Chapter 2
Impacts of Air Pollution on Reproductive Health

Mariana Matera Veras, Natália de Souza Xavier Costa, Laís Fajersztajn, and Paulo Hilário Nascimento Saldiva

2.1 Introduction

Humans are continuously exposed to mixtures of environmental contaminants and a vast body of evidence now link exposure to these chemicals with an increased incidence of reproductive and developmental disorders (Woodruff and Walker 2008; Sadeu et al. 2010).

Since the second half of the twentieth century, the harmful effects of air pollution on human health have been the subject of many studies. Episodes of high levels of air pollution experienced by cities in Europe and the United States have enlightened both government agencies and the global community public about the harmful effects of air pollution on human health. Infamous examples include both the London Fog of 1952 and Donora Smog of 1948 that were associated with significantly elevated rates of hospital admissions and mortality (Logan 1953; Helfand et al. 2001). Similarly the more recent Bophal gas disaster (India, 1984) should also be remembered. In this tragic example, a methyl isocyanate gas leak killed 2,500 people in 5 days and many more were condemned to long-term morbidity including serious reproductive dysfunctions (Sriramachari 2005). Subsequent to these episodes, clean air legislations and other regulatory actions have significantly

M.M. Veras, Ph.D. • P.H.N. Saldiva, M.D., Ph.D. (✉)
Laboratory of Experimental Air Pollution (LIM05),
Department of Pathology, School of Medicine, University of São Paulo,
Av Dr Arnaldo 455, Room 1103 1st Floor, São Paulo, São Paulo State 01246-903, Brazil

National Institute for Integrated Analysis of Environmental Risk,
São Paulo, São Paulo State, Brazil
e-mail: pepino@usp.br

N. de S.X. Costa, M.S. • L. Fajersztajn, M.S.
Laboratory of Experimental Air Pollution (LIM05),
Department of Pathology, School of Medicine, University of São Paulo,
Av Dr Arnaldo 455, Room 1103 1st Floor, São Paulo, São Paulo State 01246-903, Brazil

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reduced ambient air pollution in many regions of the world, especially in both North America and Europe (Chen et al. 2007). Despite successful regulatory oversight, air pollution in urban centers remains a substantial risk factor to global human health.

The respiratory tract is the first system to be in contact with the air pollutants. Respiratory and cardiovascular diseases are the most commonly observed effects associated with exposure to low levels of air pollution followed by neoplasia (Schwartz 2006; Pope et al. 2009; Dockery 2009). Recent studies support that common environmental air pollutants that we contact in our daily life and to which exposures are unavoidable could also affect both reproductive health and fetal development. Exposure to ambient air pollution appears to adversely impact fertility, pregnancy outcomes, and fetal health and development (Maisonet et al. 2004; Parker and Woodruff 2008).

Epidemiological studies suggest the association between exposures to air pollution and impairment of reproductive health. However, these studies also recognize and acknowledge many uncertainties with regard to this association (Slama et al. 2008), such as few evidence of plausible biological mechanisms, limited information on personal exposures, difficulties in linking particulate matter (PM) composition or single constituent to the biological effects (Pope 2000; Chen et al. 2008; Valavanidis et al. 2008; Ren and Tong 2008). Despite the adoption of different study designs and statistical evaluations and the potential of confounding variables (e.g. maternal smoking, gestational age, and socioeconomic factors), and lack of consistency in findings, these epidemiological investigations suggest a causal association.

Epidemiological studies are important to help guide further investigation. However, many unanswered questions remain with regard to the association between air pollution and reproductive health including;

- What are the mechanisms involved in decreased fertility due to the exposure to increased PM concentration?
- Which trimester of pregnancy is most relevant to the impairment of fetal development?
- Which component of the PM presents a higher risk for reduced birth weight?
- Are the mechanisms involved in decreased male fertility the same as in females?
- Could multigenerational exposure to ambient PM concentration present cumulative effects?

Future studies utilizing animal models and carefully designed human clinical investigation will help address the current gap in knowledge. Toxicological and clinical studies are necessary to confirm associations elucidate mechanisms involved, identify most susceptible subgroups, and to create ways to reduce these impacts on human health.

In this chapter, we will focus on the major epidemiological findings, current experimental evidence, and possible molecular mechanisms involved in the impairment of the reproductive process associated with exposure to common urban air pollution.

2.2 Urban Air Pollution

Air pollution is a widespread environmental contaminant. Expansion of industry and vehicular traffic has had a major impact on the overall air quality in urban areas over the last decades. This contributed to widespread contamination of the environment by thousands of harmful compounds derived from exhaust emissions. In a broad sense, air pollution can be defined as a mixture of gaseous, liquid, and solid substances containing many toxic components which include; CO, NO_2, SO_2, O_3, Pb, polycyclic aromatic hydrocarbons (PAH) and particulate matter (PM) (WHO 2005).

Because of the recognized health impacts, significant efforts have been placed on investigation and regulation of the particulate fraction of air pollution. As defined by Collbeck and Lazaridis (2010), particulate matter (PM) is a complex mixture of solid particles, liquid droplets, and liquid components contained in the solid particles constituted by many different chemical species originating from a wide variety of sources. Particles can be produced by combustion, suspension of soil material, and also from chemical reactions in the atmosphere. Nitrates, sulphates, elemental carbon, organic substances (VOC, PAH), metals (Cd, Pb) and mineral material (Al, SI, Fe and Ca) are major constituents of airborne PM (Colbeck and Lazaridis 2010; Heal et al. 2012). Particle size ranges vary considerably from a few nanometers (nm) to several micrometers (um), which strongly determine particle lifetime in the atmosphere and deposition in the respiratory tract.

The particles are classified according to their aerodynamic diameter, as PM_{10} [particles with an aerodynamic diameter smaller than 10 μm], $PM_{2.5}$ [aerodynamic diameter smaller than 2.5 μm] and $PM_{0.1}$ [aerodynamic diameter smaller than 0.1 μm] (Colbeck and Lazaridis 2010). The size and its composition are directly linked to negative health effects. The observed high toxicity of the smaller size fractions is believed to be due to the fact that they may reach the deeper portion of the lungs and may translocate into the circulation. Further these fractions contain higher concentrations of polycyclic aromatic hydrocarbons (PAH), semiquinones, metals, transition metals, and have a higher radical generating capacity (Squadrito et al. 2001; Kok et al. 2006).

2.3 Epidemiological Findings

The evidence for harmful effects at realistic urban air concentrations of air pollutants predominantly come from epidemiological studies (Slama et al. 2008; Stillerman et al. 2008). In this section, we will present recent reports that indicate that exposures to ambient levels of air pollutants (PM, NO_2 SO_2 and O_3), in addition to the recognized adverse cardio respiratory effect are associated with negative impacts on reproductive health.

Increased risks for low birth weight, prematurity, neonatal and post-neonatal mortality and congenital defects have been reported to be associated with exposures to ambient air pollution. Beyond the recognized adverse consequences on pregnancy outcomes, exposure to air pollution is associated with adverse impact on reproductive function including fertility. Furthermore, studies have shown that periods of elevated air pollution were significantly associated with changes in semen quality and damages in sperm DNA (Dejmek et al. 2000; Rubes et al. 2005).

2.3.1 Fertility and Fecundability

Very few studies have addressed the effects of ambient air pollution on human fertility. Available studies focus on the primarily impact on male fertility, probably due to readily accessible semen acquisition and analysis (Sokol et al. 2006). Detrimental changes in various semen parameters such as motility, sperm morphology, and DNA are reported, which may cause reduced fertility in males or miscarriage in females.

The positive association of the adverse effects of air pollution exposures on pregnancy outcomes has redirected the attention of the researchers to other important aspects of reproductive health including fertility. One of the first studies that investigated the effects of air pollution on fertility was conducted by Djemek et al. (2000). In this study, they have evaluated the impact of SO_2 on fecundability (the probability of conceiving during the menstrual cycle) in the first unprotected menstrual cycle (FUMC) of 2,585 parental pair in a heavily polluted region of Northern Bohemia. They found that adjusted odds ratios of conception in the FUMC may be reduced in couples exposed to mean SO_2 levels >40 pg/m^3 in the second month before conception. In a previous study with the same population, they have also found an association between PM_{10} and reduced conception rates (Dejmek et al. 1998). Slama et al. (2013) reanalyzed the data of the study by Dejmek et al. (2000) and defined the exposure window with respect of the start of the period of unprotected intercourse and considered the impact of $PM_{2.5}$, carcinogenic polycyclic aromatic hydrocarbons (c-PAH), ozone (O_3), nitrogen dioxide (NO_2) levels, in addition to SO_2 on fecundability. Their new results highlight that $PM_{2.5}$ and NO_2 levels in the 2 months before the end of the first month of unprotected intercourse were associated with decreased fecundability. This observation highlights the important concept of lag time between exposure and observed health consequences.

Selevan et al. (2000) showed that elevated period of air pollution were significantly correlated with changes in various semen parameters of young Czech men including; proportionately fewer motile sperm, less sperm with normal morphology or normal head shape, and proportionately more sperm with abnormal chromatin. Based on this preliminary findings, Rubes et al. (2005) monitored semen quality in a cohort of young Teplice residents over longer periods of time (periods of exposure to both low and high air pollution) and found a significant association between exposure to high levels of air pollution and decreased sperm chromatin integrity.

In the United States (Salt Lake City), Hammoud et al. (2010) demonstrated that $PM_{2.5}$ concentration was negatively correlated to sperm motility 2 months and 3 months after exposure, which coincides with the duration of spermatogenesis (72 days). However, a study of Hansen et al. (2010) did not support a consistent pattern of association between O_3 and $PM_{2.5}$. They performed analysis of several measures of semen quality and found only statistically significant adverse association between increased $PM_{2.5}$ averaged over the 0- to 90-day period before semen sampling and an increase in the percentage of sperm with abnormally shaped heads and the percentage of sperm with cytoplasmic droplets. However, after controlling for season and temperature results failed to reach statistical significance.

In the study of Sokol et al. (2006), there was a significant negative correlation between O_3 levels (70–90 days before collection) and average sperm concentration, which was maintained after correction for birth date, age at donation, temperature, and seasonality. These epidemiological results are in line with occupational exposures (De Rosa et al. 2003; Guven et al. 2008) and experimental studies of diesel exhaust inhalation and detrimental effects on sperm (Izawa et al. 2007).

There are very limited studies on the impact of air pollution on female fertility. We are aware of only two studies available in the literature on female fertility that were conducted by Perin et al. (2010a, b). These studies evaluated the impact of PM exposure during the follicular phase of the menstrual cycle or during the preconceptional period of women undergoing IVF/ET on early pregnancy loss and miscarriage. Both studies support an association between brief exposure to high levels of PM and the adverse gestational outcomes. This is an area that would likely benefit from additional studies.

Human fertility is declining in different parts of the world for unclear reasons. There are many hypothesis that have been used to explain this observation. Among the most supported causes of worldwide declining fertility are the delay of childbearing by modern women and other changes in social factors. However, there is also a growing incidence of impaired fecundity among young women and men, which cannot be easily explained by societal factors. Nutritional status, obesity, drugs, smoking habits, stress and increasing exposures to environmental pollutants, such as air pollution, are also plausible factors involved in human reduced fertility that deserve more attention.

2.3.2 Low Vitamin D and Immune System Alterations

Besides the "visible" effects of air pollution on fetal health, there is growing evidence of the impact of maternal exposure to urban air pollution on "non-visible" fetal outcomes. Serum vitamin D levels in the mother and fetus seems to be affected by air pollution. Vitamin D is scarce in natural food and the main source of vitamin D for humans is its synthesis from 7-dehydrocholesterol upon exposure to UVB solar radiation and conversion to circulating metabolite called 25-hydroxyvitamin D [25(OH)D] in the liver. Deficiencies in vitamin D are associated with different

bone diseases and more recently it has been involved in other diseases including cardiovascular (Kim et al. 2008) and autoimmune diseases (Lange et al. 2009).

In general, low intake of vitamin D and insufficient exposure to sunlight constitute the main causes of vitamin D deficiency. However, recent studies point out that exposure to air pollution may also contribute to low serum levels of vitamin D in women and in the unborn child as a consequence of maternal deficiency. In the study conducted by Baïz et al. (2012), maternal exposure to ambient urban levels of NO_2 and PM_{10} during the whole pregnancy was a strong predictor of low vitamin D status in newborns. Moreover, Kelishadi et al. (2013) have also found that air quality had an inverse and independent association with 25(OH)D levels of mothers and their neonates and Hosseinpanah et al. (2010) have shown that deficiency in vitamin D to be prior to pregnancy. In their study, they found that women living in polluted areas present with lower levels of serum 25-OH-D which is comparable to vitamin D deficiency.

Potential mechanisms that could explain this relationship are based on the impact of smoking on vitamin D status (Brot et al. 1999). It has been suggested that changes in inflammatory profile and oxidative stress caused by smoking affects liver function and hence vitamin D synthesis or affecting maternal intestinal absorption of vital vitamins and minerals (Need et al. 2002). Exposure to air pollutants may have similar impact on vitamin D status. Beyond observed differences in vitamin D, exposure to air pollution could result in changes of the immune system including; NK, T lymphocytes, and IgE content of umbilical blood (Herr et al. 2010, 2011). Maternal exposure to air pollution could have lasting effects of either gestational or pre-gestational exposures on their offspring. The consequences for the future health of these individuals remains unknown, but these effects could have far reaching impacts.

2.3.3 Gestational Outcomes

Studies conducted in different continents (Europe, Asia and Americas) consistently report that expectant mothers exposed to air pollution have greater risks of having negative gestational outcomes (Gouveia et al. 2004; Ha et al. 2001; Wang et al. 1997). However, it is not clear from the studies whether the effects are due to a specific pollutant or to the interactions of different pollutants and in which trimester exposures are more detrimental to fetal development. Negative gestational outcomes are predominant reproductive effects associated with exposures to ambient air pollution and are discussed in detail in Chap. 3. In this section, we will briefly highlight the gestational outcomes and its association with criteria pollutants in order to compare with experimental evidence.

The causes of the negative pregnancy outcomes are not well understood but it is clear that these outcomes have multifactorial causes and there are scientific evidence that environmental factor, such as air pollution, can contribute or aggravate these outcomes. Furthermore, there are groups within population that may be more susceptible to air pollution exposure. These groups include individuals with

preexisting circulatory and respiratory conditions and those socially and economically disadvantaged. In general people with low social and economic status live in more polluted areas, lack adequate health care, and spend more time near high traffic roads that may increase exposures to air pollutants and consequently increase the risks of adverse birth outcomes (Woodruff et al. 2003; O'Neill et al. 2003; Ponce et al. 2005; Gilbert et al. 2007; Ono et al. 2013).

2.3.3.1 Low Birth Weight

The prevalence of low birth weight (LBW), as defined by WHO as weight at birth of less than 2,500 g (5.5 lb) is estimated to be 15 % worldwide with a range of 3.3–38 % (http://www.who.int/nutrition/topics/lbw_strategy_background.pdf) and occurs mostly in developing countries; coincidentally these countries has elevated levels of air pollution (http://www.who.int/gho/phe/outdoor_air_pollution/phe_012.jpg). This topic is covered in more detail in Chap. 3.

Birth weight is an important indicator of subsequent health issues; low-birth-weight babies are more prone to develop hypertension, coronary heart disease, and non-insulin-dependent diabetes during adulthood (Osmond and Barker 2000). Evidence from studies conducted in developed and developing countries, China (Wang et al. 1997), Australia (Mannes et al. 2005), Chezec Republic (Dejmek et al. 1999); and USA (Ritz et al. 2000) point out that PM_{10}, $PM_{2.5}$ and SO_2 are the major pollutants associated with increased risks of LBW. However, other studies verified that exposures during pregnancy to CO, O_3, and NO_2 could also be associated with LBW (Morello-Frosch et al. 2010).

2.3.3.2 Preterm Birth, Intrauterine and Neonatal Mortality

Although less frequently reported, intrauterine and neonatal mortality and pre-term birth (PTB) (Glinianaia et al. 2004; Maisonet et al. 2001; Srám et al. 2005) are also outcomes associated with air pollution. Maternal first trimester exposure to ambient air pollutant exposure seems to be the critical period for PTB. However, Huynh et al. (2006) observed no association between PTB and ambient air $PM_{2.5}$ levels near the maternal residence during early pregnancy and late gestation.

In Australia, Hansen et al. (2006) observed that increased levels of O_3, NO_2 and SO_2 during 1st trimester increases the risk of PTB (OR = 1.26, 95 % CI 1.10–1.45). Another study from Korea (Leem et al. 2006) reported that increased levels of CO level during 1st trimester are responsible for the increased risk for PTB [OR = 1.26, 95 % CI 1.11–1.44, p-trend < .001]. Considering traffic proximity, the risk of PTB in Taiwan was elevated among women living close to a major freeway [<0.5 vs. 0.5–1.5 km, OR = 1.30, 95 % CI 1.03–1.65] (Yang et al. 2003). In Los Angeles, Wilhelm and Ritz (2003) found that there was a dose-response relationship between preterm birth and inverse-distance-weighted traffic density among women in their 3rd trimester [OR = 1.15, 95 % CI 1.05–1.26].

2.3.3.3 Fetal Growth and Developmental Abnormalities

Although evidence is less consistent, exposures accrued during gestation and sensitive periods of fetal organ development may be related to developmental abnormalities/congenital defects. Jedrychowski et al. (2004) observed that not only birth weight is affected; changes in other anthropometric measurements were observed, such as reduction in head circumference. Studies conducted by van den Hooven et al. (2012a) using ultrasound measurements observed that NO_2 levels were inversely associated with fetal femur length in the second and third trimester, and both PM_{10} and NO_2 levels both were associated with smaller fetal head circumference in the third trimester. Vrijheid et al. (2011) systematically reviewed epidemiologic studies on ambient air pollution and congenital anomalies and conducted a meta-analysis for a number of air pollutant–anomaly combinations. They conducted meta-analyses for 18 combinations of pollutants and cardiac anomaly groups and found that NO_2 and SO_2 exposures were related to increases in the risk of coarctation of the aorta and tetralogy of Fallot and PM_{10} exposure was related to an increased risk of atrial septal defects.

A large case-control study conducted in California reported a weak association between cleft lip/palate and ambient air O_3 levels near the maternal residence during the second month of gestation. Few studies evaluated if there were associations between maternal exposure to air pollutants and stillbirths. Results from these studies remain inconclusive. Pereira et al. (1998) found an association between daily counts of intrauterine mortality and NO_2, SO_2, and CO concentrations before ($\leq$5 days) delivery. Similarly, Faiz et al. (2013) reported that increased stillbirth is associated with increases in NO_2, SO_2, CO, and $PM_{2.5}$ concentrations in the immediate few days before delivery. In a study by Bobak and Leon (1999) stillbirth rates were not significantly associated with any indicator of air pollution.

2.3.3.4 Preeclampsia

Emerging evidence from a large European study and from three previous studies (Woodruff et al. 2008; Wu et al. 2009; Rudra et al. 2011; Olsson et al. 2013) further indicates that that there is also a positive associations between exposure to air pollution and risks of preeclampsia. However, the studies diverge to in terms of the pollutant associated with preeclampsia. In the largest study conducted in Europe, Olsson et al. (2013) found that exposure to O_3 in the first trimester of gestation are associated with increased risks of preeclampsia. Rudra et al. (2011) found a weak association between CO exposure during the first 7 months of pregnancy (per 0.1 ppm) and preeclampsia (OR = 1.07, 95 %, CI = 1.02–1.13). In another study conducted in the USA, Wu et al. (2009) reported odds ratios of 1.33 (95 %, CI = 1.18–1.49) and 1.42 (95 % CI = 1.26–1.59) for preeclampsia in the highest exposure quartiles for NO_x and $PM_{2.5}$. Increased blood pressure throughout pregnancy has also been observed in mothers who are exposed to air pollution (van den Hooven et al. 2012b; Lee et al. 2013) and both available studies agree that PM_{10} and O_3 are associated to this effect.

2.3.4 Secondary Sex Ratio

In the literature, there are many examples of studies suggesting the impact of both environmental pollution and occupational exposure to certain substances and changes in secondary sex ratio (SSR) (Terrell et al. 2011; Tragaki and Lasaridi 2009; Schnorr et al. 2001). Previous studies have shown changes in sex ratios of populations living near incinerators [lower sex ratio] (Williams et al. 1992) as well as in areas exposed to polluted air from steel foundries (higher sex ratio) (Lloyd et al. 1985). In urban areas with high levels of particulate pollution derived from traffic, there is only one study that investigated if the secondary sex ratio could be affected by air pollution. In this study, Miraglia et al. (2013) have found a significant negative association between SSR and PM_{10} concentration in São Paulo city, Brazil. Although the causality between environmental exposures and declines in secondary sex ration are still controversial, some authors suggest that the SSR as a sentinel indicator of reproductive injury (Davis et al. 1998).

2.3.5 Reproductive System Cancer

Little is known about the role of air pollution in cancers of the reproductive system cancer (e.g. prostate, ovarian and breast cancer). However, an increased risk of lung cancer associated with exposures to outdoor air pollution was consistently observed in studies from Europe, North America, and Asia (Fajersztajn et al. 2013). Thus it is reasonable to suspect that other types of cancer could be caused by long term exposure to air pollutants. The latest IARC release on cancer incidence mortality and prevalence worldwide predict a substantive increase to total 19.3 million new cancer cases per year by 2025, due to growth and ageing of the global population. However, environmental influences and lifestyle factors may also be implicated in this increase; and they highlight the fact that breast cancer incidence has increased by more than 20 %. Vehicular emission is the primary contributor to air pollution in urban areas, its composition include compounds that are recognized as carcinogens, such as diesel exhaust. Recently, the International Agency for Research on Cancer (IARC) of the World Health Organization has classified diesel and gasoline exhaust as carcinogenic to humans as possibly carcinogenic (Loomis et al. 2013).

Few studies have been conducted to evaluate if there is an association between reproductive system cancer and air pollution. These types of studies are limited by difficulties in the assessment of long term exposures, the presence of a myriad of confounding factors and co-exposures to other known carcinogens in food and water. Disinfection by products and even infections make it difficult the establishment strong associations between air pollution and cancer risk factors.

Prostate Cancer There are only two studies in the literature that found an association between prostate cancer and air pollution (Soll-Johanning and Bach 2004; Parent et al. 2013). Recently, a case–control study conducted in Montreal evaluated environmental risk factors for prostate cancer and found associations between

exposures to traffic related air pollution, assessed by exposures to NO_2, and increased risks of prostate cancer incidence. Limitations of the study include exposure assessment based on home address and time of exposure which was 25 years prior to the interview and thus which could misclassify an individual's exposure (Parent et al. 2013).

Breast Cancer In women, breast cancer has the highest incidence rate. Many risk factors have been pointed out such as genetic factors, lifestyle, reproductive history, smoking and alcohol consumption. Although many factors have been identified most of the cases remain with unknown etiology (Coyle 2004). The first evidence of a possible relationship between breast cancer and air pollution levels came from the observation that the incidence was higher in urban areas compared to rural areas (Bako et al. 1984; Hall et al. 2005; Reynolds et al. 2004). Human studies are limited, however there at least 30 substances present in urban air pollution that are known to be associated with increased mammary tumors in animals such as benzene (diesel exhaust) and polycyclic aromatic hydrocarbons (PAHs). Thus, it is plausible that traffic-related exposures may contribute to the incidence of breast cancer (reviewed by Rudel et al. 2007). In the USA, few studies assessed the relationship between air pollution exposure and breast cancer. Lewis-Michl et al. (1996) conducted a case-control interview study in New York (USA) and suggested a possible increased risk [OR = 1.29; 95 % CI: 0.77–2.15] of breast cancer among postmenopausal women who live near areas with high traffic density. Bonner et al. (2005) found that early-life exposures to relatively high concentrations of air pollution (i.e., >140 $\mu g/m^3$) were associated with an increased risk of developing postmenopausal breast cancer (OR = 2.42; 95 % CI, 0.97–6.09). In Canada, Crouse et al. (2010) found evidence of an association between the incidence of postmenopausal breast cancer and exposure to ambient concentrations of NO_2. In China, Huo et al. (2013) have shown that long-term air pollution exposure may contribute to the development of breast cancer.

Ovary Cancer In the literature, there are only two studies that have found an association between air pollution and ovarian cancer. In the first study published in 2005, Iwai et al. (2005) conducted a cross-sectional epidemiological study using the annual vital statistics and air pollution throughout Japan and found that breast, endometrial, and ovarian cancer showed significant increases in mortality rates in relation to particulate pollution. More recently in Taiwan, Hung et al. (2012) showed that individuals who resided in municipalities with higher $PM_{2.5}$ levels were at a significantly increased risk of death from ovarian cancer.

2.4 Experimental Evidence

All of the published studies acknowledged that there are many uncertainties on the association between adverse reproductive outcomes and air pollution (Pope 2000; Chen et al. 2008; Valavanidis et al. 2008; Ren and Tong 2008). Undoubtedly these

aspects point out that there is a need for further toxicological and clinical studies to confirm, to strengthen and elucidate the mechanism involved in this association, to identify most susceptible subgroups and to create ways to reduce these impacts on human health. The scientific literature is extremely scarce with regard to experimental studies conducted to evaluate reproductive efficiency using laboratory animals exposed to real urban air pollution. Available studies conducted on experimental animals, mainly mice, have corroborated human epidemiological data and have provided data showing additional effects not yet investigated in humans.

Studies using a multigenerational mouse model of exposure to "real world" ambient concentrations of air pollution, (i.e. mice mates and their litters were continuously exposed inside chambers to either filtered-clean air or non-filtered air-polluted air), found that urban air pollution compromises reproductive health in different ways across generations. This series of studies has shown that in the first generation (G1) of mice exposed to air pollution there were significant reductions in the number of viable fetuses, increased numbers of implantation failures, and a decreased male/female secondary sex ratio (Mohallem et al. 2005; Lichtenfels et al. 2007). In the second generation of mice (G2), females exposed to air pollution during gestation gave birth to litters with reduced birth weights, but no differences in litter size and viable fetuses were observed. Birth weight was significantly lower with a mean reduction of 21 % compared to fetuses from non-exposed females (Veras et al. 2009).

The negative effect of air pollution exposure during pregnancy and birth outcomes are increasingly recognized, but most epidemiological studies have focused only on exposure during the gestational period. Evidence from animal studies explored the effects of maternal exposure before pregnancy on fetal development and demonstrates that maternal exposure not only during pregnancy, but also before conception, adversely affected fetal birth weight (Veras et al. 2008; Rocha et al. 2008). In the same way, exposure to air pollutants during gestation and/or during the pre-gestational period was associated with increased post-implantation loss rates in exposed females (Veras et al. 2009). These results support the findings from Perin et al. (2010a, b) on the importance of the pre-gestational period on gestation establishment. Examination of the placenta from dams exposed to air pollution before and/or during pregnancy revealed that both pre-pregnancy and pregnancy periods of exposure to polluted air resulted in morphological changes in the placenta (Veras et al. 2008). Veras et al. (2008) found that decreases in fetal weight were accompanied by decreases in the volume of maternal blood spaces, in the mean diameter of maternal blood spaces, and in maternal:fetal surface ratio. These features were accompanied by increases in the surface area of fetal capillaries, the total diffusive conductance of the intervascular barrier, and the mass-specific conductance of that barrier. None of the studies conducted in human has evaluated whether placental changes are associated with adverse pregnancy outcomes in humans. Recently, van den Hooven et al. (2012a) using ultrasound measurements and markers of placental growth and function have shown that in human the placenta development, as observed in animals, is impaired by maternal exposure to air pollution.

Umbilical cords were also evaluated and exposures to air pollution were associated with thinner and less voluminous umbilical cords (loss of mucoid connective tissue and collagen content). Structural changes in umbilical arteries and veins and elevated immunoreactivity for 15-F2t-IsoP (oxidative stress), ETAR and ETBR (vascular tone) in their walls were found. Together these findings indicate compromised fetal development evidenced by reduced birth weight might be mediated by alteration in placental and umbilical structure and function as well as by imbalances in the endogenous regulators of vascular tone and oxidative stress (Veras et al. 2012).

The reproductive capacity of G2 nulliparous female mice was also examined and results have shown changes to estrous cyclicity and in ovarian follicle counts (decreased numbers of antral follicles) (Veras et al. 2009). Antral follicles represent the last stage in follicle development prior to ovulation and are the only follicle type capable of releasing an oocyte for fertilization and synthesizing estrogen (Hoyer and Sipes 1996; Hirshfield 1997). Increases in the rate of follicle depletion can potentially raise the possibility of premature ovarian failure and early menopause in the case of humans (Rowe 2006). Observed changes in estrous cyclicity are indicative of persistent estrus, which may reflect an impairment of ovulation as well as changes in the levels of circulating ovarian hormones (EPA 1996).

Further, in the second generation it was observed changes in couple-based outcomes. Couples exposed to air pollution presented decreased fertility indices, decreased pregnancy success and delayed onset of reproductive maturity, as evidenced by extended times to mating (Veras et al. 2009). In humans, air pollution exposures seemed to decrease conception rates (Dejmek et al. 1998). However, we still do not know if the effects are associated with impairments on female or male health.

It is important to point out that the mean concentration of $PM_{2.5}$ (24-h average concentration) used in some studies (27.5 μg/m^3, Veras et al. 2008, 2009), is less than the 35 μg/m^3 established by the U.S. National Ambient Air Quality Standards [US-NAAQS] (http://www.epa.gov/air/criteria.html) and, approximately equivalent to the World Health Organization (WHO) air quality guideline (25 μg/m^3; WHO 2005) raising the question of whether these proposed values are safe for reproductive health.

Two recent mechanistic experimental studies (*unpublished*) addressed the associations between air pollution exposure during the initial stages of pregnancy in mice and uterine response to embryo implantation. Scoriza et al. (2009) observed that in early pregnancy (6 and 8 GD) that reductions in the number of uterine natural killer (uNKcells) and mast cells could contribute to the increased rates of post implantation losses observed in mice. uNK cells are a subpopulation of lymphocytes that in normal mice promote decidual angiogenesis, trophoblast and placental cell growth, provide immunomodulation at the maternal-fetal interface for a healthy pregnancy (Bilinski et al. 2008). The role of mast cells in pregnancy is less known. However, during normal early pregnancy, the number of mast cells and their activation change (Gibbons and Chang 1972; Marx et al. 1999). These data suggest that components present in air pollution may indirectly interfere with or impair

embryonic development through changes to the maternal environment including maternal immune responses. In another study, nulliparous mice were exposed to two different doses of fine particulate air pollution ($PM_{2.5}$) for 45 days before pregnancy until gestational day 4 and expression of different uterine receptivity markers were evaluated (*Lif*, leukemia inhibitory factor; and *Muc1*, mucin, pinopods) as well as uterine histopathology. Histopathology revealed a decrease in the volume and thickness of the endometrium as well as changes in the diameter and thickness of the glandular and luminal epithelia. No significant alteration was observed in the expression (qPCR/IHC) of *Muc1* but there was significant suppression of *Lif* during the window of implantation. These findings suggest that air pollutants may affect the fine regulation of proliferation and differentiation of uterine stromal cells during decidualization via reduced LIF expression (Castro et al. 2013).

Evidences from experimental studies linking and chronic exposure to air pollution are in line with the epidemiological findings (Knottnerus et al. 1990; Peters et al. 1997; Pekkanen et al. 2000). However, the mechanisms involved in this association are not clearly known. There are many suggested potential mechanisms which include induction of p450 enzymes, DNA damage, and systemic alterations in hematocrit, blood viscosity, blood coagulation, endothelial dysfunction, oxidative stress, and inflammation (Baskurt et al. 1990; Sørensen et al. 2003; Andrysík et al. 2011). The mechanisms proposed are described in more detail in the next section.

2.5 Biological Mechanisms

The mechanisms, by which, air pollution could cause adverse health effects are characterized by their ability to directly act as pro-oxidants of lipids and proteins or as free radical generators, promoting oxidative stress, inflammatory responses and damage to mitochondrial function (Menzel 1994; Rahman and MacNee 2000; Li et al. 2003).

The first system to in contact with air pollution is the respiratory tract. Epidemiologic and experimental data show that the air pollution can cause pulmonary inflammation, decrease of pulmonary function, and aggravation of pre-existing pulmonary diseases such as asthma and bronchitis (Laumbach 2010; Saldiva et al. 2002; Seaton et al. 1995).

The bigger fraction of the PM gets trapped on the superior respiratory tract, and the smaller fraction can reach the lungs and these particles can be deposited (Amdur and Corn 1963; Amdur and Creasia 1966). In an attempt to remove such particles, alveolar macrophages phagocytize the particles, penetrating into the cellular interstitium, but part of these fine particles can be translocate across the air–blood barrier into circulation and towards secondary target organs, suggesting that the smaller the particle diameter, the greater the possibility of translocation to other organs (Takenaka et al. 1986; Ferin et al. 1992; Oberdorster and Utell 2002; Chen et al. 2006).

The majority of fine and ultrafine (<$PM_{0.1}$) particles found in the urban atmosphere derive from engine combustion. Ultrafine particles have very low mass typically with magnitudes higher particle numbers and therefore a high surface area relative to fine and coarse particles for adsorption of toxic species (Sioutas et al. 2005). Studies suggest that only a small fraction of PM can pass rapidly into systemic circulation, and that pulmonary inflammation seems to play a major role in enhancing the extra-pulmonary translocation of particles (Chen et al. 2006; Brown et al. 2002; Burch 2002; Mills et al. 2006; Wiebert et al. 2006a, b; Möller et al. 2008). Organic components of particles, which comprise a large proportion of freshly emitted exhaust and secondary aerosols, can induce a broad polyclonal expression of cytokines and chemokines in respiratory epithelium and this effect may be due to the action of PAHs, metals and related compounds that lead to the production of cytotoxic reactive oxygen species (ROS); and these inflammatory and oxidant stress responses are expected to occur at extra-pulmonary sites, as well (Sioutas et al. 2005; Ritz and Wilhelm 2008).

Several hypotheses have been proposed that air pollution can affect the reproductive system causing negative effects, such as impairment of male and female reproductive capacity, placental alterations and fetal health.

As we have previously described, exposure to air pollution is associated with detrimental pregnancy outcomes and these outcomes can be caused by a combination of maternal, fetal, and placental factors or a combination of them. . For example, air pollution can affect the utero-placental and umbilical cord flow and consequently the transport for glucose and oxygen though the placenta (Veras et al. 2008, 2012; Ritz and Wilhelm 2008; Vorherr 1982).

According to the review of Kannan and collaborators (Kannan et al. 2006, 2007), the particulate matter present on the air pollution can affect pregnancy outcomes due to:

- Increase in oxidative stress: an important mechanism of action PM can be the DNA damage induced by oxidative stress, also some metals in PM may inhibit the DNA repair enzymes.
- Inflammation: Inflammation could be associated with inadequate placental perfusion and impaired transplacental nutrient exchange, which may cause growth restriction in utero due to interference with some process or processes such as affecting nutrition of the fetus, reduced oxygenation of maternal blood, or both.
- Coagulation and blood pressure: PM exposures may increase any of the proteins of the clotting cascade, indicating a higher possibility for coagulation and may also lead to changes in hemoglobin, platelets, and white blood cells, which may potentially contribute to adverse fetal growth. PM exposure is also associated with elevations on the blood pressure in pregnant women and this could increase the risk of adverse outcomes, especially if there is preexisting hypertension (pregnancy-induced or not). Elevation of blood pressure in pregnant women has been associated with IUGR and preterm delivery.
- Hemodynamic responses: an impaired adaptation of maternal hemodynamic may lead to an impaired fetal growth. These changes may force the fetus to

adapt, down-regulate growth, and prioritize the development of essential tissues.

- Endothelial function: PM exposure may cause endothelial dysfunctions leading to vasoconstriction and could be considered as an intervening pathway in subsequent impact on fetal growth.

These pathways may or may not act independently, but it is more likely that the outcomes of the exposure to air pollution are an association among these pathways and they are probably related to the composition of the particulate matter (Saldiva et al. 2002).

There are evidences that the air pollution can affect not only the pregnancy but also the male and female reproductive fertility (Somers and Cooper 2009).

Based on epidemiological studies it was observed that exposure to air pollution affects fertility rates (Dejmek et al. 2000; Selevan et al. 2000) at different seminal parameters, motility and morphology and the sperm DNA (Rubes et al. 2005; Hansen et al. 2010; Jafarabadi 2007).

In a study conducted by Somers et al. (2002), a significant elevation in mutation frequency was reported in the offspring of animals exposed to air pollution; primarily through expanded simple tandem repeat (ESTR) DNA loci mutation events in the paternal germline.

In other studies conducted by Somers et al. (2004) and Yauk et al. (2008), they noted that ESTR mutation frequencies were also elevated the paternal germline of mice exposed to whole ambient air at the polluted industrial site, indicating that mutations were induced in spermatogonial stem cells. Maternal ESTR mutation frequencies were similar in all groups, and therefore unaffected by air pollution exposure (Somers et al. 2004). Bulky DNA adducts were not significant, suggesting that DNA reactive chemicals do not reach the germ line and cause ESTR mutation. In contrast, DNA strand breaks were elevated after 3 weeks of exposure, possibly resulting from oxidative stress arising from exposure to air pollution and its particulate matter (Yauk et al. 2008).

Sperm DNA in mice exposed to whole ambient air was globally hypermethylated compared to those exposed to filtered air. These methylation changes appeared early in the environmental exposure and were still present after 6 weeks without the air pollution exposure. Persistent changes in the methylation status of genes may have health implications for the next generation through altered gene expression (Somers et al. 2004; Yauk et al. 2008).

Environmental toxicants can alter the female reproduction by direct mechanisms (hormone disruptors) or indirect (immunological toxicants). Direct effects typically occur if an environmental chemical is structurally similar to a molecule capable of interacting with endogenous reproductive organs. Indirect effects can occur if a chemical interferes with the hormonal action. Natural hormones are critical for development, behavior, puberty beginning, sexual function, and gametogenesis. Some environmental chemicals can mimic or block the action of the natural hormone, thus negatively altering reproductive processes (McLachlan and Arnold 1996).

As steroid hormones, some environmental toxicants are lipo-soluble and cross the cell membrane by passive diffusion, thereby allowing access to any animal cell. Once these chemicals cross the cell membrane, which may interact with steroid receptors, access to the nucleus as a dimer hormone-receptor induces the activation or suppression of genes causing a biological response (McLachlan and Arnold 1996).

Several compounds present in air pollution (heavy metals, environmental oestrogens, diesel and PAHs) are able to suppress or interfere with the regulation of the hypothalamic-pituitary-gonadal axis; resulting in changes in growth and development of ovarian follicles and estrous cyclicity (Veras et al. 2009; Mamatsashvili 1970; Borgeest et al. 2004), affecting the whole process of pregnancy, including signaling pathways between the conceptus-mother or, the uterus preparation for implantation (Hoyer and Sipes 1996; Mattison and Thomford 1989; Tsukue et al. 2001; Takeda et al. 2004; Telisman et al. 2007). However, the specific contaminants that caused sperm damage and the potential impact on fertility or pregnancy outcomes were undetermined (Somers 2011).

PAHs in air pollution have the capacity to bind to steroid receptors, mimicking their action, and thus altering the production of these hormones, which can result in adverse consequences for the development and reproductive health (Kristensen et al. 1995; Wenger et al. 2009; Han et al. 2010). For example, Hood (2006) in his study suggests that exposure prior to conception, both female as male, can lead to a hormonal dysregulation causing direct damage to the reproductive organs and gametes.

Studies suggest that PAHs are able to cross the placenta and reach fetal organs causing adverse reproductive outcomes, including; stillbirths, reabsorptions, congenital abnormalities, and decreases in fetal weight. The exposure to PAHs may lead to increased DNA adducts, resulting to LBW and intrauterine growth restriction. Furthermore, the PM may bind receptors for placental growth factors leading to decreased fetal-placental exchange of oxygen and nutrients (Dejmek et al. 2000; Ritz and Wilhelm 2008).

2.6 Prevention

There are sufficient evidence of the harmful effects of exposures to environmental air pollution on reproductive health. Furthermore, it is clear that increased levels of air pollution are found in developing and underdeveloped countries in regions with high population density and higher fertility rates (Fig. 2.1). Although the risks associated with the negative reproductive outcomes tend to be small, the number of people that might be affected is significantly large. Furthermore, if we consider that negative influence on the initial stages of life (embryo/fetus) increases the risks of later life diseases, such as diabetes, metabolic syndromes and cardiovascular diseases (Osmond and Barker 2000; Gluckman and Hanson 2004) exposures to air pollution during pregnancy would have a profound impact in public health strategies to prevent most common health issues

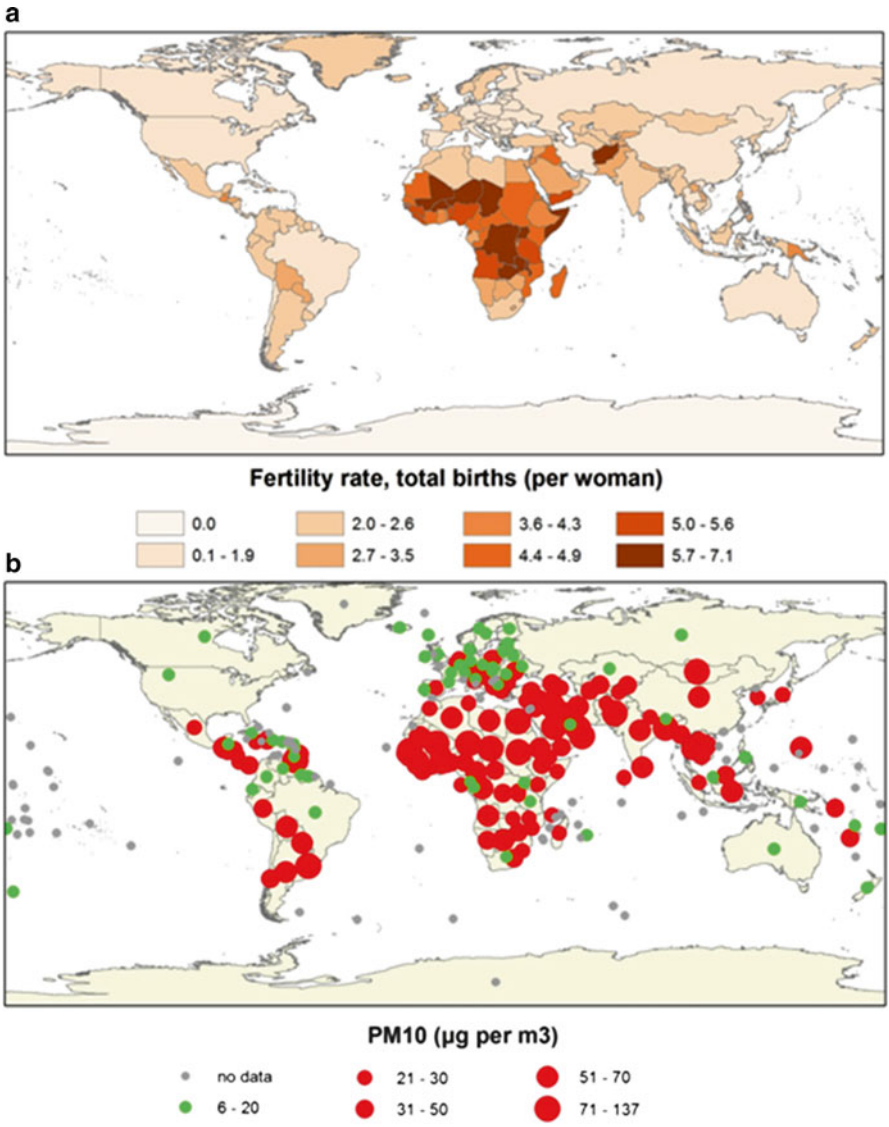

Fig. 2.1 Global scenario of gestational exposure to air pollution. The map compares the total births per women in 2009 (data from the World Bank) (**a**) (World Bank 2013a) with the annual mean concentration of particulate matter of 10 µm or less (PM10) in the same year (data from the World Bank) (**b**) (World Bank 2013b), showing that reproductive health consequences from air pollution exposure is a major concern in the developing nations where a growing population is being exposed to levels of particulate air pollution above the WHO recommended limits

The most effective way to reduce health risks associated with air pollution is to implement air quality management strategies and National Air Quality Standards (Thurston and Balmes 2012). The U.S. Environmental Protection Agency (EPA) projections that by 2020 adherence to the Clean Air Act standard for ozone alone will prevent 230 million premature deaths and 280 infant–mortalities (EPA 2011). Indeed, increasingly stringent (NAQS) already proved effectiveness in improving air quality in the United States and Western Europe in recent decades (Van Erp et al. 2008) and a global analysis concluded that flexible air quality standards lead to higher air pollution concentrations (Vahlsing and Smith 2012).

2.7 Concluding Remarks

Epidemiologic and experimental evidences converge to indicate that air pollution, at the current levels, play a deleterious role on reproductive function. In addition to the scientific questions raised from the aforementioned evidences presented in this chapter – which are the mechanisms, which are the most important pollutants or are the observed effects the result of a mixture of mixtures – some ethical considerations emerged at this moment. Indeed, the options of energy use, industrial production and mobility made by our and our preceding generations, may be affecting those that did not participate in the decision process. Moreover, there is a marked contrast in ambient air pollution concentrations, creating an uneven attributable risk across the globe. As a general rule, air pollution is the result of bad technologies, usually present in the less privileged countries. These points deserve serious consideration when translating knowledge into public policies aimed to protect children globally.

References

Amdur MO, Corn M (1963) The irritant potency of zinc ammonium sulfate of different particle sizes. Am Ind Hyg Assoc J 24:326–333

Amdur MO, Creasia DA (1966) The irritant potency of m-terphenyl of different particle sizes. Am Ind Hyg Assoc J 27(4):349–352

Andrysík Z, Vondráček J, Marvanová S, Ciganek M, Neča J, Pěnčíková K, Mahadevan B, Topinka J, Baird WM, Kozubík A, Machala M (2011) Activation of the aryl hydrocarbon receptor is the major toxic mode of action of an organic extract of a reference urban dust particulate matter mixture: the role of polycyclic aromatic hydrocarbons. Mutat Res 714(1–2):53–62

Baïz N, Dargent-Molina P, Wark JD, Souberbielle JC, Slama R, Annesi-Maesano I, EDEN Mother-Child Cohort Study Group (2012) Gestational exposure to urban air pollution related to a decrease in cord blood vitamin D levels. J Clin Endocrinol Metab 97(11):4087–4095

Bako G, Dewar R, Hanson J, Hill G (1984) Population density as an indicator of urban-rural differences in cancer incidence, Alberta, Canada, 1969–73. Can J Public Health 75(2):152–156

Baskurt OK, Levi E, Caglayan S, Dikmenoglu N, Kutman MN (1990) Hematological and hemorheological effects of air pollution. Arch Environ Health 45:224–228

Bilinski MJ, Thorne JG, Oh MJ, Leonard S, Murrant C, Tayade C, Croy BA (2008) Uterine NK cells in murine pregnancy. Reprod Biomed Online 16(2):218–226
Bobak M, Leon DA (1999) Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986–8. Occup Environ Med 56(8):539–543
Bonner MR, Han D, Nie J, Rogerson P, Vena JE, Muti P, Trevisan M, Edge SB, Freudenheim JL (2005) Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. Cancer Epidemiol Biomarkers Prev 14(1):53–60
Borgeest C, Miller KP, Gupta R, Greenfeld C, Hruska KS, Hoyer P, Flaws JA (2004) Methoxychlor-induced atresia in the mouse involves Bcl-2 family members, but not gonadotropins or estradiol. Biol Reprod 70(6):1828–1835
Brot C, Jorgensen NR, Sorensen OH (1999) The influence of smoking on vitamin D status and calcium metabolism. Eur J Clin Nutr 53:920–926
Brown JS, Zeman KL, Bennett WD (2002) Ultrafine particle deposition and clearance in the healthy and obstructed lung. Am J Respir Crit Care Med 166(9):1240–1247
Burch WM (2002) Passage of inhaled particles into the blood circulation in humans. Circulation 106(20):141–142
Castro KR, Ribeiro R, Peres M, Saldiva P, Matsuda M, Veras M (2013) Murine uterine receptivity markers are affected by particulate air pollution in a dose response manner. Placenta 34(2):A10
Chen J, Tan M, Nemmar A, Song W, Dong M, Zhang G, Li Y (2006) Quantification of extrapulmonary translocation of intratracheal-instilled particles in vivo in rats: effect of lipopolysaccharide. Toxicology 222:195–201
Chen TM, Shofer S, Gokhale J, Kuschner WG (2007) Outdoor air pollution: overview and historical perspective. Am J Med Sci 333(4):230–234
Chen H, Goldberg MS, Villeneuve PJ (2008) A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases. Rev Environ Health 23(4):243–297
Colbeck I, Lazaridis M (2010) Aerosols and environmental pollution. Naturwissenschaften 97(2):117–131
Coyle YM (2004) The effect of environment on breast cancer risk. Breast Cancer Res Treat 84(3):273–288
Crouse DL, Goldberg MS, Ross NA, Chen H, Labrèche F (2010) Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case-control study. Environ Health Perspect 118(11):1578–1583
Davis DL, Gottlieb MB, Stampnitzky JR (1998) Reduced ratio of male to female births in several industrial countries: a sentinel health indicator? JAMA 279(13):1018–1023
De Rosa M, Zarrilli S, Paesano L, Carbone U, Boggia B, Petretta M et al (2003) Traffic pollutants affect fertility in men. Hum Reprod 18(5):1055–1061
Dejmek J, Jelinek R, Benes I, Sram RJ (1998) Impact of air pollution on human fertility: acute effects of SO2, NOx and PM. Epidemiology 9(4):148
Dejmek J, Selevan SG, Benes I, Solanský I, Srám RJ (1999) Fetal growth and maternal exposure to particulate matter during pregnancy. Environ Health Perspect 107(6):475–480
Dejmek J, Jelínek R, Solansky' I, Benes I, Srám RJ (2000) Fecundability and parental exposure to ambient sulfur dioxide. Environ Health Perspect 108(7):647–654
Dockery DW (2009) Health effects of particulate air pollution. Ann Epidemiol 19(4):257–263
EPA (1996) Guidelines for reproductive toxicity risk assessment. http://www.epa.gov/raf/publications/pdfs/REPRO51.PDF. Accessed 15 June 2013
EPA (2011) Report to congress: the benefits and costs of the Clean Air Act 1990 to 2020. U.S. http://www.epa.gov/oar/sect812/feb11/fullreport_rev_a.pdf. Accessed 2 Aug 2013
Faiz AS, Rhoads GG, Demissie K, Lin Y, Kruse L, Rich DQ (2013) Does ambient air pollution trigger stillbirth? Epidemiol 24(4):538–544
Fajersztajn L, Veras M, Barrozo LV, Saldiva P (2013) Air pollution: a potentially modifiable risk factor for lung cancer. Nat Rev Cancer 13(9):674–678
Ferin J, Oberdörster G, Penney DP (1992) Pulmonary retention of ultrafine and fine particles in rats. Am J Respir Cell Mol Biol 6(5):535–542

Gibbons AF, Chang MC (1972) Number of mast cells in the rat uterus with special reference to its relation to hormonal treatment and decidual response. Biol Reprod 6:193–203
Gilbert WM, Young AL, Danielsen B (2007) Pregnancy outcomes in women with chronic hypertension: a population-based study. J Reprod Med 52(11):1046–1051
Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D (2004) Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. Epidemiol 15:36–45
Gluckman PD, Hanson MA (2004) Maternal constraint of fetal growth and its consequences. Semin Fetal Neonatal Med 9(5):419–425
Gouveia N, Bremner SA, Novaes HM (2004) Association between ambient air pollution and birth weight in São Paulo, Brazil. J Epidemiol Community Health 58(1):11–17
Guven A, Kayikci A, Cam K, Arbak P, Balbay O, Cam M (2008) Alterations in semen parameters of toll collectors working at motorways: does diesel exposure induce detrimental effects on semen? Andrologia 40(6):346–351
Ha EH, Hong YC, Lee BE, Woo BH, Schwartz J, Christiani DC (2001) Is air pollution a risk factor for low birth weight in Seoul? Epidemiol 12(6):643–648
Hall SA, Kaufman JS, Millikan RC, Ricketts TC, Herman D, Savitz DA (2005) Urbanization and breast cancer incidence in North Carolina, 1995–1999. Ann Epidemiol 15(10):796–803
Hammoud A, Carrell DT, Gibson M, Sanderson M, Parker-Jones K, Peterson CM (2010) Decreased sperm motility is associated with air pollution in Salt Lake City. Fertil Steril 93(6):1875–1879
Han Y, Xia Y, Zhu P, Qiao S, Zhao R, Jin N, Wang S, Song L, Fu G, Wang X (2010) Reproductive hormones in relation to polycyclic aromatic hydrocarbon (PAH) metabolites among non-occupational exposure of males. Sci Total Environ 408(4):768–773
Hansen C, Neller A, Williams G, Simpson R (2006) Maternal exposure to low levels of ambient air pollution and preterm birth in Brisbane, Australia. BJOG 113(8):935–941
Hansen C, Luben TJ, Sacks JD, Olshan A, Jeffay S, Strader L, Perreault SD (2010) The effect of ambient air pollution on sperm quality. Environ Health Perspect 118(2):203–209
Heal MR, Kumar P, Harrison RM (2012) Particles, air quality, policy and health. Chem Soc Rev 41:6606–6630
Helfand WH, Lazarus J, Theerman P (2001) Donora, Pennsylvania: an environmental disaster of the 20th century. Am J Public Health 91:553
Herr CE, Dostal M, Ghosh R, Ashwood P, Lipsett M, Pinkerton KE, Sram R, Hertz-Picciotto I (2010) Air pollution exposure during critical time periods in gestation and alterations in cord blood lymphocyte distribution: a cohort of livebirths. Environ Health 9:46
Herr CE, Ghosh R, Dostal M, Skokanova V, Ashwood P, Lipsett M, Joad JP, Pinkerton KE, Yap PS, Frost JD, Sram R, Hertz-Picciotto I (2011) Exposure to air pollution in critical prenatal time windows and IgE levels in newborns. Pediatr Allergy Immunol 22(1):75–84
Hirshfield AN (1997) Overview of ovarian follicular development: considerations for the toxicologist. Environ Mol Mutagen 29(1):10–15
Hood RD (2006) Developmental and reproductive toxicology: a practical approach, 2nd edn. CRC Press, Boca Raton
Hosseinpanah F, Pour SH, Heibatollahi M, Moghbel N, Asefzade S, Azizi F (2010) The effects of air pollution on vitamin D status in healthy women: a cross sectional study. BMC Public Health 10:519
Hoyer PB, Sipes IG (1996) Assessment of follicle destruction in chemical-induced ovarian toxicity. Annu Rev Pharmacol Toxicol 36:307–331
Hung LJ, Chan TF, Wu CH, Chiu HF, Yang CY (2012) Traffic air pollution and risk of death from ovarian cancer in Taiwan: fine particulate matter (PM2.5) as a proxy marker. J Toxicol Environ Health A 75(3):174–182
Huo Q, Zhang N, Wang X, Jiang L, Ma T, Yang Q (2013) Effects of ambient particulate matter on human breast cancer: is xenogenesis responsible? PLoS One 8(10):e76609. doi:10.1371/journal.pone.0076609. eCollection 2013
Huynh M, Woodruff TJ, Parker JD, Schoendorf KC (2006) Relationships between air pollution and preterm birth in California. Paediatr Perinat Epidemiol 20(6):454–461

Iwai K, Mizuno S, Miyasaka Y, Mori T (2005) Correlation between suspended particles in the environmental air and causes of disease among inhabitants: cross-sectional studies using the vital statistics and air pollution data in Japan. Environ Res 99(1):106–117

Izawa H, Kohara M, Watanabe G, Taya K, Sagai M (2007) Diesel exhaust particle toxicity on spermatogenesis in the mouse is aryl hydrocarbon receptor dependent. J Reprod Dev 53(5):1069–1078

Jafarabadi M (2007) Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. Hum Reprod 22(12):3263

Jedrychowski W, Bendkowska I, Flak E, Penar A, Jacek R, Kaim I, Spengler JD, Camann D, Perera FP (2004) Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: an epidemiologic prospective cohort study in Poland. Environ Health Perspect 112(14):1398–1402

Kannan S, Misra DP, Dvonch T, Krishnakumar A (2006) Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environ Health Perspect 114(11):1636–1642

Kannan S, Misra DP, Dvonch JT, Krishnakumar A (2007) Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential. Cien Saude Colet 12(6):1591–1602

Kelishadi R, Sharifi-Ghazvini F, Poursafa P, Mehrabian F, Farajian S, Yousefy H, Movahedian M, Sharifi-Ghazvini S (2013) Determinants of hypovitaminosis D in pregnant women and their newborns in a sunny region. Int J Endocrinol 2013:1–6

Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ (2008) Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). Am J Cardiol 102:1540–1544

Knottnerus JA, Delgado LR, Knipschild PG, Essed GG, Smits F (1990) Haematologic parameters and pregnancy outcome: a prospective cohortstudy in the third trimester. J Clin Epidemiol 43:461–466

Kok TM, Driece HA, Hogervorst JG, Briedé JJ (2006) Toxicological assessment of ambient and traffic-related particulate matter: a review of recent studies. Mutat Res 613(2–3):103–122

Kristensen P, Eilertsen E, Einarsdóttir E, Haugen A, Skaug V, Ovrebø S (1995) Fertility in mice after prenatal exposure to benzo[a]pyrene and inorganic lead. Environ Health Perspect 103(6):588–590

Lange NE, Litonjua A, Hawrylowicz CM, Weiss S (2009) Vitamin D, the immune system and asthma. Expert Rev Clin Immunol 5:693–702

Laumbach RJ (2010) Outdoor air pollutants and patient health. Am Fam Physician 81(2):175–180

Lee PC, Roberts JM, Catov JM, Talbott EO, Ritz B (2013) First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. Matern Child Health J 17(3):545–555

Leem JH, Kaplan BM, Shim YK, Pohl HR, Gotway CA, Bullard SM, Rogers JF, Smith MM, Tylenda CA (2006) Exposures to air pollutants during pregnancy and preterm delivery. Environ Health Perspect 114(6):905–910

Lewis-Michl EL, Melius JM, Kallenbach LR, Ju CL, Talbot TO, Orr MF, Lauridsen PE (1996) Breast cancer risk and residence near industry or traffic in Nassau and Suffolk Counties, Long Island, New York. Arch Environ Health 51(4):255–265

Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, Wang M, Oberley T, Froines J, Nel A (2003) Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 111(4):455–460

Lichtenfels AJ, Gomes JB, Pieri PC, El Khouri Miraglia SG, Hallak J, Saldiva PH (2007) Increased levels of air pollution and a decrease in the human and mouse male-to-female ratio in São Paulo, Brazil. Fertil Steril 87(1):230–232

Lloyd OL, Smith G, Lloyd MM et al (1985) Raised mortality from lung cancer and high sex ratios of births associated with industrial pollution. Br J Ind Med 42(7):475–480

Logan WP (1953) Mortality in the London fog incident, 1952. Lancet 1:336–338

Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K, on behalf of the International Agency for Research on Cancer Monograph Working Group IARC, Lyon, France, on behalf of the International Agency for Research on Cancer Monograph Working Group IARC, Lyon, France (2013) The carcinogenicity of outdoor air pollution. Lancet Oncol 14(13):1262–1263

Maisonet M, Bush TJ, Correa A, Jaakkola JJ (2001) Relation between ambient air pollution and low birth weight in the Northeastern United States. Environ Health Perspect 109(3):351–356

Maisonet M, Correa A, Misra D, Jaakkola JJ (2004) A review of the literature on the effects of ambient air pollution on fetal growth. Environ Res 95(1):106–115

Mamatsashvili MI (1970) Detrimental effect of carbon monoxide and sulfur dioxide on fertility of female rats. Hyg Sanit 35(4–6):277–279

Mannes T, Jalaludin B, Morgan G, Lincoln D, Sheppeard V, Corbett S (2005) Impact of ambient air pollution on birth weight in Sydney, Australia. Occup Environ Med 62(8):524–530

Marx L, Arck P, Kieslich C, Mitterlechner S, Kapp M, Dietl J (1999) Decidual mast cells might be involved in the onset of human first-trimester abortion. Am J Reprod Immunol 41:34–40

Mattison DR, Thomford PJ (1989) The mechanisms of action of reproductive toxicants. Toxicol Pathol 17(2):364–376

McLachlan JA, Arnold SF (1996) Environmental estrogens. Am Sci 84:452–461

Menzel DB (1994) The toxicity of air pollution in experimental animals and humans: the role of oxidative stress. Toxicol Lett 72(1–3):269–277

Mills NL, Amin N, Robinson SD, Anand A, Davies J, Patel D, de la Fuente JM, Cassee FR, Boon NA, Macnee W, Millar AM, Donaldson K, Newby DE (2006) Do inhaled carbon nanoparticles translocate directly into the circulation in humans? Am J Respir Crit Care Med 173(4):426–431

Miraglia SG, Veras MM, Amato-Lourenço LF, Rodrigues-Silva F, Saldiva PH et al (2013) Follow-up of the air pollution and the human male-to-female ratio analysis in Sao Paulo, Brazil: a times series study. BMJ Open 3(7). pii: e002552. doi:10.1136/bmjopen-2013-002552

Mohallem SV, de Araújo Lobo DJ, Pesquero CR, Assunção JV, de Andre PA, Saldiva PH, Dolhnikoff M (2005) Decreased fertility in mice exposed to environmental air pollution in the city of Sao Paulo. Environ Res 98(2):196–202

Möller W, Felten K, Sommerer K, Scheuch G, Meyer G, Meyer P, Häussinger K, Kreyling WG (2008) Deposition, retention, and translocation of ultrafine particles from the central airways and lung periphery. Am J Respir Crit Care Med 177(4):426–432

Morello-Frosch R, Jesdale BM, Sadd JL, Pastor M (2010) Ambient air pollution exposure and full-term birth weight in California. Environ Health 28(9):44

Need AG, Kemp A, Giles N, Morris HA, Horowitz M, Nordin BE (2002) Relationships between intestinal calcium absorption, serum vitamin metabolites and smoking in postmenopausal women. Osteoporos Int 13:83–88

O'Neill MS, Jerrett M, Kawachi I et al (2003) Health, wealth, and air pollution: advancing theory and methods. Environ Health Perspect 111:1861–1870

Oberdorster G, Utell MJ (2002) Ultrafine particles in the urban air: to the respiratory tract – and beyond? Environ Health Perspect 110:440–441

Olsson D, Mogren I, Forsberg B (2013) Air pollution exposure in early pregnancy and adverse pregnancy outcomes: a register-based cohort study. BMJ Open 3(2):1–8

Ono Y, Takagi K, Seki H, Takai Y, Samejima K, Matsunaga S, Matsumura H (2013) Neonatal outcome in infants of chronically hypertensive mothers. J Obstet Gynaecol Res 39(6):1142–1146

Osmond C, Barker DJ (2000) Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 108 Suppl 3:545–553

Parent MÉ, Goldberg MS, Crouse DL, Ross NA, Chen H, Valois MF, Liautaud A (2013) Traffic-related air pollution and prostate cancer risk: a case-control study in Montreal, Canada. Occup Environ Med 70(7):511–518

Parker JD, Woodruff TJ (2008) Influences of study design and location on the relationship between particulate matter air pollution and birthweight. Paediatr Perinat Epidemiol 22(3):214–227
Pekkanen J, Brunner EJ, Anderson HR, Tiittanen P, Atkinson RW (2000) Daily concentrations of air pollution and plasma fibrinogen in London. Occup Environ Med 57:818–822
Pereira LAA, Loomis D, Conceicao GMS et al (1998) Association between air pollution and intrauterine mortality in Sao Paulo, Brazil. Environ Health Perspect 106:325–329
Perin PM, Maluf M, Czeresnia CE, Januário DA, Saldiva PHN (2010a) Impact of short-term preconceptional exposure to particulate air pollution on treatment outcome in couples undergoing in vitro fertilization and embryo transfer (IVF/ET). J Assist Reprod Genet 27(7):371–382
Perin PM, Maluf M, Czeresnia CE, Nicolosi Foltran Januário DA, Saldiva PHN (2010b) Effects of exposure to high levels of particulate air pollution during the follicular phase of the conception cycle on pregnancy outcome in couples undergoing in vitro fertilization and embryo transfer. Fertil Steril 93(1):301–303
Peters A, Döring A, Wichmann HE, Koenig W (1997) Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349(9065):1582–1587
Ponce NA, Hoggatt KJ, Wilhelm M, Ritz B (2005) Preterm birth: the interaction of traffic-related air pollution with economic hardship in Los Angeles neighborhoods. Am J Epidemiol 162(2):140–148
Pope CA 3rd (2000) Epidemiology of fine particulate air pollution and human health: biologic mechanisms and who's at risk? Environ Health Perspect 108 Suppl 4:713–723
Pope CA 3rd, Ezzati M, Dockery DW (2009) Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 360(4):376–386
Rahman I, MacNee W (2000) Oxidative stress and regulation of glutathione in lung inflammation. Eur Respir J 16(3):534–554
Ren C, Tong S (2008) Health effects of ambient air pollution-recent research development and contemporary methodological challenges. Environ Health 7:56
Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D et al (2004) Regional variations in breast cancer among California teachers. Epidemiol 15(6):746–754
Ritz B, Wilhelm M (2008) Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. Basic Clin Pharmacol Toxicol 102(2):182–190
Ritz B, Yu F, Chapa G, Fruin S (2000) Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. Epidemiol 11(5):502–511
Rocha E, Silva IR, Lichtenfels AJ, Amador Pereira LA, Saldiva PH (2008) Effects of ambient levels of air pollution generated by traffic on birth and placental weights in mice. Fertil Steril 90(5):1921–1924
Rowe T (2006) Fertility and a woman's age. J Reprod Med 51:157–163
Rubes J, Selevan SG, Evenson DP, Zudova D, Vozdova M, Zudova Z, Robbins WA, Perreault SD (2005) Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. Hum Reprod 20(10):2776–2783
Rudel RA, Attfield KA, Schifano JN et al (2007) Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. Cancer 109:2635–2666
Rudra CB, Williams MA, Sheppard L, Koenig JQ, Schiff MA (2011) Ambient carbon monoxide and fine particulate matter in relation to preeclampsia and preterm delivery in western Washington State. Environ Health Perspect 119(6):886–892
Sadeu JC, Hughes CL, Agarwal S, Foster WG (2010) Alcohol, drugs, caffeine, tobacco, and environmental contaminant exposure: reproductive health consequences and clinical implications. Crit Rev Toxicol 40(7):633–652
Saldiva PHN, Clarke RW, Coull BA, Stearns RC, Lawrence J, Krishna Murthy GG, Diaz E, Koutrakis P, Suh H, Tsuda A, Godleski JJ (2002) Lung inflammation induced by concentrated ambient air particles is related to particle composition. Am J Respir Crit Care Med 165:1610–1617
Schnorr TM, Lawson CC, Whelan EA et al (2001) Spontaneous abortion, sex ratio, and paternal occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ Health Perspect 109(11):1127–1132

Schwartz J (2006) Long-term effects of exposure to particulate air pollution. Clin Occup Environ Med 5(4):837–848

Scoriza J, Saldiva PHN, Caldini EG, Veras MM (2009) Effects of pre-gestational and gestational exposure to air pollution (particulate matter) on mast cell density in implantation sites of mice. In: Abstracts of the II symposium on reproductive immunology, Rio de Janeiro, 2009

Seaton A, Macnee W, Donald K, Godden D (1995) Particulate air pollution and acute health effects. Lancet 345:176–178

Selevan SG, Borkovec L, Slott VL, Zudová Z, Rubes J, Evenson DP, Perreault SD (2000) Semen quality and reproductive health of young Czech men exposed to seasonal air pollution. Environ Health Perspect 108(9):887–894

Sioutas C, Delfino R, Singh M (2005) Exposure assessment for atmospheric ultrafine particles (UFPs) and implications for epidemiologic research. Environ Health Perspect 113:947–955

Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, Glinianaia S, Hoggatt KJ, Kannan S, Hurley F, Kalinka J, Srám R, Brauer M, Wilhelm M, Heinrich J, Ritz B (2008) Meeting report: atmospheric pollution and human reproduction. Environ Health Perspect 116(6):791–798

Slama R, Bottagisi S, Solansky I, Lepeule J, Giorgis-Allemand L, Sram R (2013) Short-term impact of atmospheric pollution on fecundability. Epidemiology 24(6):871–879

Sokol RZ, Kraft P, Fowler IM, Mamet R, Kim E, Berhane KT (2006) Exposure to environmental ozone alters semen quality. Environ Health Perspect 114(3):360–365

Soll-Johanning H, Bach E (2004) Occupational exposure to air pollution and cancer risk among Danish urban mail carriers. Int Arch Occup Environ Health 77(5):351–356

Somers CM (2011) Ambient air pollution exposure and damage to male gametes: human studies and in situ 'sentinel' animal experiments. Syst Biol Reprod Med 57:63–71

Somers CM, Cooper DN (2009) Air pollution and mutations in the germline: are humans at risk? Hum Genet 125(2):119–130

Somers CM, Yauk CL, White PA, Parfett CLJ, Quinn JS (2002) Air pollution induces heritable DNA mutations. Proc Natl Acad Sci 99:15904–15907

Somers CM, McCarry BE, Malek F, Quinn JS (2004) Reduction of particulate air pollution lowers the risk of heritable mutations in mice. Science 304:1008–1010

Sørensen M, Daneshvar B, Hansen M, Dragsted LO, Hertel O, Knudsen L, Loft S (2003) Personal PM2.5 exposure and markers of oxidative stress in blood. Environ Health Perspect 111:161–166

Squadrito GL, Cueto R, Dellinger B, Pryor WA (2001) Quinoid redox cycling as a mechanism for sustained free radical generation by inhaled airborne particulate matter. Free Radic Biol Med 31(9):1132–1138

Srám RJ, Binková B, Dejmek J, Bobak M (2005) Ambient air pollution and pregnancy outcomes: a review of the literature. Environ Health Perspect 113(4):375–382

Sriramachari S (2005) Bhopal gas tragedy: scientific challenges and lessons for future. J Loss Prev Process Ind 18(4–6):264–267

Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ (2008) Environmental exposures and adverse pregnancy outcomes: a review of the science. Reprod Sci 15(7):631–650

Takeda K, Tsukue N, Yoshida S (2004) Endocrine-disrupting activity of chemicals in diesel exhaust and diesel exhaust particles. Environ Sci 11(1):33–45

Takenaka S, Dornhofer-Takenaka H, Muhle H (1986) Alveolar distribution of fly ash and of titanium dioxide after long-term inhalation by Wistar rats. J Aerosol Sci 17:361–364

Telisman S, Colak B, Pizent A, Jurasović J, Cvitković P (2007) Reproductive toxicity of low-level lead exposure in men. Environ Res 105(2):256–266

Terrell ML, Hartnett KP, Marcus M (2011) Can environmental or occupational hazards alter the sex ratio at birth? A systematic review. Emerg Health Threats J 4:1–18

Thurston GD, Balmes JR (2012) Particulate matter and the environmental protection agency setting the right standard. Am J Respir Cell Mol Biol 47(6):727–728

Tragaki A, Lasaridi K (2009) Temporal and spatial trends in the sex ratio at birth in Greece, 1960–2006: exploring potential environmental factors. Popul Environ 30(3):114–128

Tsukue N, Toda N, Tsubone H, Sagai M, Jin WZ, Watanabe G, Taya K, Birumachi J, Suzuki AK (2001) Diesel exhaust (DE) affects the regulation of testicular function in male Fischer 344 rats. J Toxicol Environ Health A 63(2):115–126

Vahlsing C, Smith KR (2012) Global review of national ambient air quality standards for PM10 and SO2 (24 h). Air Qual Atmos Health 5:393–399

Valavanidis A, Fiotakis K, Vlachogianni T (2008) Airborne particulate matter and human health: toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 26(4):339–362

van den Hooven EH, Pierik FH, de Kluizenaar Y, Willemsen SP, Hofman A, van Ratingen SW, Zandveld PY, Mackenbach JP, Steegers EA, Miedema HM, Jaddoe VW (2012a) Air pollution exposure during pregnancy, ultrasound measures of fetal growth, and adverse birth outcomes: a prospective cohort study. Environ Health Perspect 120(1):150–156

van den Hooven EH, Pierik FH, Kluizenaar Y, Hofman A, van Ratingen SW, Zandveld PY, Russcher H, Lindemans J, Miedema HM, Steegers EA, Jaddoe VW (2012b) Air pollution exposure and markers of placental growth and function: the generation R study. Environ Health Perspect 120(12):1753–1759

Van Erp AM, O'Keefe R, Cohen AJ, Warren J (2008) Evaluating the effectiveness of air quality interventions. J Toxicol Environ Health A 71:583–587

Veras MM, Damaceno-Rodrigues NR, Caldini EG, Maciel Ribeiro AA, Mayhew TM, Saldiva PH, Dolhnikoff M (2008) Particulate urban air pollution affects the functional morphology of mouse placenta. Biol Reprod 79:578–584

Veras MM, Damaceno-Rodrigues NR, Guimarães Silva RM, Scoriza JN, Saldiva PH, Caldini EG, Dolhnikoff M (2009) Chronic exposure to fine particulate matter emitted by traffic affects reproductive and fetal outcomes in mice. Environ Res 109(5):536–543

Veras MM, Guimarães-Silva RM, Caldini EG, Saldiva PH, Dolhnikoff M, Mayhew TM (2012) The effects of particulate ambient air pollution on the murine umbilical cord and its vessels: a quantitative morphological and immunohistochemical study. Reprod Toxicol 34(4):598–606

Vorherr H (1982) Factors influencing fetal growth. Am J Obstet Gynecol 142:577–588

Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, Nieuwenhuijsen MJ (2011) Ambient air pollution and risk of congenital anomalies: a systematic review. Environ Health Perspect 119:598–606

Wang X, Ding H, Ryan L, Xu X (1997) Association between air pollution and low birth weight: a community-based study. Environ Health Perspect 105(5):514–520

Wenger D, Gerecke AC, Heeb NV, Schmid P, Hueglin C, Naegeli H, Zenobi R (2009) In vitro estrogenicity of ambient particulate matter: contribution of hydroxylated polycyclic aromatic hydrocarbons. J Appl Toxicol 29(3):223–232

WHO (2005) Air quality guidelines – global update 2005. http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf. Accessed 10 July 2013

Wiebert P, Sanchez-Crespo A, Falk R, Philipson K, Lundin A, Larsson S, Möller W, Kreyling WG, Svartengren M (2006a) No significant translocation of inhaled 35-nm carbon particles to the circulation in humans. Inhal Toxicol 18(10):741–747

Wiebert P, Sanchez-Crespo A, Seitz J, Falk R, Philipson K, Kreyling WG, Möller W, Sommerer K, Larsson S, Svartengren M (2006b) Negligible clearance of ultrafine particles retained in healthy and affected human lungs. Eur Respir J 28(2):286–290

Wilhelm M, Ritz B (2003) Residential proximity to traffic and adverse birth outcomes in Los Angeles county, California, 1994–1996. Environ Health Perspect 111(2):207–216

Williams FL, Lawson AB, Lloyd OL (1992) Low sex ratios of births in areas at risk from air pollution from incinerators, as shown by geographical analysis and 3-dimensional mapping. Int J Epidemiol 21(2):311–319

Woodruff TK, Walker CL (2008) Fetal and early postnatal environmental exposures and reproductive health effects in the female. Fertil Steril 89:47–51

Woodruff TJ, Parker JD, Kyle AD, Schoendorf KC (2003) Disparities in exposure to air pollution during pregnancy. Environ Health Perspect 111(7):942–946

Woodruff TJ, Carlson A, Schwartz JM, Giudice LC (2008) Proceedings of the summit on environmental challenges to reproductive health and fertility: executive summary. Fertil Steril 89(2 Suppl):e1–e20

World Bank (2013a) Fertility rate (total births per women). http://data.worldbank.org/indicator/SP.DYN.TFRT.IN. Accessed 15 July 2013.

World Bank (2013b) PM10, country level (micrograms per cubic meter). http://data.worldbank.org/indicator/EN.ATM.PM10.MC.M3. Accessed 15 July 2013.

Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B (2009) Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California. Environ Health Perspect 117(11):1773–1779

Yang CY, Chang CC, Chuang HY, Ho CK, Wu TN, Tsai SS (2003) Evidence for increased risks of preterm delivery in a population residing near a freeway in Taiwan. Arch Environ Health 58(10):649–654

Yauk CL, Polyzos A, Rowan-Carroll A, Somers CM, Godschalk RW, Van Schooten FJ et al (2008) Germ-line mutations, DNA damage, and global hypermethylation in mice exposed to particulate air pollution in an urban/industrial location. Proc Natl Acad Sci 105:605–610