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Ambient Air Pollution and Reproductive Health

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1. Introduction

Adverse health effects of ambient air pollution on mortality and morbidity in adults and children have been extensively studied across the world (Barnett et al. 2006; Bell et al. 2004; Dominici et al. 2003; Gold et al. 1999; Jerrett et al. 2005; Middleton et al. 2008; Pope 1999; Pope et al. 1991; Pope and Kanner 1993; Samoli et al. 2007; Wietlisbach et al. 1996). Considerable consistency across studies has been observed for many health endpoints including total mortality, cardiopulmonary mortality and morbidity. Moreover, air pollution studies suggest that the opposite ends of the age spectrum are more susceptible than the general population (Dockery and Pope 1994; Saldiva et al. 1995; Schwartz et al. 1994). Therefore, fetuses are thought to be a vulnerable subgroup of the population who could be most endangered by the effects of air pollution (Pope 2000). Early studies had shown that maternal active and passive smoking could impair reproductive outcomes. Thus, there is a strong belief that prenatal exposure to air contaminants, which is similar to the effects of maternal smoking, can also lead to some adverse pregnancy outcomes. The number of studies linking air pollution with adverse pregnancy outcomes has recently grown steadily since the late 1990s. The adverse effects of air pollutants including particulate matter (PM), nitrogen oxide (NOx), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3) on measures of fetal size, gestational duration and other reproductive outcomes have been studied.

Adverse reproductive outcomes including low birth weight (LBW: birth weight <2,500g) or preterm delivery (PTD: birth at <37 weeks of gestation) have arisen fairly consistently in recent years. During 1990-2006, the rates have risen 21% for PTD and 19% for LBW in the United States, respectively (Martin et al. 2008). Studies have suggested that LBW or PTD has been associated with not only childhood mortality and morbidity but also the risk of diseases in adulthood such as heart diseases and diabetes (Clapp Iii and Lopez 2007; Osmond and Barker 2000; Rinaudo and Lamb 2008; Thompson 2007). The prevention of adverse pregnancy outcomes is a renewed national and international priority in maternal and child health (Damus 2008). There is an emerging need to identify the etiological factors of adverse birth outcomes such as environmental exposures, which could be modifiable in order to help reverse the increasing rates.

In this chapter, we review the health effects of ambient air pollution on pregnancy outcomes such as LBW, very low birth weight (VLBW: <1,500g), small for gestational age or intrauterine growth retardation (SGA or IUGR, i.e. birth weight below the 10th percentile for that gestational age), PTD, and birth defects. Further, we discuss the potential biological mechanisms underlying the associations between air pollution and adverse reproductive outcomes. Finally, we briefly introduce the methodology including study designs, exposure measurements, windows of exposure, confounders, and future directions for study of air pollution and pregnancy outcomes.

2. Health effects of air pollution on birth outcomes

Birth outcomes, including outcomes of fetal size such as LBW, VLBW, SGA, and IUGR, outcomes of gestational age such as PTD, and birth defects, have frequently been studied in epidemiological research on health effects of air pollution. The associations between air pollution and these birth outcomes may suggest different etiologic and pathogenic mechanisms. Moreover, air pollution is a mixture of pollutants, which also vary in nature and possible health effects. Therefore, existing evidence of health effects of air pollution on birth outcomes are briefly examined by types of birth outcome and/or criteria air pollutants including PM, NO_x, SO_2, and CO as below. Although the associations between O_3 exposure and birth outcomes have also been investigated by several studies, available evidence seems only to support an association with birth defects (Shah and Balkhair 2011). Therefore, the health effects of O3 are merely discussed for birth defects.

2.1 Health effects on fetal size - LBW, VLBW, SGA and IUGR

The effects of ambient air pollutants on fetal size, specifically LBW have been well studied during the past decades. Overall, there were some positive findings, which suggest that air pollution exposure, through all periods during pregnancy, is associated with adverse health effects on fetal size including LBW, VLBW, SGA and IUGR. However, air pollution consists of many components, making it difficult to pinpoint which pollutant can actually affect fetal size. Therefore, we present below the results from some selected studies by criteria air pollutants individually.

2.1.1. Particulate matter (PM)

PM generally attracts much more attention in epidemiological research of air pollution because of its physical and chemical characteristics of consisting of organic and inorganic components. The effects of PM on birth outcomes have been reported to be more pronounced compared to other pollutants. Several exposure indices of PM such as total suspend particles (TSP), particulate matter smaller than 10μm aerodynamic diameter (PM_{10}) and smaller than 2.5μm aerodynamic diameter ($PM_{2.5}$) have been used in studies. Wang et al firstly reported that exposure to TSP in the third trimester of pregnancy was significantly associated with LBW (Wang et al. 1997). After that, many studies have been conducted to report associations between particulate air pollution and LBW, SGA, as well as IUGR. Bobak et al found that annual concentration of TSP during the year of birth was associated with an increased risk of LBW (Bobak and Leon 1999). Rogers et al also found that annual TSP in the year of birth is associated with the risk of LBW (Rogers et al. 2000). Consistent evidence on adverse health effects of PM on birth weight has been reported when PM_{10} and $PM_{2.5}$ have been used as measures of exposure. Mannes et al found that each 1 $\mu g/m^3$

increase in PM_{10} is associated with on average a birth weight reduction of 4 grams (95% confidence interval (CI): 3g to 6g) after adjusting for other important covariates (Mannes et al. 2005). Dugandzic et al also found that PM_{10} exposure in the highest quartile during the first trimester increased the risk of LBW by 33% (OR= 1.33, 95% CI: 1.02 to 1.74) compared to exposure in the lowest quartile (Dugandzic et al. 2006). Similar results of health effects of PM_{10} on LBW were also observed in Xu et al's study (Xu et al. 2010). In addition, $PM_{2.5}$ is found to be associated with a reduction in birth weight by Parker et al in California in 2005. They found that exposure to $PM_{2.5}$ in the highest quartile during pregnancy is associated with a reduction in infant birth weight of -36.1 g (95% CI: -16.5 g to -55.8 g) compared to exposure in the lowest quartile of <11.9 $\mu g/m^3$ after adjusting for other covariates (Parker et al. 2005). Another study reported by Rich et al also found that every 4 $\mu g/m^3$ increase in $PM_{2.5}$ exposure during the first and the third trimester increases the risk for SGA by 4.5% (95% CI: 0.5-8.7) and 4.1% (95% CI: 0.3-8.0), respectively (Rich et al. 2009). In addition, Dejmek et al 1999 also found that exposure to a high tertile of $PM_{2.5}$ during the first gestational month is associated with an increased risk of IUGR (OR=2.11, 95% CI: 1.20-3.70) among northern Bohemian women (Dejmek et al. 1999). Liu et al (2007) reported that every 10 $\mu g/m^3$ increase in $PM_{2.5}$ is associated with roughly six to seven percent increase (95% CI: 3-10%) in the risk of IUGR after adjusting for other risk factors (Liu et al. 2007). However, other studies have not found a significant association between particulate air pollution and fetal size (Maisonet et al. 2001; Salam et al. 2005).

2.1.2 NO_x

Health effects of nitric oxide (NO) and nitrogen dioxide (NO_2) on birth weight have also been studied. Studies on health effects of NO on fetal size is limited (Bobak 2000; Bobak and Leon 1999; Landgren 1996) and no existing evidence shows adverse health effects of NO on fetal size. Several studies show the associations between NO_2 exposure and LBW (Ballester et al. 2010; Bell et al. 2007; Ha et al. 2001; Lee et al. 2003). Some other studies also show that exposure to NO_2 is associated with increased risks of SGA. For example, an earlier report also found that each 10 parts per billion (ppb) increase in NO_2 exposure during the first month of pregnancy increases the risk of IUGR by 5% after adjusting for important maternal, infant and other environmental factors (Liu et al. 2003). Similar results were found by Mannes et al in 2005. This study indicated that each 1 ppb increase in NO_2 exposure during pregnancy is associated with 1 to 34 grams reductions in birth weight among infants in Sydney, Australia (Mannes et al. 2005). Liu et al (2007) also reported that every 20ppb increase in NO_2 exposure during the first, second, and third trimesters is associated with increased risks of IUGR by 16%, 14%, and 16%, respectively (Liu et al. 2007). However, several recent studies did not find a significant association between NO_2 exposure and fetal size (Gehring et al. 2010; Madsen et al. 2010).

2.1.3 SO_2

SO_2 is another important component of air pollution, and has been found to be associated with fetal size. Liu et al 2003 found that every 5.0 ppb increase in SO_2 exposure during the first month of pregnancy increases the risk of IUGR by approximately 7% (OR = 1.07, 95% CI: 1.01–1.13) among Canadian women (Liu et al. 2003). Several other studies have also linked SO_2 exposure with LBW. Wang et al have found that each 100 $\mu g/m^3$ increase in SO_2 exposure during pregnancy is associated with 11% increase (OR= 1.11, 95% CI: 1.06-1.16) in the risk of LBW and a 7.3 gram reduction in birth weight among Chinese women (Wang et

al. 1997). Bobak and Leon also found that every 50 μg/m^3 increase in SO_2 exposure during the whole pregnancy period is associated with a 10 % increase (OR=1.10, 95% CI: 1.02 –1.17) in the risk of having a LBW infant (Bobak and Leon 1999). Dugandzic et al 2006, in their cohort study in Canada, found that SO_2 exposure in the highest quartile during the first trimester is associated with a 36% increase in the risk of having a LBW infant (OR=1.36, 95% CI:1.04 to 1.78) (Dugandzic et al. 2006).

2.1.4 CO

Carbon monoxide is found to be associated with decreased birth weight. The earliest study reported by Alderman suggests a potential link between maternal CO exposure and risk of LBW (Alderman et al. 1987). Later, Ritz and Yu reported a significant association between CO exposure and risk of LBW in 1999 (Ritz and Yu 1999). Liu et al (2003) also found that each 1 ppb increase in CO exposure during the first month of pregnancy is associated with a 6% increase in the risk of IUGR (OR = 1.06, 95% CI:1.01–1.10) among Canadian women (Liu et al. 2003). Another later report by Liu et al in 2007 found that after adjusting for important maternal, infant and environmental factors, every 1ppb increase in CO exposure during the first, second, and third trimester of pregnancy is associated with a 18%, 15%, and 19% increase in the risk of IUGR, respectively (Liu et al. 2007). Significant findings were also reported in other studies (Lee et al. 2003; Maisonet et al. 2001). However, the evidence of health effects of CO exposure on fetal size is less consistent. Some studies have not shown a significant association (Huynh et al. 2006; Salam et al. 2005). Moreover, one other study found a protective effect of CO exposure on LBW (Lin et al. 2004).

2.2 Health effects on gestational age - PTD

PTD has also been extensively studied in the past decades. Studies have reported the effects of various air pollutants such as PM, NO_x, SO_2, and CO on PTD. The effect size and time of exposure of a specific air pollutant are inconsistent across studies because of the differences in study design, exposure assessment, and confounders being controlled for.

2.2.1 PM: TSP, PM_{10} and $PM_{2.5}$

Two studies had used TSP as a measure of exposure. One study reported that a decrease in the gestation age of 0.042 weeks was associated with each 100 μg/m^3 increase in TSP with a 7-day lag (Xu et al. 1995) while the other showed no significant association between TSP and PTD (Bobak 2000). Meanwhile, several studies have reported a significant association between PM_{10} exposure and PTD. A cohort study showed 16% and 20% increased risks of preterm birth for a 50 μg/m^3 increase in TSP exposure during the first month of pregnancy and during the 6 weeks before birth, respectively (Ritz et al. 2000). A study conducted in Australia suggested that exposure to PM_{10} during the first trimester was associated with a 15% increase in the risk of PTD (Hansen et al. 2006). A time-series analysis conducted in Pennsylvania also suggested a significant association between PTD and PM_{10} exposure with 2-day as well as 5-day lag (Sagiv et al. 2005). Another time-series study conducted in Shanghai also shows that a 4.4% increase in the risk of PTD was PTD was observed for each 10 μg/m^3 increase in PM_{10} exposure during the 8 weeks before pregnancy (Jiang et al. 2007). However, some other studies did not observe a significant effect of PM_{10} on PTD (Brauer et al. 2008; Kim et al. 2007; Lee et al. 2008).
The effect of exposure to $PM_{2.5}$ was also assessed by several studies. Huynh et al (2006) found that exposure to to the highest quartile of $PM_{2.5}$ (> 22.1μg/m^3) during pregnancy is

associated with a 15% increase in the risk of PTD compared to the lowest quartile of exposure. In the same study, similar results were found for exposure during the first month (OR=1.21, 95%CI: 1.12, 1.30) and last two weeks of pregnancy (OR=1.17 , 95%CI: 1.09, 1.27) (Huynh et al. 2006). A two-stage design study being conducted in Los Angeles reported that exposure to $PM_{2.5}$ > 21.4 μg/m^3 during the first trimester increased the risk of PTD by about 10% (OR=1.10, 95%CI: 1.01, 1.20).

2.2.2 NO_x

The association of NO_2 exposure and PTD was explored in several studies. Bobak et al reported that 10% and 11% increased risks of PTD were observed for each 50 μg/m^3 increase of NO_x during the first and third trimesters, respectively (Bobak 2000). NO_2 is also found to be associated with PTD among residents in Lithuania (Maroziene and Grazuleviciene 2002). Each 10 μg/m^3 increase in NO_2 exposure during pregnancy period and first trimester is associated with 25% (OR = 1.25, 95%CI: 1.07–1.46) and 67% (OR = 1.67, 95% CI: 1.28–2.18) increase in the risk of PTD, respectively. A time series analysis indicated that daily PTD rate is associated with average exposure to NO_2 during the 6 weeks preceding delivery (Darrow et al. 2009). A recent cohort study conducted in Spain reported that the risk of PTD was shown to be significant when women were exposed to NO_2 levels >46.2 μg/m^3 during the second (OR=1.11, 95% CI: 1.03-1.25) and third trimesters (OR=1.10, 95% CI: 1.00-1.21) as well as throughout the entire pregnancy (OR=1.29, 95% CI: 1.13-1.46) (Llop et al. 2010). However, evidence on the effect of NO_2 on PTD is inconsistent. Several other studies did not show a significant association (Gehring et al. 2010; Liu et al. 2003; Ritz et al. 2007).

2.2.3 SO_2

The earliest study conducted in China reported a significant effect of SO_2 on PTD. It shows that each 100 μg/m^3 increase in SO_2 during the 7 days preceding delivery is associated with .075 wk (12.6h) decrease in duration of gestation (Xu et al. 1995). Bobak et al reported that exposure to SO_2 during all trimesters was significantly associated with the risk of PTD (Bobak 2000). Liu et al in 2003 also reported the significant effects of SO_2 on PTD among women living in Vancouver, Canada. This study indicated that each 5.0 ppb increase in SO_2 exposure during the last month of pregnancy is associated with a 9% increase in risk of PTD (Liu et al. 2003). A time series analysis also revealed that a 15% increased risk for PTD was observed for each 15 ppb increase in average SO_2 in the 6 weeks before birth in Pennsylvania (Sagiv et al. 2005). Similar findings from another time-series analysis conducted in Shanghai were observed (Jiang et al. 2007). Leem et al found that exposure to the highest quartile of SO_2 during first trimester increased the risk of PTD by 21% compared to the lowest quartile of exposure (OR= 1.21, 95% CI: 1.04-1.42) in Korea (Leem et al. 2006). A study in Australia also revealed that SO_2 levels in the first and third trimester of pregnancy were a significant predictor of preterm birth (ORs between 2.30 to 3.15) (Jalaludin et al. 2007). However, no significant effect of SO_2 was observed in other studies (Brauer et al. 2008; Darrow et al. 2009; Landgren 1996).

2.2.4 CO

CO is among one of the air pollutants that have been demonstrated to have negative effects on PTD. Ritz et al reported that exposure to CO during the first month of pregnancy and 6 weeks before birth was significantly associated with an increased risk of PTD in the inland regions of Southern California (Ritz et al. 2000). A study reported by Liu et al showed that

an 8% increase (95% CI: 1%-15%) in the risk of PTD was observed for each 1.0 parts per million (ppm) increase in exposure to CO during the last month of pregnancy (Liu et al. 2003). Leem et al found that exposure to the highest quartiles of CO during first trimester increased the risk of PTD by 26% (OR= 1.26, 95% CI: 1.11-1.44) in Korea (Leem et al. 2006). Similar results reported by Wilhelm and Ritz in 2005 suggest that exposure to the highest quartile of CO during the first trimester increases the risk of PTD by 27% (95% CI: 7%-50%) (Wilhelm and Ritz 2005). Another cohort study found that exposure to high level of CO during the first trimester of pregnancy (> 1.25 ppb) is associated with 1.25 (95% CI: 1.12, 1.38) times of the risk of PTD compared to low level of CO exposure (< 0.59ppb) after adjusting for important maternal, infant, and environmental characteristics (Ritz et al. 2007). However, several other studies including a recent study did not observe significant effects of CO on PTD (Darrow et al. 2009; Huynh et al. 2006; Rudra et al. 2011).

2.3 Health effects on birth defects

Birth defects are another group of adverse birth outcomes that have recently been found to be associated with air pollution in several studies. Types of birth defects that have been reported to be associated with air pollution include heart defects and cleft palate. Ritz et al examined the effects of air pollutants including CO, NO_2, O_3, and PM_{10} on cardiac and orofacial defects in southern California. They found that second-month CO and O_3 exposures were significantly associated with cardiac defects after adjusting for maternal age, ethnicity, education, access to prenatal care, infant gender, decade of infant birth, parity, time since last pregnancy, birth type, and other air pollutants (Ritz et al. 2002).

Gilboa et al in 2005 investigated the effects of air pollutants such as CO, PM_{10} and SO_2 on different types of heart defects (e.g tetralogy of Fallot, and atrial and ventricular septal defects) among Texas women (Gilboa et al. 2005). Specifically, this study found that exposure to CO in the highest quartile (>0.7ppm) during pregnancy was associated with 2.04 times of the risk of tetralogy of Fallot compared to the lowest quartile after adjusting for infant sex, plurality, maternal education, maternal race, and season of conception (Gilboa et al. 2005). In the same study, PM_{10} and SO_2 were also found to be significantly associated with isolated atrial septal defects (OR = 2.27, 95% CI: 1.43-3.60) and isolated ventricular septal defects (OR =2.16, 95% CI: 1.51-3.09), respectively.

Marshall et al in 2010 examined the effects of criteria air pollutants including CO, O_3, NO_2, SO_2, PM_{10} and $PM_{2.5}$ on oral cleft defects in New Jersey. This study suggested that exposure to the highest quartile (>0.033ppm) of O_3 during the 3-8th month of pregnancy is associated with 2.2 times (95% CI: 1.0-4.9) greater risk of cleft palate compared to exposure to the lowest quartile (<0.015ppm). However, this study found no significant effects of other air pollutants on cleft defect. On the contrary, CO was surprisingly found to be a protective factor of cleft palate defect (OR=0.4, 95% CI: 0.2-0.7) (Marshall et al. 2010).

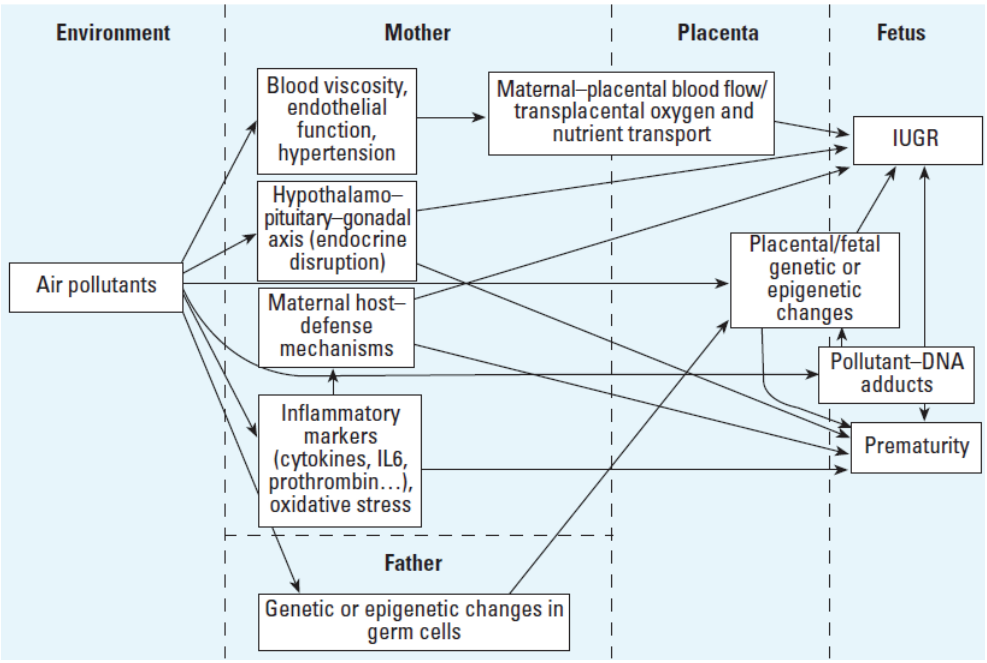
Another study conducted in the northeast of England had examined the effects of black smoke and SO_2 on congenital heart defects. This analysis found a weak association between maternal exposure to black smoke and heart defects but not for SO_2 exposure (Dadvand et al. 2011).

In summary, criteria air pollutants have been linked with adverse birth outcomes of fetal size, gestational age and birth defects. Several recent publications had also systematically reviewed epidemiologic evidence on the associations between maternal air pollution exposure and birth outcomes (Bosetti et al. 2010; Glinianaia et al. 2004; Maisonet et al. 2004;

Shah and Balkhair 2011). Although the heterogeneity and/or absence of associations between individual air pollutant and birth outcomes exists in published studies, current epidemiological evidence suggests that maternal exposure to PM and SO_2 is associated with several adverse birth outcomes. Reviewing the biologically plausible mechanistic pathways underlying the impacts of air pollution on birth outcomes would greatly contribute to our understanding of these associations.

3. Biologically plausible mechanisms

Although the specific mechanisms through which air pollution affects birth outcomes remain to be fully understood, with emerging bio-molecular technologies, an increasing number of studies show evidence towards potential mechanisms linking air pollution with birth outcomes. Air pollution has been frequently shown to affect the respiratory, cardiovascular, circulatory, and nervous system through multiple potential pathways, some of which might be appropriate for linking air pollution with birth outcomes (Block and Calderon-Garciduenas 2009; Brook 2008; Kunzli and Tager 2005). Several publications have described the biologically plausible mechanistic pathways through which air pollution impacts on birth outcomes (Kannan et al. 2006; Slama et al. 2008). We also used a figure from Slama et al's publication to show the possible biological mechanisms (see figure 1). These mechanisms are described in the following section.



Source: Slama et al. Envrionmental Health Perspective, 2008, 116(6):795

Fig. 1. Possible biological mechanisms by which air pollutants may affect birth outcomes

3.1 Oxidative stress and inflammation

It has been believed that oxidative stress and inflammation play central roles in adverse health effects of air pollution (Donaldson et al. 2001; Tao et al. 2003). Oxidative stress is a condition in which the body encounters more reactive oxygen species than its ability to properly remove them, resulting in excess peroxides and free radicals that can ultimately damage cell components and biological processes (Leeuwenburgh and Heinecke 2001). For example, several studies reported that transition-metal constituents in PM can induce oxidative stress (Kadiiska et al. 1997; Prahalad et al. 2001). PM can also activate inflammatory cells to generate of oxidative stressors such as reactive oxygen species and reactive nitrogen species (Tao et al. 2003). Consequently, oxidative stress can directly lead to DNA damage and may affect the embryo at its earlier stage of growth (Mohorovic 2004; Risom et al. 2005). Moreover, oxidative stress may also influence sperm motility and concentration, which is relevant for male reproductive health (Agarwal et al. 2006).

Air pollution-induced inflammation is considered as another potential biological mechanism through which air pollution cause adverse effects in organs such as the lung (Kunzli and Tager 2005). Inflammation could be a direct result of oxidation or up-regulation of pro-inflammatory mediators induced by air pollutants (Risom et al. 2005). Several studies have shown that air pollutants can enter the blood stream from lung and get deposited onto various body organs via active transport or passive diffusion (Chen et al. 2008; Peters et al. 2006). If air pollutants reach the placenta, they will also induce acute placental inflammation, which subsequently results in impaired transplacetal nutrient exchanges (Bobak 2000). In addition, inflammation could change maternal immunity, reduce host defense, thus increase the maternal risk of infections, which may in turn increase the risks of adverse birth outcomes (Wilhelm and Ritz 2005).

3.2 Changes in rheological factors of blood and endothelial function

Changes of blood coagulability and viscosity as a result of exposure to air pollutants have been suggested in the studies of cardiovascular health effects of air pollution (Coppola et al. 1989; Peters et al. 1997). In addition to the changes in rheological factors of blood, air pollution exposure could also influence endothelial functions. A study found that plasma concentrations of asymmetric dimethyl arginine, which suggests an impaired vascular function, were increased after exposure to $PM_{2.5}$ (Valkonen et al. 2001). Another study also found that exposure to air pollution could cause conduit arterial vasoconstriction in healthy adults (Brook et al. 2002). These studies suggest that exposure to air pollution may trigger endothelial dysfunction, which leads to vasoconstriction. If air pollution could cause the changes in rheological factors of blood such as blood viscosity and blood coagulability, and artery vasoconstriction among pregnancy women, it in turn could influence the transplacental oxygen and nutrient transport which further impacts fetal development.

3.3 Endocrine disruption

Air pollution has also been linked to endocrine dysfunctions that can potentially have negative impacts of birth outcomes. Air pollutants, particularly PM, may interfere with the endocrine system and affect progesterone production (Furuta et al. 2004; Takeda et al. 2004). Although this pathway has been less extensively studied, the possibility of the effects of air pollution on the endocrine system was suggested in recent investigations. Growing evidence suggests that inhalation of environmental tobacco smoke (ETS) contributes to disruptions in thyroid function (Carrillo et al. 2009). Air pollution, similar to ETS, could also

interfere with thyroid function. Disruption of thyroid function is associated with fetal development (Blazer et al. 2003; Patel et al. 2011). In addition, polycyclic aromatic hydrocarbon (PAH) was also found to have anti-estrogenic activity and can disrupt endocrine functions (Tran et al. 1996). Studies also found that endocrine disruption among pregnant women might cause IUGR (Kanaka-Gantenbein et al. 2003). Therefore, the link between air pollution and IUGR might involve this pathway. Moreover, a study found that air organic compounds such as PAH can also directly affect epidermal growth factor (EGF) and insulin-like growth factor type I and II (IGF-1 and IGF-2) receptors, leading to inhibition of placental cell growth and proliferation (Dejmek et al. 2000). This could cause a decreased fetal-placental exchange of oxygen and nutrients, which are the critical factors regulating fetal growth.

3.4 Hemodymanic changes

Air pollution exposure has been linked to hemodynamic responses such as changes in blood pressure, heart rate and rhythm, and cardiac autonomic tone (Ibald-Mulli et al. 2004). Specifically, PM exposure is associated with increase in heart rate, heart rate variability, and the frequency of ectopic beats. It is also associated with increase in systolic and diastolic blood pressure (Linn et al. 1999; van den Hooven et al. 2011). The effects of air pollution on hemodymanic changes can suggest a potential mechanism through which it can affect birth outcomes. The hemodymanic changes discussed are all risk factors for hypertension and other cardiovascular diseases. Therefore, exposure to air pollution can increase risks of health conditions (e.g. hypertension) that can ultimately increase the risk of adverse birth outcomes. For example, exposure to PM_{10} has been found to increase the risk of pregnancy-induced hypertension (van den Hooven et al 2011), which is found to be associated with elevated risk of preterm birth (OR=3.30), low birth weight (OR=4.68), fetal growth restriction (OR=2.94), and low Apgar scores 1 minute (OR=2.99) and 5 minutes (OR=2.08) (Olusanya and Solanke 2011).

3.5 Germ-line mutations

Although most of the mechanisms suggested are maternally related, recent studies suggest that paternal factors, especially germ-line mutation resulted from pollution exposure can also greatly influence birth outcomes. In animal studies, it was found that, germline mutation frequencies in wild herring gulls nesting At a polluted site were 2.8 to 8.5 times higher than birds that nested in non-polluted sites. This is consistent with what was discussed earlier—air pollution can adversely impact DNA replication process (Somers and Cooper 2009). In mice, similar results are found where there is an increased frequency of expanded simple tandem repeats among mice that are exposed to air pollution (Somers and Cooper 2009). Moreover, Somers et al 2002 also found evidence that air pollution is capable of inducing heritable DNA mutations (Somers et al. 2002). Since the sentinel animals that were used to study the association of air pollution and DNA mutations were from areas populated with humans, it is very likely that air pollution can also lead to germline mutations among humans, which ultimately can affect birth outcomes. Moreover, several studies have been conducted to support the hypotheses that air pollution is associated with elevated levels of DNA fragmentation in human sperm (Jafarabadi 2007; Rubes et al. 2005).

In conclusion, research on potentially biological mechanisms through which air pollution can affect birth outcomes is still limited. We review several potential mechanisms above

which have been suggested in previous studies. Meanwhile, it is important to recognize the need of further research to increase our understanding about the biological mechanisms underlying the impact of various air pollutants.

4. Methodology

As we reviewed above, evidence on the associations between air pollution and birth outcomes are not consistent in all cases. The heterogeneity and/or absence of association could be due to the differences in study design, exposure measurement, identification of windows of exposure, and selection of confounders. We discussed some common methods in these areas below.

4.1 Study designs

To assess whether air pollution exposure has an effect on pregnancy outcomes, the investigators need to compare the pregnancy outcome occurrence of individuals who have been subject to different exposure levels and, in particular, by comparing the occurrence or prevalence rate of pregnancy outcomes of exposed persons with those of unexposed or less exposed persons (Strickland et al. 2009). Specifically, descriptive studies, ecological studies, case-control studies, and cohort studies can be used to examine the relationship between air pollution and pregnancy outcomes.

The first step in investigating the pregnancy outcomes associated with air pollution exposure could be a **descriptive study**. Descriptive studies examine the distribution of pregnancy outcomes in a defined population. They are helpful in assessing the possibility that an association exists, and identifying hypotheses to be evaluated in analytical studies. Any type of pregnancy outcomes can be used for conducting descriptive studies. Descriptive data are commonly applied to examine patterns of pregnancy outcomes by place, time and person. *Geographic comparisons* based on standardized morbidity rates can be made among different geographic regions. The variations between these regions concerning occurrence of pregnancy outcomes contribute to the basis of causal hypotheses. *Temporal trends* in pregnancy outcomes rates can also be valuable to indicate the possible effects of air pollution.

Ecological studies are studies in which the investigators analyze hypothesized associations between air pollution and pregnancy outcomes using groups of people, rather than individuals, as the unit of analysis. It compares aggregate measures of exposure, such as average exposure or proportion of population exposed, with aggregate measures of pregnancy outcomes rates, for the same population. A traditional approach is to use *geographical areas* (Bobak and Leon 1999) as the basis for defining the study groups, and then correlations between aggregate measures of exposure and pregnancy outcomes at the same geographical location are analyzed. The *time series* design is a special and emerging type of ecological study with widespread application in epidemiological studies of short-term exposure to air pollution and pregnant outcomes (Darrow et al. 2009; Jiang et al. 2007; Lee et al. 2008; Sagiv et al. 2005; Zhao et al.). It investigates the relationship between air pollution levels and pregnancy outcomes - each measured and aggregated over the same time units (e.g., days, weeks) during a specified time period. Modeling time-series data is challenging because the relatively small effect of air pollutants is hard to be identified and quantified in the presence of strong confounding. Typically, one of the most widely-used statistical approaches for time series analysis of air pollution and health is the generalized additive

model (GAM). A strength of time-series analyses is the inherent control of individual-level risk factors that do not vary temporally. However, in studies of adverse pregnancy outcomes, risk factors considered time-invariant at the individual level may vary seasonally when aggregated into a pregnancy risk set. Therefore, time-series investigations of seasonally-varying exposures and adverse pregnancy outcomes should consider the potential for bias due to seasonal heterogeneity in the risk set. Moreover, this study design must be used with caution due to the important but hardly predictable ecological bias for which group-level associations do not accurately reflect individual-level associations.

A **case-control study** examines associations between air pollution exposures and adverse pregnancy outcomes by comparing cases, or individuals who developed the outcome with controls who are a sample of the source population from which the cases were identified. Controls are usually individuals who are similar to the cases in terms of risk characteristics, but who have not developed the pregnancy outcomes. Having selected cases and controls, the investigators then determine the prior air pollution exposure of the cases and controls. Hospital-based cases are usually selected for their high accessibility and cooperative attitude but this method is subject to bias. A population-based case control study (Rogers et al. 2000) is the principal alternative, for which all incident cases of the outcome in a defined geographic area are included as cases. The selection of controls can be more challenging. The most commonly used control groups are a random sample of the source population from which the cases are selected or persons seeking medical care at the same institutions as the cases for conditions believed to be unrelated to the health outcome of interest. Individual or frequency matching is another efficient strategy to select controls so that the distributions of some a priori selected risk factors are identical or nearly the same for the controls as for the cases (Dadvand et al. 2011; Hansen et al. 2009).

A cohort study selects subjects who are at the risk of developing a particular pregnancy outcome, and then are divided into groups according to their air pollution exposure status. The study groups are then followed over time to determine the subsequent incidence of the pregnancy outcome within each group. This study design enables investigators to measure incidence rates and to estimate all effect measures, such as rate ratio (RR) and rate difference. Cohort studies have been an effective method to assess the long-term health effects of acute or chronic exposure to air pollution. A fixed cohort consists of a group of individuals who are identified at a point or interval of tine and then followed over time. A dynamic cohort allows the inclusion of members over time as they fit the selection criteria. A historical or retrospective cohort study is conceptually identical, but less expensive and easier to conduct, to a prospective cohort study except that the study takes place after the causal events have unfolded. Most studies of air pollution and birth outcomes have used a population-based cohort study to examine their associations by linking information from birth certificate records with data from air monitoring (Aguilera et al. 2008; Brauer et al. 2008; Kim et al. 2007; Ritz et al. 2007). This approach allows conducting a study with a large study sample size at very low cost because of the utilization of existing datasets. However, it also easily suffers from exposure misclassification and inadequate controlling of confounders.

Two-phase (stage) designs nesting a sample within a cohort, for which both outcome and some exposure information are available, have a long history in epidemiology. In this approach, some additional information at the individual level is obtained for a sample nested within a cohort. Furthermore, the additional information can be used to assess potential confounding effects on the estimated relationships between exposures of interest and outcomes within the context of the larger cohort. Therefore, this is a special case control

design and can better control confounding by use of survey data and minimization of any selection or response bias. The two-phase study design has been recently applied to investigate the associations between air pollution and birth outcomes (Ritz et al. 2007). This approach holds promising because it provides a better capability of controlling for confounding than a classical population-based cohort study of air pollution and birth outcomes.

4.2 Methods of exposure assessment

Air pollution exposure assessment in most studies of air pollution and birth outcomes relies on existing networks of ambient monitoring stations. This approach of exposure assessment is mostly to assign exposure to maternal residential location based on the nearest monitor site or the monitor sites within the same administrative unit of maternal address (e.g. county) (Alderman et al. 1987; Dejmek et al. 1999; Xu et al. 1995; Zhao et al. 2011). However, the method is more likely to result in exposure misclassification because the monitoring networks are relatively sparse and insufficient for capturing all spatial variations in exposure and individual time-activity pattern is also not considered. Another approach for maternal exposure assessment is to develop surrogate measures, i.e. proximity methods , for example, the distance to sources of air pollution for estimating the level of air pollution exposure (Kashima et al. 2011; Yorifuji et al. 2011). Although proximity methods are straightforward, they have largely been thought as a form of exploratory analysis in traffic-related air pollution studies because they have considerable limitations such as invalid assumption of isotropic dispersion of pollution and inadequate consideration of other factors of meteorological condition and topography. Recently, interpolation methods have been applied to estimate maternal air pollution exposure, such as the inverse distance weighting (Xu et al. 2010) and Kriging method (Leem et al. 2006; Seo et al. 2010). Interpolation models produce a continuous surface of pollution concentration, and then extract individual exposure from the surface based on residential locations. This approach is limited by issues regarding exaggerated variation of predictions, spatial coverage and representatives of the existing monitoring sites, and incapability of taking other possible predictors into accounts. Furthermore, dispersion models have been developed to address a number of limitations for air pollution exposure assessment (Batterman et al. 2010; Hoffmann et al. 2009a; Hoffmann et al. 2009b). These models have been regarded as a more realistic representation of the problem by making use of data on emissions, meteorological conditions, and topography in conjunction with information from empirical monitoring systems in predicting spatial exposure estimates of air pollution concentration. Some studies have applied this method for maternal air pollution exposure assessments (Ihrig et al. 1998; Madsen et al. 2010; Wu et al. 2009). However, the features of dispersion models such as assumption of Gaussian dispersion, relatively costly data input, and complicated models, validation, impede their wide applications in estimating air pollution exposure. Land Use Regression (LUR) Models are the methods which have been developed to predict air pollutant concentrations at a given site based on the surrounding land use and traffic characteristics (Briggs et al. 1997; Briggs et al. 2000; Clougherty et al. 2008). This approach establishes a multivariate regression model, where monitored air pollution data serves as a dependent variable and traffic information, land use/cover, and other geographic information are considered as independent variables (Ryan and LeMasters 2007). The model can be expanded using GIS approaches, and thus is capable of predicting the level of air pollution at any location of an area. The advance in GIS technology and availability of detailed geo-reference data further increase the feasibility of implementing LUR models and

reduce the costs of modeling. Although many studies have demonstrated their success in predicting air pollution levels, a number of limitations remain. First, the LUR models have been primarily utilized for urban areas, but few of them have been expanded to suburban or rural areas because of lack of information. Second, LUR models are limited to explaining spatial variation of air pollutants, but few of them have addressed temporal variations. This is because the model predictors are temporally stable, such as land use, elevation, and population density (Molter et al. 2010; Rose et al. 2011). A recent review has highlighted the potential for improving the LUR approach by including a spatial and a temporal component in the models (Hoek et al. 2008). Several studies have used this method for maternal exposure assessments (Gehring et al. 2011). The main characteristics of the exposure methods described above are summarized in Table 1.

Although several exposure assessment models have been developed to improve maternal air pollution exposure, personal air pollution exposure remains challenge in the field because limited studies have considered microenvironment in personal exposure estimate. Some methods such as personal dosimetry and biomarkers may need to be considered in future studies.

Methods	Characteristics	Strengths	Limitations
Air monitoring networks	Using existing air data for individual exposure estimation	Easy to access the data; Low cost;	Lack of space coverage; increase likelihoods of misclassification
Proximity methods	Developing surrogate measures such as distance to the road as exposure index	Straightforward; Requires basic GIS techniques;	Invalid assumption of isotropic dispersion of pollution; inadequate consideration
Geo-statistical methods	Using geo-statistical methods to created predicted surfaces of air pollutants	Continuous space coverage; Require few other spatial data;	Exaggerated variation of predictions; required extensive monitoring network; incapability of controlling for other covariates
Dispersion models	Making use of data on emissions, meteorological conditions, topography and information from empirical monitoring systems for spatial prediction	Continuous space coverage; More realistic representation of the problem;	Invalid assumption of Gaussian dispersion; relatively costly data input; Complicated model validation
Land Use Regression (LUR) Models	Predicting air pollutant concentrations at a given site based on the surrounding land use and traffic characteristics	Continuous space coverage; Simple regression model;	Requires temporal variation of predictor; Unmatched of existing spatial data;

Table 1. Characteristics of common methods of exposure assessment in studies of air pollution on birth outcomes

4.3 Windows of exposure

It is believed that the fetus at some particular period of pregnancy is more sensitive to adverse health effects of air pollution. While some studies attempted to determine the effects of air pollution exposure during specific phases of pregnancy, evidence currently available does not support any firm conclusions. Most studies of air pollution and birth outcomes have examined windows of exposure such as the whole pregnancy, each trimester and/or each month of pregnancy. This inconsistency in defining windows of exposure across studies makes it extremely difficult to determine a specific critical period of exposure for each birth outcome. However, according to previous research, negative effects of various air pollutants can be seen as early as the first month of pregnancy. For example, the effects of SO_2, $PM_{2.5}$, and PM_{10} exposure are seen as soon as during the first gestation month for low birth weight, preterm delivery and intrauterine growth restriction (Dejmek et al. 1999; Huynh et al. 2006; Liu et al. 2003; Ritz et al. 2000). For studies which considered all three pregnancy trimesters, exposures during the first and third trimesters appeared to be significantly associated with some birth outcomes. For example, Bukowski et al 2007 demonstrated in their study that variation in birth weight might be determined by fetal size during the first 12 weeks after conception (Bukowski et al. 2007).

Most of the studies reviewed had only examined exposure during pregnancy. However, pre-pregnancy exposure to air pollutants which may affect genetic or epigenetic component in parents see **Germ-line mutations)**, might in turn impact birth outcomes. Therefore, future studies might also consider examining pre-pregnancy windows of exposure.

4.4 Confounders

Confounding threats the validity of observational research. This concern is particularly pertinent in studies of air pollution and birth outcomes as the effects of air pollution on birth outcomes are small. Strickland et al had thoroughly discussed the issue of confounding in epidemiological studies of air pollution and birth outcomes (Strickland et al. 2009). Under the counterfactual disease model, the effect of a factor on a disease is determined by comparing the risk of disease in a population exposure to the factor with one in the same population without exposure to the factor (i.e. under a counterfactual condition). As Strickland et al suggested, risk in the population under a counterfactual condition cannot be observed. A substitute population requires representing the risk in the population under a counterfactual condition. Confounding occurs if the risk in the substitute population is different from the risk in the population under a counterfactual condition.

Birth certificates have been used as the primary data source for information of confounders in most of studies of air pollution and birth outcomes. The birth records usually have information on maternal and infantile characteristics such as maternal age, race, educational attainment, pregnancy complications, and infant gender, etc. Confounding in the studies may arise from imperfect classification of existing information, i.e. residual confounding and unmeasured other variables such as socioeconomic status and maternal nutrition. Residual confounding refers to the confounding due to an imperfect classification of the groups of variables, e.g. maternal age groups and educational groups. Within the group, the confounding of the variable may still exist. For confounding effects of unmeasured factors in birth records, the two-phase study, as we described above, may provide a way to deal with the issue. However, selecting potential confounders requires caution. Some factors which are the intermediate factors in the pathway of air pollution and birth outcomes should not

be selected as confounders. For example, some pregnancy complications such as preeclampsia might be caused by air pollution and also risk factors of adverse birth outcomes (Wu et al. 2009).

5. Recommendations of future studies

Several limitations exist in previous air pollution studies on birth outcomes. A few papers have already discussed these issues and provide directions for future studies (Slama et al. 2008; Woodruff et al. 2009). Specifically, the following—but not limited to—issues are of major concern: 1) Accurate individual air pollution exposure including identification of windows of exposure remains a major challenge in the field; 2) The effects of specific components of PM have rarely been investigated; 3) Research of air pollution on fetal health rarely considers the concurrent effects of multiple air pollutants; 4) Little has been done to examine the potential effect modifiers of the relationship between air pollution and birth outcomes; 5) Research including experimental and epidemiological studies on biologically plausible mechanisms is limited. These issues might need to be adequately addressed in future.

1. Development of accurate air pollution exposure assessment remains an important work. The exposure models are in need of improvement in terms of spatial and temporal resolution by incorporating some new technologies such as remote sensing. Individual time-activity patterns in combination with the information from the exposure models might be used together for personal exposure assessment. Some methods of personal monitoring and biomarkers might be considered in prospective cohort studies.
2. Few studies have considered PM composition in relation to birth outcomes (Bell et al. 2010). Different sources of PM may have different chemical constituents and thus have different toxicity. The studies on PM composition might provide clues to explain the heterogeneity of health effects of PM across studies. Further, it would provide information on target chemicals or sources for prevention efforts.
3. Individual is simultaneously exposed to multiple air pollutants. As we reviewed, several criteria air pollutants have adverse effects on birth outcomes. It may be more reasonable to assume that there is a mixture of pollutants that is considered harmful to birth outcomes. However, few studies have investigated the adverse health effects of an air pollution mixture on birth outcomes. It is an important area of ongoing research of air pollution on fetal health. Some sophisticated models need to be developed to examine the effect of a mixture of pollutants because of high collinearity between air pollutants.
4. Air pollution studies on mortality and morbidity have suggested that people with different personal characteristics might respond to air pollution in different ways (Dubowsky et al. 2006; Zanobetti et al. 2000; Zeka et al. 2006). The National Research Council has identified the potential effect modifiers as a key data gap and has emphasized the need for continued study of the most susceptible populations related to air pollution (NRC 2004). However, little has been done to examine the potential modifiers of the health effects of air pollution on birth outcomes. Limited evidence suggests that the effect sizes of air pollution on adverse pregnancy outcomes may be different by fetal gender (Ghosh et al. 2007; Jedrychowski et al. 2009), pregnancy complication (Rich et al. 2009), and maternal nutrition (Jedrychowski et al. 2007; Kannan et al. 2006). Much remains to be learned about these relationships and what else could cause fetuses to be especially sensitive to the adverse health effects of air pollution.

5. Research to identify relevant biological mechanisms is needed to augment our understanding about the relationships. Epidemiological studies could consider other perinatal end points such as preeclampsia and placental size in future studies. The findings from these studies would provide important supporting evidence on the potential biological mechanisms as discussed above.

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