated stillbirths, death occurring pre-partum, and 43% increase in non-macerated stillbirths, death occurring intrapartum, among women who use polluted fuel compared to those who use clean fuel (AOR = 1.66, 95% CI: 1.23–2.25; AOR = 1.43, 95% CI: 1.15–1.85) (59). Among three cross-sectional studies conducted in India, two studies found a 26%, and 171% increase in stillbirths among women exposed to biomass fuels (AOR = 1.26, 95% CI: 1.12–1.43; AOR = 2.71, 95% CI: 0.99–∞, respectively) (49, 50). The third cross-sectional study reported that stillbirth rate increased by 24%, 36%, and 23% among women who used wood fuel, kerosene and other fuels respectively compared to the use of electricity (48). A case-control study found a 50% increase in stillbirths among women exposed to cooking smoke (AOR = 1.5, 95% CI: 1.0–2.1), and a time series study found a 111% increase in stillbirth rates among women who use biomass fuel compared to women who use cleaner fuel (AOR = 2.11, 95% CI: 1.74–2.57) (45, 53). There was only one study that did not find an association between exposure to cooking smoke and increased risk of stillbirth (55). These results suggest a strong association between cooking smoke exposure and stillbirth.

Nitrogen dioxide

Nitrogen dioxide and spontaneous abortion—Six studies were conducted, of which one reported a positive relationship between NO_2 exposure and spontaneous abortion, with

estimated small magnitude (33). The case-control study from Iran found a 4% increase in spontaneous abortion among those exposed to higher concentrations of NO_2, compared to those exposed to lower concentrations of NO_2 (AOR = 1.04, 95% CI: 1.02–1.05). A prospective cohort in the United States reported an 18% increase on spontaneous abortion for those individuals in the top 90th percentile of annual average daily traffic exposure compared to the bottom 75th percentile, in which the main pollutant analyzed was NO_2 (AOR = 1.18, 95% CI: 0.87–1.60) (61). However, the other four studies failed to support the above findings (27, 28, 31, 39). These results are inconclusive, suggesting more studies need to analyze this association.

Nitrogen dioxide and stillbirth—Three studies, two cohort studies and a cross-sectional study, found increased stillbirths with exposure to NO_2 (38, 47, 60). The retrospective cohort from the United States found an 8% increase in stillbirth rates per 10-ppb increase in NO_2 throughout the entire pregnancy, and a 3% increase in stillbirth rates per 10-ppb increase in NO_2 during the third trimester (AOR = 1.08, 95% CI: 1.03–1.13; AOR = 1.03, 95% CI: 0.99–1.08) (38). The prospective cohort from China found a 13% increase in stillbirth rates per 10 $\mu g/m^3$ increase in NO_2 in the third trimester (AOR = 1.13, 95% CI: 1.07–1.21) (60). The cross-sectional study from the United States found a 27% increase in stillbirth rates per 10-ppb increase in NO_2 concentration (AOR = 1.27, 95% CI: 1.04–1.55) (47). Five additional studies measured the association between NO_2 and stillbirth but produced insignificant results (27, 44, 46, 52, 56). These studies suggest inconclusive results.

Sulfur dioxide

Sulfur dioxide and spontaneous abortion—Two case-control studies found significant associations between sulfur dioxide exposure and spontaneous abortion (27, 31, 32). A study from Croatia found frequencies of spontaneous abortion were lower when the local coal power plant was closed compared to when the power plant was open ($p < 0.05$) (32), and a study from China found fetal loss within 14 weeks was associated with exposure to SO_2 (AOR = 19.76, 95% CI: 2.34–166.71) (31). These results suggest a strong relationship between sulfur dioxide exposure and spontaneous abortion.

Sulfur dioxide and stillbirth—Three studies found significant associations between SO_2 and stillbirth (32, 47, 60). The case-control study from Croatia found that frequencies of stillbirth were lower in the control group compared to the exposed group ($p < 0.05$) (32). A cross-sectional study from the United States found a 26% increase in stillbirths per 3-ppb increase in SO_2 in the third trimester (AOR = 1.26, 95% CI: 1.03–1.37), and a prospective cohort from China found a 26% increase in stillbirths per 10 $\mu g/m^3$ increase in SO_2 in the third trimester (AOR = 1.26, 95% CI: 1.16–1.35) (47, 60). However, there are also six studies that found no association between SO_2 and stillbirth (27, 38, 44, 46, 52, 56).

Carbon monoxide

Carbon monoxide and spontaneous abortion—Only three studies analyzed carbon monoxide exposure and spontaneous abortion, and the results are conflicting (27, 33, 39). A case-control study from Iran found a 95% increase in spontaneous abortions in cases compared to controls (AOR = 1.95, 95% CI: 1.50–2.55) (33), but a time series study found

no association between spontaneous abortion and exposure to carbon monoxide, and a prospective cohort found null results (27, 39). These studies produced inconclusive results, suggesting more studies need to be done in this area.

Carbon monoxide and stillbirth—So far, three published studies found significant associations between carbon monoxide and stillbirth (38, 47, 60). The retrospective cohort from the United States found a 1% increase in stillbirth per 1-ppm increase in CO in the third trimester and a 4% increase in stillbirth per 1-ppm increase in CO throughout the entire pregnancy (AOR = 1.01, 95% CI: 0.95–1.07; AOR = 1.04, 95% CI: 0.97–1.12) (38). A cross-sectional study from the United States found a 14% increase in stillbirth per 0.4-ppm increase in CO in the third trimester and a 13% increase in stillbirth per 0.4-ppm increase in CO throughout the entire pregnancy (AOR = 1.14, 95% CI: 1.06–1.24, AOR = 1.13, 95% CI: 0.99–1.29) (47). A prospective cohort found a 1% increase in stillbirth per 10 $\mu g/m^3$ increase in CO in the third trimester (AOR = 1.01, 95% CI: 1.00–1.01) and an 18% increase in stillbirth per 10 $\mu g/m^3$ increase in CO throughout the entire pregnancy (AOR = 1.18, 95% CI: 1.04–1.34) (60). However, a case-control study from Taiwan found null results (52) and three other studies found no association (27, 46, 56).

Ozone

Ozone and spontaneous abortion—Four studies examined the effect of ozone on spontaneous abortion, with three producing strong results (27, 28, 33, 39). A time-series study from Italy found a 34% increased risk of spontaneous abortion per 10 $\mu g/m^3$ increase in ozone (AOR = 1.34, 95% CI: 1.26–1.42) (28). A case-control study from Iran found a 10% increased risk of spontaneous abortion in cases exposed to ozone compared to controls (AOR = 1.10, 95% CI: 1.06–1.13) (33). A prospective cohort found a 12% increased risk of spontaneous abortion per interquartile range increase in ozone throughout the entire pregnancy (HR = 1.12, 95% CI: 10.7–1.17) (39). Another time series study produced null results (27). These results suggest an association between ozone and spontaneous abortion, but more studies are needed to investigate this association.

Ozone and stillbirth—Six studies examined the effect of ozone on stillbirth (27, 38, 46, 52, 56, 60). A retrospective cohort from the United States found an 18% increased risk in stillbirth per interquartile range increase in average daily exposure in the first trimester, and a 39% increased risk in stillbirth per interquartile range increase in average daily exposure throughout the whole pregnancy (ARR = 1.18, 95% CI: 1.00–1.39; ARR = 1.39, 95% CI: 1.05–1.84) (56). Another retrospective cohort from the United States found a 3% increase in stillbirth per 10-ppb increase in ozone in the third trimester and a 1% increase in stillbirth per 10-ppb increase in ozone throughout the entire pregnancy (AOR = 1.03, 95% CI: 1.01–1.05; AOR = 1.01, 95% CI: 0.99–1.04) (38). However, the other four studies failed to observe an association between ozone and stillbirth (27, 46, 52, 60).

Other pollutants

Other pollutants and spontaneous abortion—Overall, three studies examined the effects of other pollutants not mentioned above on spontaneous abortion risk (29, 30, 35). One cross-sectional study from Brazil examined the association between different levels of

heavy metals and organochlorine compounds and risk of spontaneous abortion, but no significant results were found (29). A second cross-sectional study was conducted in Egypt which examined the association between total dust count, suspended dust concentration, and respirable dust concentration, with a significant correlation for respirable dust count ($r = 0.72$, $p < 0.05$) (30). A case-control study from China observed a 35% increased risk of missed abortion among women whose maternal blood BaP-DNA level showed evidence of PAH exposure (AOR = 1.35, 95% CI: 1.11–1.64) (35). A missed abortion is where the embryo has died but a miscarriage has not yet occurred.

Other pollutants and stillbirth—Overall, two studies examined the effects of other pollutants not mentioned above on stillbirth risk (29, 30). One cross-sectional study from Brazil examined the association between different levels of heavy metals and organochlorine compounds and risk of stillbirth (29), and a cross-sectional study from Egypt examined the association between total dust count, suspended dust concentration, and respirable dust concentration with risk of stillbirth (30). Both studies showed null results.

Occupational pollutants

Overall, two cross-sectional studies from Finland and two cohort studies from China examined the association between occupational pollutants and risk of spontaneous abortion (40–43). One cross-sectional study examined spontaneous abortion risk in an industrial community (40). Pollutants that were examined included sulfur dioxide, hydrogen sulfide and carbon disulfide. An increased rate of spontaneous abortion was found for women employed in rayon textile and paper products jobs (10.3 and 16.7, respectively, $p < 0.10$). Another occupational cross-sectional study from Finland examined the association between solvents, automobile exhaust fumes, PAH, chemical exposures, metals, textile dust and spontaneous abortion risk, however, no association was found (41). A retrospective cohort study from Shanghai, China examined the miscarriage risk among women textile workers (42). Pollutants that were measured included cotton dust, wool dust, silk dust, synthetic fibers, mixed fibers, solvents, acids and bases, resins, lubricants and metals. Women exposed to synthetic fibers had an 89% increased miscarriage risk (AOR = 1.89, 95% CI: 1.20–3.00) and women exposed to mixed fibers had a 231% increased miscarriage risk (AOR = 3.31, 95% CI: 1.30–8.42) compared to those women who were unexposed. A retrospective cohort study from Beijing, China showed a 190% increased risk of spontaneous abortion among those exposed to petrochemicals compared to those unexposed to petrochemicals (AOR = 2.9, 95% CI: 2.0–4.0) (43).

Animal studies

Overall, we found eight animal studies for this review, from which seven studies provide strong evidence that air pollution causes both spontaneous abortion and stillbirth. Animals that were analyzed in these studies included sows, mice and cattle. Pollutants analyzed included CO, PM_{10}, NO_2, benzo(*a*)pyrene, diesel exhaust particles, H_2S, SO_2, and volatile organic compounds. Both short- and long-term exposures were included due to a shorter life span.

Two studies in particular observed a dose-response relationship with exposure to air pollutants and spontaneous abortion. A study found that as the ambient level of CO increased from 150 ppm, 200 ppm, 250 ppm, 300 ppm, to 350 ppm for 48–96 h, overall stillbirths rates were 0.0%, 6.7%, 34.8%, 42.3%, and 80.0%, respectively (19). Although 48–96 h is a much shorter exposure window than compared to the human exposure window, we decided to include it in this review due to the limited number of animal studies, and the study can at least provide certain useful evidence. Another study observed pregnant mice exposed to levels of diesel exhaust particles ranging from 0.3, 1.0, to 3.0 mg/m^3, with abortion rates of 9.1%, 10.0%, and 16.7%, respectively (23).

Mice exposed to PM_{10} and NO_2 showed a decreased fertility as higher numbers of live-born mice were born in the clean chamber compared to the polluted chamber (median = 6.0 and 4.0, respectively, p-value = 0.037) (20). A study examining the effects of benzo(*a*)pyrene on rats found that out of eight females fed benzo(*a*)pyrene, there was one successful birth and eight unsuccessful births (22). Of the eight females fed benzo(*a*)pyrene, five became pregnant and only one gave birth. The female that gave birth had four pups, of which two were stillborn. The remaining pregnant females did not give birth, indicating spontaneous abortion or fetal absorption, while three out of the six female controls became pregnant and all three females delivered healthy litters. Another study observed pregnant sows in Poland that were exposed to high levels of CO (21). In the first group of sows that experienced carbon monoxide poisoning, 28/28 aborted. In the second group 26/28 aborted, in the third group 25/28 aborted, and in the group of unexposed sows none aborted. Another study that focused on carbon monoxide poisoning in sows found 28% of piglets were stillborn in the first CO poisoning incident, and 52.9% were stillborn in the second CO poisoning incident (26). Waldner et al. conducted two animal studies focusing on exposure in cows from the oil and gas industry and birth outcomes (24, 25). The first study with 23 herds of cattle investigated a natural gas leak from a pipeline and calf mortality found null results (24). The other study showed that the risk of spontaneous abortion and stillbirth was 2.6% for cows with higher exposure to oil- and gas-production facilities compared to those who were less exposed (25). Overall, the animal studies included in this review provide supporting evidence that pollutants such as CO, diesel exhaust particles, benzo(*a*) pyrene and pollutants from oil and gas production lead to an increased risk for spontaneous abortion and stillbirth.

Biological mechanisms

The biological mechanisms behind particulate matter and spontaneous abortion and stillbirth are not well understood. It has been hypothesized that particulate matter may impair reproductive health in women by: [1] affecting the placental interface between the mother and the fetus by compromising delivery of maternal blood and nutrients to the placenta, impairing embryo development (62); [2] contributing to oxidative stress through oxidative activities of combustion-derived particles adversely affecting the embryo in its earliest stage of growth, which can lead to DNA damage and inflammation (63, 64); [3] escaping phagocytosis by alveolar macrophages and translocating to extrapulmonary organs due to the high respiratory deposition of ultrafine particles (65); or [4] increasing concentration of DNA adducts, which may lower the efficiency of the transplacental function, resulting in decreased fetal health ultimately leading to stillbirth (66). The exposure to the fetus at

different periods of development may have differing effects because of differences in physiologic maturity of the fetus (63, 64). While many pathways between PM and spontaneous abortion and stillbirth have been proposed, none have been proven.

The overall mechanisms through which air pollution exposure potentiates stillbirth and spontaneous abortion remains unclear, with the toxic effects of CO on the fetus the only pathway that is well established. First, CO reduces the oxygen-carrying capacity of maternal hemoglobin, which could affect oxygen delivery to the fetal circulation (67); second, CO crosses the placental barrier due to fetal hemoglobin having a greater affinity for binding CO than adult hemoglobin, therefore further compromising oxygen delivery to the fetus.

Pathways involving NO_2, SO_2, and O_3 are still under investigation. These pollutants can cross the placenta and damage the embryo during critical stages of development by causing irreversible damage to dividing cells (66, 68), or by triggering hypoxic damage or immune-mediated injury (63, 68). Cooking smoke, or smoke from solid fuel combustion, is comprised of many different pollutants, including particulate matter, carbon monoxide, and other organic compounds.

Methodological issues

One reason for the limited number of data on air pollution and spontaneous abortions is partially due to data collection. Women can have a spontaneous abortion before they even realize they are pregnant, resulting in a large portion of unrecognized spontaneous abortions. In developing countries, spontaneous abortion and stillbirth are still a major health problem, with much of the data underre-ported or unreliable (69). Another issue is the definition of the outcomes. Every country, or state in the United States, has their own definition of what constitutes a spontaneous abortion and stillbirth. The various definitions make it difficult to compare the results across the studies. Some studies included in this review presented associations between pollutant exposure during individual trimesters and stillbirths. Considering that women could be exposed to pollutants for only a short period during third trimester; at least some stillbirths occurring during this period could be attributed to an acute exposure to these pollutants. For example, Mendola et al. showed that acute (1 week before delivery) exposures to ozone could increase risk of stillbirths (56). On the other hand, findings from studies on the associations between third trimester exposure to pollutants and stillbirths should be interpreted with caution because of the lack of specificity in quantifying the exposure period before the occurrence of stillbirth outcome.

Many of the studies used air monitoring station data to represent individual air pollution exposure, without taking into account indoor air pollution and mobility of human activity. This limitation could result in misclassification bias. Many papers in this review reported results relating to various combinations of pollutants. Multiple pollutant models were used, and caution should be used when interpreting this data.

Summary

Our findings are inconsistent with what was found by Siddika et al. (18) and Zhu et al. (5). For $PM_{2.5}$, Zhu et al. (5) indicated there was no evidence of a statistically significant effect

on stillbirth with an increase of 10 μg/m^3. These findings were consistent with those found by Siddika et al. (18). However, Siddika et al. (18) found an increase per 4 μg/m^3 in the first and second trimesters, though not significant. They also found a small, non-significant increased risk of stillbirth with SO_2 and CO exposure throughout the entire pregnancy. It is hard to compare these results with ours, as we did not do a meta-analysis. However, the evidence presented in this review suggests various air pollutants as a risk factor for spontaneous abortion and stillbirth. Consistent results were observed for PM_{10} exposure and spontaneous abortion, and for PM_{10} and $PM_{2.5}$ exposure in the third trimester and increased risk of stillbirth. Exposure to cooking smoke also produced consistent and strong results with increased risk of stillbirth. Exposure to SO_2 and CO showed inconsistent results. Pollutants such as heavy metals, organochlorine compounds, PAH, and total dust count produced no evidence. More evidence is needed.

Research funding:

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Environmental Health Sciences R21ES026429.

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Table 1:

Summary of the animal studies literature.

Reference	Subjects (n)	Pollutants analyzed	Results				
Dominickand Carson (19)	18 Sows	CO	**Ambient CO level, ppm**	**Live births**	**Stillbirths**	**Stillbirths, %**	
			Control	22	1	4.3	
			150	13	0	0	
			200	14	1	6.7	
			250	15	8	34.8	
			300	15	11	42.3	
			350	5	20	80	
Mohallem et al. (20)	40 Female mice	PM_{10}, NO_2	**Chamber**	**Live-born pups**	**Live-born pups per mouse (median)**	**Reabsorptions/fetal deaths per mouse (median)**	
			Clean	106	6	1	
			Polluted	75	4	2	
Pejsak et al. (21)	1100 Sows	CO	**Farrowing unit**	**Number of sows that aborted**			
			D (January 2006)	28/28			
			D (March 2006)	25/28			
			H	26/28			
Rigdon and Rennels (22)	14 Female rats	Benzo[a]pyrene		**Untreated**	**Treated**		
			Successful births	3	1		
			Unsuccessful births	3	8		
Tsukue et al.(23)	60 Female mice	DEP	**Diesel exhaust particle concentration, mg/m^3**				
				Control (0.0)	0.3	1.0	3.0
			Number of abortions, %	0 (0%)	1 (9.1%)	1(10.0%)	2(16.7%)
Waldner et al. (24)	23 Herds of cattle	H_2S	**Health measure**	**Investigational herds (n = 18)**	**Control herds (n = 5)**		
			Abortion risk	0.0 (0.0–3.0)	0.0 (0.0–3.9)		
			Stillbirth risk	1.6(0.0–6.0)	1.9(1.3–3.3)		
			*Data expressed as median % (range %)				

Reference	Subjects (n)	Pollutants analyzed	Results		
Waldner (25)	28,144 Cows for abortion assessment, 28,402 Calves for stillbirth assessment	SO_2, H_2S, VOC		**Summary risk for study population**	
			Productivity outcome	**%**	**n**
			Risk of abortion	2.6	739
			Risk of stillbirth	2.6	739
Wood (26)	16 Sows	CO	**Incident**	**Total piglets born**	**Piglets dead at birth (% of total)**
			Incident 1	1198	335(28%)
			Incident 2	68	36 (52.9%)

Table 2:

Summary of the literature investigating the relationship between air pollutants and spontaneous abortion.

Reference	Location	Study design	Study population (SAB/ confirmed pregnancies)	Outcome definition	Exposure	Exposure assessment	Major findings	Notes
Dastoorpoor et al. (27)	Iran	Time series	1334/49,173 Births	Fetal loss ≤20 weeks' gestation	PM_{10}, CO, NO, NO_2, SO_2, O_3	Khuzestan Province EPA daily measurements	Rate ratio (95% Cl) per 10 μg/m^3 increase: Cumulative Lag (Lag 0 to 14) PM_{10}:1.01 (1.00,1.02) CO: 0.28 (0.07, 1.08) NO: 1.00(0.84,1.20) NO_2: 1.10(0.99,1.23) SO_2: 1.01 (0.96, 1.07) O_3: 1.00(0.98,1.10) Lag 0: SO_2: 1.01 (1.00, 1.02)	Adjustments for trend, seasonality, temperature, relative humidity, weekdays, holidays
Di Caula and Bilancia (28)	Italy	Time series	984 Cases	Fetal loss within 180 days of gestation	PM_{10}, NO_2) O_3	Regional environmental agency average monthly levels	ARR (95% Cl) per 10 μg/m^3 increase: PM_{10}:**1.20 (1.08,1.34)** NO_2: 0.96 (0.87, 1.05) 0_3:**1.34 (1.26,1.42)**	Adjustments for temperature and humidity
Guimarães et al. (29)	São Paulo, Brazil	Cross-sectional	199/4296	Fetal loss <20 weeks' gestation	Heavy metals, organochlorine compounds	Questionnaire and interview	AOR (95% Cl): Area l[a]: 1.04 (0.66,1.65) Area 2[b]: 1.06 (0.64, 1.74) Area 3[c]: 1.55 (0.98, 2.46) Area 4[d]: 1.12 (0.69, 1.81) Area 5: Control	Adjustments for time of residence in region, age group, education, marital status, family income, current and past occupational exposure, alcohol and tobacco use, prenatal care; [a]: Industrial and petrochemical landfill [b]: Industrial center [c]: Chemical and pesticides landfills [d]: Chemical industry and port
Hafez etal. (30)	Egypt	Cross-sectional	565/1934	Did not report definition	TDC, SDC, RDC	Questionnaire	AOR: TDC (Mppcf): 33.04 SDC (μig/m^3): 0.03 RDC (μg/m^3): **0.72 (p<0.05)**	Adjustments for education, lead concentration, occupation, SES, smoking, RDC, SDC; No Cl reported
Hou etal. (31)	Tianjin, China	Case-control	959 Cases 959 Controls	Evidence of fetal pole ≥6 mm within intra-uterine	SO_2, TSP, PM_{10}, NO_2	Tianjin air monitoring stations daily and monthly concentrations	AOR fetal loss within 14 weeks (95% Cl): SO_2:**19.76 (2.34,166.71)**	Only SO_2 and TSP selected for logistic regression model Adjustments for

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Reference	Location	Study design	Study population (SAB/ confirmed pregnancies)	Outcome definition	Exposure	Exposure assessment	Major findings	Notes
				gestationalsac, but absence of heartbeat			TSP**: 2.04 (1.01, 4.13)**	maternal age, gravidity, parity, gestational age
Mohorovic eta 1.(32)	Croatia	Case-control	3/138 vs. 6/122	Did not report definition	SO_2	Maternal methemoglobin	**Frequencies of SAB lower in clean period compared to dirty period (p<0.05)**	Frequencies lower in the control compared to the "exposure"
Moridi et al. (33)	Tehran, Iran	Case-control	148 Cases 148 Controls	Fetal loss <14 weeks' gestation	PM_{10}, CO, NO_2, O_3,SO_2	Tehran air quality control company annual average concentration	AOR (95% Cl) cases vs. controls: PM_{10}: 1.01 (1.00, 1.02) CO: **1.95 (1.50, 2.55)** NO_2:**1.04 (1.02,1.05)** O_3:**1.10 (1.06,1.13)**	$S0_2$p value > 0.05; Adjustments for maternal and paternal age, cigarette smoke exposure, occupation, pre-pregnancy BMI, other demographic parameters
Samaraweera and Abeysena (34)	Sri Lanka	Case-control	230/731	Confirmed diagnosis of partial or full expulsion of fetus ≤28 weeks	Cooking smoke	Self-report	AOR (95% Cl) exposure to smoke generated by cooking in a kitchen without a chimney: Second trimester: **3.83 (1.50, 9.90)**	Adjustments for maternal age, pre-pregnancy BMI, parity, previous abortions, education, employment, walking/standing/sitting/ sleeping per day, stressful life events, medication, passive smoke, cooking smoke
Wuetal. (35)	Tianjin, China	Case-control	81 Cases 81 Controls	Confirmed dead in-utero fetus <14 weeks' gestation	PAH	Interview, aborted tissue, maternal blood draw (102 subjects)	AOR of missed abortion (95% Cl): **1.35(1.11,1.64)** Maternal blood BaP-DNA level per adduct/10^8 nucleotides	Adjustments for maternal education and household income
Perin et al. (36)	São Paulo, Brazil	Retrospective cohort	34/177 IVF/ET patients, 18/354 Control patients	First trimester loss: loss in first 12 weeks	PM_{10}	São Paulo EPA (CETESB) daily levels	AOR Women exposed to >56.72 μg/m^3 vs. ≤56.72 ng/m^3: **2.585 (p = 0.00)**	OR for women exposed to the Q4 period (>56.72 μg/m^3) during the follicular phase of conception compared to women exposed to Q1–Q3 periods (0, 56.72 μg/m^3).
Perin etal. (37)	São Paulo, Brazil	Retrospective cohort	45/348 IVF/ET patients	Pregnancy diagnosed with pos. serum p"hCG that failed to reach the 12 weeks gestation	PM_{10}	São Paulo EPA (CETESB) daily levels	AOR (95% Cl) Women exposed to >56.72 μg/m^3 vs. ≤56.72 (μg/m^3: **5.05(1.04,25.51)**	Adjustments for level of PM_{10}
Green etal. (38)	CA, USA	Prospective cohort	499/4979	Pregnancy ending ≤20 weeks	NO_2, AADT	California Air Resources Board and Spatial Variation	AOR (95% Cl): 1.18 (0.87,1.60) for top 90th Percentile of AADT vs. bottom 75th percentile AADT	Adjustments for maternal age, race/ethnicity, SES, cigarette smoke exposure, employment status, stressful life events

Reference	Location	Study design	Study population (SAB/ confirmed pregnancies)	Outcome definition	Exposure	Exposure assessment	Major findings	Notes
Haetal. (39)	United States	Prospective cohort	97/246	Neg. pregnancy test after pos. test, clinically confirmed loss, or onset of menstruation	$PM_{2.5}$, PM_{10}, CO, NO_2, O_3,SO_2	Community multiscale air quality models	HR for IQR increase: Entire pregnancy: $PM_{2.5}$:**1.13 (1.03,1.24)** PM_{10}: 1.02 (0.99, 1.06) CO: 1.00 (1.00, 1.00) NO_2: 1.03(0.98,1.08) O_3: 1.12(1.07,1.17) SO_2: 1.01 (0.77, 1.34)	Adjustments for season study site, maternal age, race, education, income, parity condition on gravidity, early pregnancy caffeine intake, BMI, early pregnancy adherence to multivitamin intake, maternal blood cotinine level, paternal blood cotinine level

SAB, Spontaneous abortion; $PM_{2.5}$, particulate matter ≤ 2.5 μm; PM_{10}, particulate matter ≤ 10 μm; CO, carbon monoxide; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone; TDC, total dust count; SDC, suspended dust concentration; RDC, respirable dust concentration; TSP, total suspended particles; H_2S, hydrogen sulfide; AADT, annual average daily traffic; IVF, in vitro fertilization; ET, embryo transfer; AOR, adjusted odds ratio; COR, crude odds ratio; ARR, adjusted risk ratio; HR, hazard ratio; IQR, interquartile range; BMI, body mass index; CI, confidence intervals. Values in bold indicate significant confidence intervals.

Table 3:

Summary of the literature investigating the relationship between occupational exposure and spontaneous abortion.

Reference	Location	Study design	Study population (SAB/ confirmed pregnancies)	Exposure	Outcome definition	Exposure assessment	Major findings	Notes
Hemminki and Niemi (40)	Finland	Cross-sectional	116/1792	SO_2, H_2S, CS_2	Fetal loss <20 weeks' gestation	Institute of Meteorological Sciences data regional mean concentrations	Increased rate of SAB ($p< 0.10$) for women employed in rayon textile and paper products jobs	Increased rate for women employed in rayon textile jobs and paper products jobs
Lindbohm etal. (41)	Finland	Cross-sectional	4896/68,327	Solvents, automobile exhaust fumes, PAH, chemical exposures, metals, textile dust	Fetal loss <20 weeks' gestation	1975 National Population and Housing Census	ARR (95% Cl): exposed vs. unexposed Solvents: 0.79 (0.58, 1.07) Automobile exhaust fumes: 1.16 (0.73, 1.85) PAH: 0.89 (0.60, 1.30) Other chemicals: 0.93 (0.78,1.29) Metals: 0.78 (0.54,1.13) Textile dust: 1.07 (0.93, 1.23)	Adjustments for age, place of residence, parity, marital status, age + parity interaction
Wong et al. (42)	Shanghai, China	Retrospective cohort	84/1429	Cotton dust, wool dust, silk dust, synthetic fibers, mixed fibers, solvents, acids and bases, resins, lubricants, metals	Miscarriage <20 weeks' gestation	Self-report	AOR (95% Cl): exposed vs. unexposed Cotton dust: 0.98 (0.62, 1.56) Wool dust: 0.87 (0.40,1.87) Silk dust: 1.66(0.67,4.08) Synthetic fibers: **1.89 (1.20, 3.00)** Mixed fibers: **3.31 (1.30,8.42)** Solvents: 0.54 (0.24,1.21) Acids and bases: 0.60 (0.21,1.71) Resins: 1.91 (0.64, 5.68) Lubricants: 0.78 (0.49,1.24) Metals: 0.44 (0.13,1.45)	Adjustments for age at pregnancy, education level, smoking status of women and spouse, alcohol use, women's year of birth, first pregnancy, all pregnancies
Xuetal. (43)	Beijing, China	Retrospective cohort	175/2853	Petrochemicals	Self-report	Interview	AOR (95% Cl) exposed vs. unexposed: **2.9** (2.0,4.0)	Adjustments for age, education, plant, shift work, standing/kneeling hours at work, noise level, dust concentration, passive smoke, diet

SAB, Spontaneous abortion; SO_2, sulfur dioxide; H_2S, hydrogen sulfide; CS_2, carbon disulfide; AOR, adjusted odds ratio; ARR, adjusted relative risk. Values in bold indicate significant confidence intervals.

Table 4:

Summary of the literature investigating the relationship between air pollutants and stillbirth.

Reference	Location	Study design	Study population (stillbirths/confirmed pregnancies)	Outcome definition	Exposure	Exposure assessment	Major findings	Notes
Bobakand Leon (44)	Czech Republic	Ecological	971/223,929	Delivery of dead infant >28 weeks' gestation or weighing >1000g	SO_2, NO_2,TSP	Czech National Public Health Service daily average	AOR (95% Cl) per 50 ng/m^3 increase: SO_2: 0.90 (0.70,1.16) NO_2: 1.21 (0.89,1.64) TSP: 0.92 (0.74, 1.15)	Adjustments for mean income, mean savings, mean number of people per car, proportion of births outside marriage, proportion of divorces to new marriages, legally induced abortions, proportion of gypsies in the population
Dastoorpoor etal. (27)	Iran	Time series	907/49,173	Fetal death >20 weeks' gestation	PM_{10}, CO, NO, NO_2,SO_2,O_3	Khuzestan Province EPA daily measurements	Rate ratio (95% Cl) per 10 ug/m^3 increase: PM_{10}: 0.99 (0.98,1.00) CO: 0.54 (0.11, 2.70) NO: 0.93 (0.76, 1.13) NO_2: 1.00(0.89,1.12) SO_2: 0.91 (0.85, 0.97) O_3: 0.96 (0.94, 0.99)	Cumulative lag (Lag 0–14) Adjustments for trend, seasonality, temperature, relative humidity, weekdays, holidays
Mishra etal. (45)	India	Time series	18,567 Cases	Delivery of dead infant >28 weeks' gestation	Cooking smoke	Questionnaire	(A)OR: Model 1[a]: **2.11 (95% Cl: 1.74, 2.57)** Model 2[b]: **1.52 (95% Cl: 1.23,1.89)** Model 6[C]: **1.44 (95% Cl: 1.05,1.97)**	[a]: Biomass fuel vs. cleaner fuel [b]: Has smoked vs. never smoked [c]: Full model adjusted for nutritional status, BMI, education, religion, SES, household conditions, residence, region
Pereira etal. (46)	São Paulo, Brazil	Time series	Daily counts intrauterine mortality	Age of pregnancy >28 weeks', weight >1000g, or fetal length >35 cm	PM_{10}, CO, NO_2, SO_2,O_3	Sao Paulo Air pollution controlling agency (CETESB) daily concentrations	ARR of daily intrauterine deaths (per 10 μg/m^3 increase in PM_{10} on the concurrent day): **1.01 (95% Cl: 1.00,1.02)**	No significant associations observed for CO, NO_2,SO_2,O_3 Adjustments for limited confounders at area-based level
Faiz et al. (47)	NJ, USA	Cross-sectional	1446/343,077	Between 20 and 42 weeks' gestation (140–294 days of pregnancy) birth weight of >500g	$PM_{2.5}$, NO_2, SO_2, CO	EPA hourly measurements, every third day measurements for $PM_{2.5}$	AOR(95%CI): $PM_{2.5}$ (per 4 μg/m^3): Third trimester: 1.08 (0.79,1.48) Entire pregnancy: 1.07 (0.86,1.33) NO_2(perlO-ppb): Third trimester: 1.05 (0.90,1.23) **Entire pregnancy: 1.27 (1.04,1.55)**	Adjustments for maternal age, race/ethnicity, education, prenatal care, smoking status, neighborhood, calendar month, year of conception, mean temperature during first trimester

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							CO(per0.4-ppm): **Third trimester: 1.14 (1.06,1.24)** Entire pregnancy: 1.13 (0.99,1.29) SO_2(per3-ppb): **Third trimester: 1.26 (1.03,1.37)** Entire pregnancy: 1.13 (0.99,1.29)	
Guimarães et al. (29)	São Paulo, Brazil	Cross-sectional	22/4296	Fetal death ≥20 weeks' gestation	Heavy metals, organochlorine compounds, PAH	Questionnaire and interview	AOR(95%CI): Area 1[a]: 2.66 (0.51,13.81) Area 2[b]: 1.44 (0.20,10.32) Area 3[1]: 4.17 (0.83, 20.88) Area 4[d]: 4.76 (0.98, 23.15) Area 5: Control area	Adjustments for time of residence in region, age group, education, marital status, family income, current and past occupational exposure, alcohol and tobacco use, prenatal care; [a]: Industrial and petrochemical landfill [b]: Industrial center [c]: Chemical and pesticides landfills [d]: Chemical industry and port
Hafez et al. (30)	Egypt	Cross-sectional	651/1934		TDC, SDC, RDC	Questionnaire	AOR (All p> 0.05): TDC (mppcf) 92.35 SDC (μg/m^3) 0.01 RDC (μg/m^3) 0.86	Adjustments for education, lead concentration, occupation, SES, smoking, RDC, SDC
Lakshmi et al. (48)	India	Cross-sectional	3112 stillbirths/188,917 total births	Fetal death ≥28 weeks' gestation	Cooking fuel: wood, kerosene, other	Questionnaire	Prevalence ratio (compared to electricity): Wood: **1.24** (95% Cl: **1.08,1.41)** Kerosene: **1.36** (95% Cl: **1.10, 1.67)** Other: **1.23** (95% Cl: **1.05,1.44)**	Adjustments for literacy status, age at last pregnancy, gravid status, fetal complications, previous history of abortion, place of delivery, standard of living, house type, religion, and caste
Sehgaletal. (49)	India	Cross-sectional	26,103,870/26,519,041	≥1000g birthweight or ≥28 weeks' gestation	Biomass fuels/HAP	NSSO/SRS Report	AOR (95% Cl) biomass fuel users: **1.26(1.12,1.43)**	Adjustments for rural or urban areas
Wylie etal. (50)	East India	Cross-sectional	55/1744	Delivery of dead infant in hospital	Biomass fuels	Interview	AOR (95% Cl) wood users vs. gas users: 2.71 (0.99, ∞)	Adjustments for maternal habits, prenatal care, sociodemographic characteristics
Ebisu et al. (51)	CA, United States	Case-control	5377/26,885	Fetal death >20 weeks' gestation	$PM_{2.5}$ constit-uents	EPA monitoring stations, every third or sixth day concentrations	AOR (95% Cl) per IQR increase: All stillbirth: **$PM_{2.5}$ total mass: 1.06 (1.01,1.11)**	Adjustments for food stamp rate, matched exposure to apparent temperature, natural cubic spline of LMP with 2 df per year

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							Gestational age <28 weeks: **$PM_{2.5}$ total mass: 1.05 (0.99,1.12)** Gestational age ≥28 weeks: $PM_{2.5}$ total mass: 1.09 (1.01,1.17)	
Hwang et al. (52)	Taiwan	Case-control	9325/102,575	Fetal death >20 weeks' gestation	PM_{10},$SO_2$$NO_2$, CO, O_3	Taiwan EPA hourly concentrations	AOR(95%CI): PM_{10} (per 10 μg/m^3) 0.98 (0.94,1.01) SO_2 (per 1-ppb) 1.01 (0.99,1.03) NO_2 (per 10-ppb) 0.98 (0.92,1.04) CO (100-ppb) 1.00 (0.98,1.02) 0 (per 10-ppb) 0.97 (0.91,1.04)	Adjustments for maternal age, sex of the infant, season of conception
Mavalankar etal. (53)	India	Case-control	451 Stillbirths 1465 Controls	Delivery of dead infant in hospital	Cooking smoke	Interview	AOR(95%CI): **1.5(1.0,2.1)**	Adjustments for maternal education, previous stillbirth, >1 previous child death, last birth premature, maternal weight, anemia, antenatal factors, intrapartum factors, maternal education, caste, place of residence, toilet facilities, parity
Mohorovic etal. (32)	Croatia	Case-control	1/138 vs. 4/122	Did not report definition	SO_2	Maternal methemoglobin	**Frequencies of stillbirth lower in clean period compared to dirty period ($p < 0.05$)**	Frequencies lower in the control compared to the"exposure"
DeFranco etal. (54)	OH, USA	Cohort	1848/351,036	Fetal death ≥20 weeks' gestation	$PM_{2.5}$	EPA daily measures	AOR(95%CI) > 12μg/m^3vs. ≤12μg/m^3: First trimester: 0.77 (0.58,1.02) Second trimester: 0.80 (0.62,1.04) Third trimester: **1.42 (1.06,1.91)** Average over pregnancy: 1.21 (0.96,1.53)	Adjustments for maternal age, smoking status, race, education, prenatal care
Tielsch etal. (55)	India	Cohort	358/13,173 Deliveries	Delivery of dead infant >28 weeks' gestation	Cooking fuel	Interview	ARR(95%CI): 1.34(0.76,2.36)	Head of household occupation, number of children in household, place of delivery, roof material, religion, maternal age, education, night blindness, parity, tv/radio ownership, electricity in house, SHTS

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Green etal. (38)	CA, USA	Retrospective cohort	13,999 Stillbirths/ 3,012,270 Live births	Fetal death >20 weeks' gestation	$PM_{2.5}$,SO_2, NO_2, CO, O_3	California Resource Board average daily levels	AOR(95%CI): $PM_{2.5}$(per10μg/m^3): Third trimester: 1.01 (0.96,1.06) Entire pregnancy: 1.06 (0.99,1.13) NO_2(per 10-ppb): Third trimester: 1.03 (0.99,1.08) Entire pregnancy: **1.08** (1.03,1.13) O_3, (per 10-ppb): Third trimester: **1.03 (1.01, 1.05)** Entire pregnancy: 1.01 (0.99,1.04) CO (per 1-ppm): Third trimester: 1.01 (0.95,1.07) Entire pregnancy: 1.04 (0.97,1.12) SO_2 (per 10-ppb): Third trimester: 0.95 (0.85,1.07) Entire pregnancy: 1.02 (0.91,1.14)	Adjustments for maternal education, maternal race/ ethnicity, maternal age, sex of infant/fetus, mean daily temperature, year of conception, season of last menstrual period, and residence; only significant results were included
Mendola et al. (56)	United States	Retrospective cohort	992/223,375	Fetal death ≥23 weeks' gestation	$PM_{2.5}$, PM_{1O}, SO_2 NO_x, CO, O_3	Modified community multiscaleair quality (CMAQ) models	ARR (95% Cl), IQR increase in average daily exposure: First trimester: **O_3:1.18 (1.00,1.39)** Whole pregnancy: **O_3:1.39 (1.05,1.84)**	No significant associations observed for $PM_{2.5}$, PM_{10}, SO_2 NO_2 CO Adjustments for maternal age, race, parity, smoking and alcohol use during pregnancy, insurance status, marital status, pre-existing hypertension, pre-existing diabetes, season of conception, birth year, site, average temperature
Pearce et al. (57)	Northern England	Retrospective cohort	812/90,537	Delivery of dead infant ≥28 weeks' gestation	PM_4	Air pollution monitoring stations/weekly black smoke levels	AOR (95% Cl) per 10 μg/m^3: First trimester: 1.00 (0.99,1.02) Second trimester: 1.00 (0.99,1.02) Third trimester: 1.01 (0.99,1.02) Whole pregnancy: 1.01 (0.99,1.03)	Adjustments for trimester, year of birth, parity, maternal age, sex of the infant
Kim etal.(58)	Seoul, Korea	Prospective cohort	67/1514	Intrauterine fetal death		National Institute of Environmental	AOR (per 10 μg/m^3 increase in PM_{10}):	Adjustments for infant sex, infant order, maternal age,

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						Research hourly exposure	First trimester: 0.95 (95% Cl: 0.85,1.02) Second trimester: 1.07 (95% Cl: 0.98, 1.17) Third trimester: **1.08 (95% Cl: 1.02,1.14)**	maternal education, paternal education, season of birth, alcohol intake, BMI, maternal weight before delivery
Patel et al. (59)	India, Pakistan, Kenya, Zambia, Guatemala	Prospective cohort	1740/65,912	Fetal death >20 weeks' gestation	HAP, cooking smoke	Questionnaire	AOR (polluting fuel vs. clean fuel): Macerated: **1.66 (95% Cl: 1.23, 2.25)** Non-macerated: **1.43 (95% Cl: 1.15,1.85)**	Adjustments for maternal age, education, parity, delivery location, birth weight, infant gender, and tobacco use
Yang et al. (60)	Wuhan, China	Prospective cohort	95,354	Fetus born between 20 and 42 weeks' with no sign of life	$PM_{2.5}$, PM_{10}, SO_2 NO_2, CO, O_3	Air pollution monitoring stations, daily mean concentration	AOR (per 10 μg/m^3 increase): Third trimester: **$PM_{2.5}$:1.12 (1.07,1.19)** **PM_{10}:1.08 (1.04,1.11)** **SO_2:1.26 (1.16,1.35)** **NO_2:1.13 (1.07,1.21)** **CO: 1.01 (1.00,1.01)** Entire pregnancy: **$PM_{2.5}$:1.60 (1.34,1.91)** **CO: 1.18 (1.04,1.34)**	No significant associations observed for O_3 Adjustments for maternal age, occupation, high risk pregnancy, season of conception, prenatal care, infant sex, pregnancy induced hypertension, history of abortion

$PM_{2.5}$, Particulate matter ≤ 2.5 μm; PM_4, particulate matter ≤ 4 μm; PM_{10}, particulate matter ≤ 10 μm; CO, carbon monoxide; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone; TDC, total dust count; SDC, suspended dust concentration; RDC, respirable dust concentration; TSP, total suspended particles; PAH, polycyclic aromatic hydrocarbons; EPA, Environmental Protection Agency; HAP, household air pollution; AOR, adjusted odds ratio; IQR, interquartile range; SHTS, secondhand tobacco smoke. Values in bold indicate significant confidence intervals.