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Air Pollution Exposure During Pregnancy and Reproductive Outcomes

Ferran Ballester and Carmen Iñiguez
University of Valencia, Nursing School, Valencia,
Center for Public Health Research (CSISP), Valencia,
Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP)
Spain

1. Introduction

Air pollution is largely recognized as a risk factor for several outcomes including increased mortality, increased hospital admissions and emergency visits for both respiratory and cardiovascular diseases, and impairment of respiratory function, including reduced lung function, exacerbation of asthma and chronic obstructive pulmonary disease (Brunekreef & Holgate, 2002). Some populations have shown to be more susceptible to these effects, and among them including those people in the tails of the age distribution, i.e. the elderly and infants (Laumbach, 2010).

The study of fetal growth and birth outcomes has become an important emerging field of environmental epidemiology (Sram et al., 2005). Birth outcomes are important indicators of pregnancy and infant care as well as newborn and infant health. Besides that, reduction in fetal growth has been associated with health problems and developmental delays during childhood, from an increase in hospitalizations (Morris et al., 1998) to poor cognitive and neurological development (Richards et al., 2002) as well as with an increased risk of chronic diseases later in life (Barker, 2007).

Fetuses, like infants, present a special vulnerability, compared to adults, regarding environmental toxicants due to differences in exposure, physiological immaturity, and longer life expectancy after exposure (Perera et al., 2002; Schwartz, 2004). Results from epidemiological and experimental studies show that fetuses and infants are especially susceptible to the toxic effects of pollutants such as suspended particles, polycyclic aromatic hydrocarbons (PAH), and tobacco smoke (Perera et al., 2003). In recent years, a growing body of epidemiological research has focused on the potential impact of prenatal exposure to air pollution on birth outcomes.

In recent years a number of authors have reviewed the evidence on the relation between prenatal exposure to air pollutants and reproductive outcomes (Glinianaia et al., 2004; Maisonet et al., 2004; Lacasaña et al., 2005; Sram et al., 2005; Wang & Pinkerton, 2007; Hackley et al., 2007; Wigle et al., 2008; Bosetti et al., 2010; Vrijheid et al., 2011; Shah & Balkhair, 2011). In these reviews several outcomes have been related to exposure to air pollution during pregnancy, including low birth weight, reduced birth size, fetal growth retardation, pre-term birth, stillbirth, congenital malformations, and infant mortality.

A limited number of studies have linked different birth defects to routinely measured air pollutants, but results thus far are equivocal at best (Ritz, 2009). Practically the same could be said concerning stillbirth. Very few epidemiologic studies have elaborated on the impact of air pollution on the risk for stillbirth; results were inconsistent and the studies did not elaborate on the susceptible time of pregnancy. As an example, a recent study conducted in northern England found no association between black smoke air pollution and the risk of stillbirth during pregnancy (Pearce et al., 2010).

Some methodological problems have been argued in the epidemiological studies assessing the impact of air pollution on reproductive outcomes. Authors of recent methodological reviews (Ritz & Wilhelm, 2008; Slama et al., 2008; Woodruff et al., 2009) agree that new prospective studies should allow adequate evaluation of fetal growth (i.e. through ultrasound measurements), valid assessment of air pollution exposure, consider different time windows of exposure, and collect sufficient information on confounding variables.

Our objective in this chapter is to examine and summarize the evidence on the relation between ambient air pollution during pregnancy and birth outcomes. Additionally, we aim to describe some methodological problems and make recommendations for future studies.

2. Methodological aspects

In the past decade, there has been a sharp increase in the number of scientific studies describing possible effects of air pollution on perinatal health. These studies resulted in a considerable amount of research articles published on this topic. Reviews of the preceding literature have been published generally concluding that the evidence, although suggestive of an adverse effect, was difficult to synthesize. Variability existed of course in the nature of the pollutants and outcomes investigated but also there were important differences in the availability of data, study design and statistical analysis.

To discuss the contribution of methodological aspects on findings, heterogeneity is the basis to identify priorities and make recommendations for future research. This aim led to several international workshops and published reviews covering the main challenges and the main methodological aspects of perinatal air pollution epidemiology (Slama et al., 2008). Also trying to discern how differences in research methods contributed to variations in findings, the datasets from 20 different studies along six countries have been analyzed using a standardised protocol (Parker et al., 2011), within a recent initiative by international collaborators (Woodruff et al., 2010).

A synopsis of key methodological issues surrounding the study of air pollution effects on perinatal health is highlighted bellow.

2.1 Study design

Time-series is the typical design in air pollution epidemiology, and it has been used to study preterm birth and fetal death (Pereira et al., 1998, Sagiv et al., 2005). Under this design, population-aggregated daily counts of health events relating to daily levels of pollutants are analyzed. The time series approach, by design, controls for confounders constant over time. In consequence, there is much less concern for personal characteristics than for weather-related confounders. However, this approach only addresses short-term effects and relies on temporal variations. It appears that taking into consideration geographical variations and also medium-term temporal contrasts could be more efficient in reducing residual confounding. Furthermore, traditional time-series design assumes that the population at risk remains stable

across time, a hypothesis that may be not satisfied dealing with adverse birth outcomes because of seasonality of birth influenced by socio-demographic factors (Boback et al., 2001).
Linkage of **registry data** such as birth certificates, with exposure measures of ambient air quality, typically from outdoor stationary monitors has been applied much more in the last decade, resulting in a fast-growing body of evidence on adverse effects of air pollution on fetal development (Salam et al., 2005). This approach has the advantage of allowing large-size studies at a very low cost because it relies on routinely collected data. Its limitation is that relevant information at the individual level is unavailable from birth registers and its absence in analyses may clearly lead to misclassification and confounding.
Potential confounders in this context are socio-economic and occupational status, adverse behaviours such as alcohol or tobacco use, or poor diet. Apart from confusion, effect modification can occur as certain subpopulations of women and fetuses may be especially vulnerable to air pollutants. To this respect, several studies suggest a stronger effect for males that for females (Jedrychowski et al., 2009; Ghosh et al., 2007).
For these reasons, prospective **cohort studies** with recruitment of women at earlier stages of pregnancy are a promising alternative: They collect detailed information on potential confounders and allow the personal assessment of exposure and the use of biomarkers (Estarlich et al., 2011). As an added value, under some conditions, causality may be inferred from them. Its main limitation is the associated high cost, leading to reduced sample sizes.
The trade-off between small studies rich in individual information and big studies based on registries with scarce information about confounders and risk factors should be taken in consideration (van den Hooven et al., 2009). A possibility is to combine the strengths of these two designs by conducting **case–control studies** (Hansen et al., 2009) with collection of additional information at the individual level for a sample nested within a big cohort constituted from birth records.

2.2 Exposure assessment

Various approaches may be used to estimate air pollution exposure, from the use of biomarkers of exposure to environmental models. Obviously, the most accurate information of individual exposure should be derived from short-term **personal monitoring** and **biomarkers**. However, both are scarcely used because of their extreme cost and inability to discern the appropriate timing of measurement or source contributions. Studies using personal measurements are relatively small in size and commonly used as validation studies of other modelling approaches (Nethery et al., 2009).
As was said before, there are a number of studies (Xu et al., 1995; Boback 2000; Ritz et al., 2000) with exposure assessment based on data from **monitoring networks.** These studies use data from the monitoring station closest to the subject's home address or interpolating data for neighbouring monitors, for which measurements are averaged over the entire pregnancy or over each trimester of pregnancy. Advantages of this approach are the use of readily available exposure data, simple implementation and, as pollutants are assessed on an hourly or daily basis, high flexibility in terms of the temporal exposure window considered (Lepeule et al., 2010). Nevertheless, the individual exposure assignment based exclusively on them is prone to inaccuracy because the number of sampling locations is often scarce failing to capture the spatial variability. Furthermore sampling locations could be biased towards specific sources of pollution (i.e. traffic, background, industry) and not always provide continuously measured data (i.e. Particles ≤2.5 μm diameter ($PM_{2.5}$) in the US is often measured every 3–6 days).

Nitrogen dioxide (NO_2) is one air pollutant frequently used as a **surrogate** for traffic related pollution in prospective studies, both in adults and in children (Jerrett et al., 2008; Brunekreef, 2007). This is the case because outdoor NO_2 levels correlate well with traffic generated pollutants. NO_2 concentrations may be easily measured using passive samplers, and are routinely measured by air quality networks allowing for correction for temporal variations. Several epidemiologic studies have examined associations between maternal exposure to nitrogen dioxide during pregnancy and reproductive outcomes such as prematurity, fetal growth retardation and birth weight (e.g., Aguilera et al., 2009; Ballester et al., 2010; Bell et al., 2007; Liu et al., 2007; Ritz & Wilhelm 2008; Slama et al., 2008; Brauer et al., 2008). Some of them have introduced other geostatistical models based on measurement campaigns with fine spatial resolution and geographic information systems (GIS) plus temporal adjustment based on background monitoring stations (Lepeule et al., 2010).

Recently, GIS-based approaches have become more commonly used to capture small area variations in pollution. The great development experienced by the GIS managing and displaying spatial data (Vine et al., 1997; Bellander et al., 2001; Briggs, 2005, 2007) has been decisive in this respect. Within GIS-based approaches, air dispersion models (Malvqvist 2011), traffic proximity models and Land-use regression are among the most used. Exposure assessments using **traffic proximity** (Jerrett et al., 2008; Brunekreef, 2007) or distance-weighted traffic densities as a proxy for individual exposure to air pollution relies on the premise that traffic is a major source of local air pollution. A potential problem with this method is the underlying assumption that pollution spreads uniformly away from its source. **Land-use regression** (LUR) methods apply regression to map air pollution using geographical variables such as land use, traffic intensity and population density as predictors. (Ghering et al., 2011; Iñiguez et al., 2009; Henderson et al.,2007; Aguilera et al., 2009; Slama et al., 2008; Wheeler et al., 2008). LUR models are an attractive option because they are able to capture fine spatial variability at a very low cost.

Whatever the method used for mapping outdoor levels of air pollution, in most studies personal exposure is the estimated concentration at a home address derived from the map. A large proportion of personal exposure is commuting time, workplace exposure or come from indoor sources, therefore personal exposure assessments should be improved by considering **time-activity patterns** and indoor sources such as tobacco smoke and cooking. In the case of studies dilated in time, taking into account a possible change of address could be also an important point. Obviously, improving exposure assessment and reducing exposure misclassification would lead to strengthen effect estimates.

Another methodological challenge recently highlighted is the convenience of exploring **critical windows of exposure** shorter than the whole pregnancy. Pregnancy is a period of big change and the timing of exposure could be as important as the intensity. Studies suggest that exposures at the periconceptional period or first trimester may lead to suboptimal placental or fetal development in earliest stages of pregnancy with ulterior adverse consequences on the duration of pregnancy and fetal growth. At this time, there is a lack of toxicological information to help guide selection of relevant exposure periods for most reproductive outcomes, but an appropriate scale, searching for critical windows may be months or trimesters. For low birth weigth (LBW) and preterm birth, first and third trimester air pollution exposures appears as the most relevant, while for birth defects, the development time of the specific organ has to be considered (Ritz, 2008).

Although trimesters is the most common scale, offering comparability with existing studies, exposure windows shorter than trimesters have also been proposed. In this case it is

important to consider if that accuracy is possible given the exposure metrics. (Woodruf, 2009). LUR models are meant to characterize spatial rather than temporal variability in air pollution levels. Aiming to explore critical exposure windows within pregnancy, fine temporal resolution added to fine spatial resolution is required. Temporal patterns observed at ambient monitor stations (measured most days) could be used to adjust LUR model estimates as done by Slama et al. (2007). This assumes the spatial surface (variability) is stable over time and additional monitoring may be needed to verify this assumption.

Another point is the statistical treatment of exposure. The usual way is to consider a **linear** effect but this assumption widely depends on the examined toxicant. High exposures can lead to outcomes such as spontaneous abortions or stillbirth, removing fetuses at risk for and adverse birth outcome such as LBW or preterm birth, translating to non-linearity in dose effects. Therefore, to explore the shape of relationships by means of non-linear models may be advisable.

Finally, it is also advisable the use of **multipollutant models** to try to disentangle individual effects. However, multipollutant models may be unfeasible due to high correlation in time and space between air pollutants sharing sources. Given that people breath a mixture of air pollutants, to study synergistic effects may also be important.

2.3 Outcomes

The majority of published air pollution and perinatal health studies have evaluated the effect of exposure on fetal growth (usually assessed on the basis of attained weight at birth) and the effect on the duration of gestation. Other important but less studied outcomes related to pregnancy are infertility, fetal loss (including stillbirth and spontaneous abortion) and congenital malformations. These outcomes are briefly defined below in order of its eventual occurrence.

Infertility is the failure of a couple to reproduce after a reasonable time with regular and unprotected sexual intercourse to obtain a pregnancy. One year is usually considered as a deadline, then fertility is treated as a dichotomy, assessing the proportion of couples that fail to conceive within a 12-month period. Because there is not a discontinuity in the probability of conception after 12 cycles, a common alternative approach is to examine the monthly probability of conception in a life-table approach. Both approaches can be derived by assessing time to pregnancy.

Fetal loss is defined as a spontaneous end of pregnancy, without living birth, occurring between conception and the end of labor and excluding induced abortions and medical termination of pregnancy and ectopic pregnancies. Since the clinical, physical and psychological consequences of a fetal loss increase with the time of occurrence, fetal losses are divided in three categories according gestational age (GA): early fetal losses, occurring before than 6 weeks (usual time of detection of pregnancy), spontaneous abortions, occurring between 6 weeks and the time when the fetus is viable, and stillbirth, occurring after this point. The gestational age cut-point between spontaneous abortions and stillbirths could vary between 20 and 28 weeks according local legal definitions. However in epidemiological studies, the 20 or 22 gestational weeks cut-points are most often used.

Congenital malformations: The definition of congenital malformations classically includes structural malformations, syndromes and chromosomal anomalies present in the fetus or the newborn as defined by ICD-10 Q00.0 to Q89.9. It is recognized that a number of congenital malformations are detected during childhood or even adulthood. Since some of them are a major cause of abortion (Eurocat, 2005), these functional defects are identified only in a subset

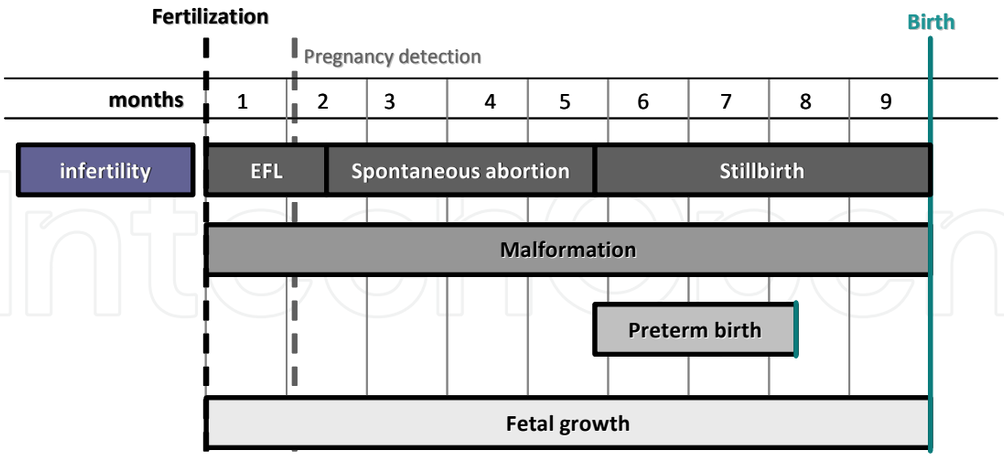
of all fetuses affected. The prevalence of (detected) congenital malformations ranges from 2% (when only major malformations are selected) to 7% when minor forms are included.

Prematurity is defined by the duration of gestation in completed weeks or days. The most common cut-point is 37 weeks (259 days). Accordingly, a preterm birth is defined as an infant born before the completion of the 37th week of gestation. Other dichotomous outcome measures with stringent cut-points aiming to define more extreme deviations from the normal gestational duration are: Extremely premature birth (< 28 weeks or 196 days) and Very preterm birth (< 32 weeks or < 224 days). Prematurity is an important indicator of perinatal and future health. In fact, preterm babies account for 75% of perinatal mortality and more than half of the long- term morbidity (Skalkidou A, et al., 2010).

Fetal Growth is also an important predictor of postnatal health, often based on the attained weight at birth. Birth weight is the standard measure of fetal growth because it is a sensible endpoint and data are greatly available by medical registers. Other measures of neonatal anthropometry such as length, head, abdominal circumference, etc. might provide additional information as well as longitudinal information about fetal parameters (ultrasounds), but they are rarely used in epidemiological studies because of their scarce availability. Different metrics based on birth weight have been used to identify suboptimal fetal growth including a reduction in birth weight (as a continuous variable), low birth weight (LBW), very low birth weight (VLBW), small for gestational age (SGA), intrauterine growth restriction (IUGR) and fetal growth restriction (FGR).

Low birth weight (LBW) is defined by the World Health Organization (WHO) as a birth weight less than 2500 grams, while very low birth weight is defined as a birth weight less than 1500 grams. As birth weight greatly depends of gestational duration, often both outcomes are combined to examine fetal growth, as is the case for small for gestational age.

A newborn is defined as small for gestational age (SGA) if its birth weight is lower than the 10th percentile of a suitable gestational age-specific weight reference. Therefore, identification of SGA births requires relevant reference curves.



EFL: Early fetal loss

Fig. 1. Overview of the main pregnancy-related outcomes covered

The term *intra-uterine growth restriction* supposes that the fetus was retarded in its growth by a pathological process during fetal life. However, there is a lack of a clinical definition for IUGR and many studies use the same statistical limits to identify SGA or IUGR infants. In other studies an infant is defined as IUGR if it is a full-term infant with a low birth weight.

SGA fails at distinguishing "constitutionally small" infants, according to anthropometric characteristics, to those who are "growth retarded," that is, smaller than what their parental characteristics, sex, gestational duration would predict.
A newborn is defined as *fetal-growth retarded* if he fails to achieve its genetic growth potential in utero. The classification is done by adjusting birth weight by gestational age, infant sex and maternal characteristics.

3. Results

As introduced above, during the last years different authors have reviewed the epidemiological evidences about the potential effects of air pollution exposure during pregnancy and reproductive outcomes. In the table 1 we summarized the pollutant and outcomes included in the main systematic reviews on these topic.

Review	Period of study	Pollutants included	Outcomes (and # of studies)						Total # of studies
			Stillbirth	Preterm birth	BW, LBW, VLBW	SGA, IUGR	Perinatal & Infant mortality	Others	
Glinianaia et al., 2004	1996-2001	TSP, PM_{10}	3	3	3	3	-	-	12
Maisonet et al., 2004	1996-2001	TSP, PM_{10}, $PM_{2.5}$, CO, SO_2, NO_2, O_3	-	5	9	3	-	-	12
Sram et al., 2005	1966-2001	TSP, PM_{10}, $PM_{2.5}$, CO, SO_2, NO_2, O_3, PAH, POM	2	4	9	4	7	-	23
Lacasaña et al., 2005	1994-2003	TSP, PM_{10}, $PM_{2.5}$, CO, SO_2, NO_2, NOx, O_3, PAH	2	10	17	3	8	Congenital malformation (#: 2)	31
Bosseti et al., 2010	1966-june 2010	TSP, PM_{10}, $PM_{2.5}$	-	13	17	4	-	-	30
Shah & Balkhair, 2011		TSP, PM_{10}, $PM_{2.5}$, CO, SO_2, NO_2, NO, O3, HAP, BETX	-	11	25	10	-	-	41

BW: birth weight; LBW: low birth weight (<2500 g), VLBW: very low birth weight (<1500 g)
SGA: small for gestational age, IUGR: intrauterine growth restriction
TSP: total suspended particulate; PM_{10}: particulate matter <10 μm; $PM_{2.5}$: particulate matter <2.5 μm, PAH: polycyclic aromatic hydrocarbon, POM: polycyclic organic matter; BTEX: benzene, toluene, ethyl-benzene, xylene

Table 1. Systematic reviews of the epidemiological studies assessing the relation between prenatal exposure to air pollution and reproductive outcomes

3.1 Infertility

Throughout the last decades the crude human birth rate (live births per 1000 population) declined, suggesting a potential decline in fecundity (the potential to conceive). Detection of environmental contaminants in human tissues, together with reports of a global decline in semen quality, promoted the hypothesis that environmental toxicants could be important causal agents of such decline (Foster et al., 2008).

Epidemiological studies demonstrated exposure to ambient levels of air pollutants, especially airborne particulate matter, has been linked in particular to DNA fragmentation (Selevan et al., 2000) (Evenson et al., 2005) and in general to abnormal sperm morphology and reduced sperm performance in men. (Somers 2011; Hammoud et al., 2010). Recent experimental animal data indicated that female fertility is also affected by air pollutants (Veras et al., 2010).

3.2 Fetal loss

A previous review of environmental toxicants and reproductive outcomes only suggested as related to fetal loss the exposure to dichlorodiphenyltrichloroethane and bisphenol-A (Stillerman et al., 2008). Apart from a proven adverse effect of second-hand smoking exposure (Peppone et al., 2009; George et al., 2006), the evidence of an impact of air pollution on this reproductive outcome remains scarce. Only exposure to airborne particulate matter has been related to fetal loss in a study performed in mice (Veras et al., 2009). The authors found the mean post-implantation loss rate increased by 70% among those exposed to particulate matter before and during pregnancy versus no exposed.

3.3 Prematurity

Besides prenatal growth (birth weight and growth restriction), prematurity is the outcome for which there exist more published articles. In their recent review, Bosetti et al (2010) identified 13 studies assessing the relationship between exposure to **particulate matter** and preterm birth. Most of them (n: 9) considered PM_{10} as the fraction of interest (Ritz et al., 2000; Sagiv et al., 2005; Wilhelm and Ritz 2005; Leem et al., 2006; Hansen et al., 2006; Kim et al., 2007; Jiang et al., 2007; Lee et al., 2008; Brauer et al., 2008). Four, generally more recent studies, included fine particulates ($PM_{2.5}$) (Wilhelm and Ritz, 2005; Huynh et al., 2006; Ritz et al., 2007; Brauer et al., 2008); and the oldest ones investigated the effects of total suspended particulates (TSP) (Xu et al., 1995; Bobak, 2000). Overall, 9 studies found significant associations between PM exposure during pregnancy and risk of preterm birth. Four out the 13 studies were time series in design, i.e. capturing effects related with short-term exposures. The rest had designs more appropriate for evaluating more chronic exposure: 8 registry-based cohorts and one case-control study. Where a significant relation was found estimates of the association for an increase of 10 $\mu g/m^3$ for PM_{10} or TSP in time series studies ranked from an increase in preterm risk of 1% (Xu et al., 1995) to 4.4% (Jiang et al., 2007). Among the studies assessing chronic exposure, significant estimates for a PM_{10} increase of 10 $\mu g/m^3$ were around 2-4 % (Ritz et al., 2000; Hansen et al., 2006; Leem et al 2006; Jiang et al., 2007), and of 1% in a case control study in California, USA (Huynh et al., 2006) for a $PM_{2.5}$ increase of 10 $\mu g/m^3$ in the last 2 weeks of pregnancy. In another study in California (Ritz et al., 2007), a 29% increase in risk of preterm birth for exposure to $PM_{2.5}$ above 21.36 $\mu g/m^3$ during the first trimester was found. Most of the studies examined the relation taking into account air pollution exposure by trimesters. First and third trimester exposures were those most frequently associated with the risk of preterm delivery. Also, in a

study in Taiwan using the extended Cox model with time-dependent PM_{10} exposures for each trimester during pregnancy (Suh et al., 2009), estimates for first and third trimester were slightly higher than those of the second trimester. A recent time series study in the city of Guangzhou (China) (Zhao et al., 2011) using the Generalized Additive Model (GAM) extended Poisson regression model and Principal Component Analysis described a relation between daily PM_{10} increases of 10 $\mu g/m^3$ and significant increases in preterm risk less than 1%, suggesting that, at least for short-term exposures, the likely impact of PM on preterm risk is small.

Besides particulate matter, **nitrogen oxides (**NOx) have also been frequently assessed as the exposure of interest related with preterm risk. In their review up to 2003, Lacasaña et al. (2005) identified 8 articles examining the relation between pregnancy exposures to NO_X and risk of preterm delivery, with nitrogen dioxide (NO_2) being the most studied pollutant. However, the overall results were inconsistent. In the past six years, nine more studies have been published analyzing the relationship between NO_2 exposure during pregnancy and the risk of preterm birth (Hansen et al., 2006; Leem et al., 2006; Jalaludin et al., 2007; Ritz et al., 2007; Brauer et al., 2008; Darrow et al., 2009; Llop et al., 2010; Gehring et al., 2011; Zhao et al., 2011). Three of the studies found no significant association (Hansen et al., 2006; Brauer et al., 2008; Gehring et al., 2011). Jalaludin et al. (2007) observed an unexplained protective effect for NO_2 exposure during the first month and first trimester of pregnancy, while five other studies found a significant relationship between preterm births and NO_2 exposure at both the beginning and/or the end of pregnancy (Leem et al., 2006; Ritz et al., 2007; Darrow et al., 2009; Llop et al., 2010; Zhao et al., 2011). Another recent study conducted in Los Angeles (USA) analyzed the relationship between NOx levels and preterm birth (Wu et al., 2009) and found this association was significant when exposure occurred throughout the pregnancy, even at relatively low air pollution levels. On the contrary, the Brauer et al. (2008) study conducted in Vancouver found a significant relation between NO exposure obtained with the inverse of the distance method and preterm birth, OR: 1.26 (95% Confidence interval, 95% CI: 1.08–1.47). Llop et al. (2010) assessed the concentration-response function. The results suggest a threshold level around 46 $\mu g/m^3$ of NO_2 concentration, after which the risk of preterm birth increases.

Following another recent review (Shah & Balkhair, 2011), 5 studies fulfilling methodological criteria have assessed the relation between **sulfur dioxide** (**SO_2)** exposure during pregnancy and preterm delivery (Xu et al., 1995; Landgren et al., 1996; Bobak 2000; Liu et al., 2003; Sagiv et al., 2005). All but one (Landgren et al., 1996) reported significant associations with preterm delivery. Three of the studies describing significant associations considered the relationship linear, and reported a increased risk for preterm birth ranging from 3.5% (Bobak et al., 2001; Sagiv et al., 2005) in the Czech Republic and Pennsylvania to 6.4% in Vancouver (Liu et al., 2003) for a 10 $\mu g/m^3$ increase in SO_2 levels. The Xu et al. study (1995) in Beijing, China examined a log linear relationship and found a 21% increase in the risk of preterm delivery for each ln $\mu g/m^3$ increase in SO_2 levels. In general, associations were higher for exposures at late pregnancy, i.e. third trimester or last weeks before birth. On the contrary, in a study in Croatia in the vicinity of a coal power plant, Mohorovic (2004) found the first two months of pregnancy as the critical time for preterm delivery in relation with SO_2 exposure.

Carbon monoxide (CO) exposure has also been an object of analysis in relation with preterm birth. Ritz et al (2000; 2007) and Wilhelm and Ritz (2005) have focused on this pollutant in their birth certificate based study in southern California. They first reported

carbon monoxide and PM associations for preterm birth in the South Coast Air Basin using data from 1989 to 1993 (Ritz et al., 2000). The study continued from 1994 to 2000 (Wilhelm & Ritz, 2005), and reported an 8-24% increase in risk of preterm birth per 1-ppm (1.145 mg/m^3) increase in CO during the first trimester among women who lived close to stations measuring carbon monoxide. Depending on the distance to the monitoring station, they also observed a 9-30% increase in the risk of preterm birth when average CO concentrations were high (≥1.9 ppm) 6 weeks before birth. Finally, they conducted a case-control survey nested within their birth cohort and collected detailed risk factor information to assess the extent to which residual confounding and exposure misclassification may impact air pollution effect estimates (Ritz et al., 2007). For the first trimester, the odds of preterm birth consistently increased with increasing CO exposures, regardless of the type of data (cohort/sample) or covariate adjustment. . Women exposed to carbon monoxide above 0.91 ppm during the last 6 weeks of pregnancy experienced increased odds of preterm birth. The results did not change substantially after further adjustment, except for time-activity patterns, which strengthened the observed associations. They considered CO may be a better marker of vehicle exhaust toxins than $PM_{2.5}$, since the latter includes both particles directly emitted in vehicular exhaust and those created secondarily through atmospheric reactions (Ritz et al., 2007).

A few studies included other specific air pollutants. Llop et al (2010) assessed the relation between prenatal exposure to **benzene**, as a marker for both traffic and industrial sources. The researchers found an association with preterm risk at benzene levels above 2.7 µg/m^3 throughout the entire pregnancy. The authors acknowledged, however, this was an isolated finding with no precedent in the literature, and therefore, it should be regarded with caution.

Instead of examining specific air pollutants, researchers have investigated the role of other indicators of **traffic or industrial air pollution**. Wilhelm & Ritz (2003) used a distance-weighted traffic density measure to take into account residential proximity to and level of traffic on roadways surrounding homes. They obtained a clear exposure-response pattern with preterm birth, with a RR of 1.08 (95% CI: 1.01-1.15) for the highest exposure. In Taiwan, Yang et al. (2003) investigated the association between traffic-related air pollution and preterm deliveries in a zone along the Zhong-Shan Freeway in Taiwan. The prevalence of deliveries of preterm birth infants was significantly higher among mothers who lived within 500 m of the freeway than among mothers who resided 500-1,500 m from the freeway. The adjusted odds ratio was 1.30 (95% CI:1.03-1.65) for delivery of preterm infants born to mothers who lived within 500 m of the freeway. Brauer et al. (2008) used a geostatistical method to assess exposure to traffic air pollution. In this study, however, no associations were observed between the simple road proximity measures and preterm birth < 37 weeks, and there were no cases of births < 30 weeks that were within 50 m of a highway. Similarly, no association was found when traffic proximity was assessed in the Generation R study in Holland (van de Hooven et al., 2009). In a recent study in Shizuoka, Japan, Yorifuji et al. (2011) classified 14,226 liveborn single births from 1997 to 2008, according to proximity to major roads. They found positive associations between proximity to major roads and preterm birth at all considered gestational ages. Living within 200 m increased the risk of birth before 37 weeks by 1.5 times (95% CI : 1.2-1.8), birth before 32 weeks by 1.6 times (1.1-2.4), and birth before 28 weeks by 1.8 times (1.0-3.2). Proximity specifically increased the risk of preterm births with preterm premature rupture of the membranes and with pregnancy hypertension.

Lastly, regarding industrial pollution some studies in Taiwan revealed associations between preterm birth and maternal residence within 3km of a major oil refinery (OR: 1.41, 95% CI 1.08-1.82) (Lin et al., 2001), near three oil refineries (OR: 1.14, 95% CI=1.01-1.28) (Yang et al 2004), within 2 km of a cement plant (OR: 1.30, 95% CI 1.09–1.54) (Yang et al., 2003), within 2 km of an industrial complex, including petrochemical, petroleum, steel, and shipbuilding industries (OR: 1.11, 95% CI 1.02-1.21) (Tsai et al., 2003) or within 3 km of coal-based electricity-generating stations (OR: 1.14, 95% CI 1.01-1.30) (Tsai et al., 2004).

3.4 Fetal growth (crude neonatal anthropometry (birth weight, LBW), GA adjusted neonatal anthropometry (SGA, IUGR), ultrasounds

Fetal growth deficit, measured in different ways and with different indicators, is with no doubt the most studied reproductive outcome in relation to air pollution exposure during pregnancy. Because of its availability from medical records, weight at birth and low birth weight (LBW, i.e. weight at birth < 2500 g) have been the main reproductive outcomes assessed in the first studies examining the impact of air pollution on fetal development. Birth weight may be considered as a fetal growth measure if the analyses are adjusted by gestational age or if LBW studies are restricted to term newborn. Also, a considerable number of studies have also evaluated the impact of air pollution exposure during pregnancy on SGA or IUGR. Particulate matter (either as TSP, PM_{10} or as $PM_{2.5}$) and NO_2 have been the pollutants most frequently examined in studies on air pollution and birth outcomes. Two of the six reviews mentioned previously have included only particulate matter as exposure (Glinianaia et al., 2004, Bosetti et al., 2010).

The use of passive sensors has allowed for a better spatial resolution when assessing individual exposure to air pollution (Raaschou-Nielsen et al., 2000; Gauderman et al., 2005). For these reasons and because studies involving more particles have been subjected to frequent literature reviews, this chapter addresses more detailed studies evaluating the relationship between **NO_2** exposure and birth weight, as well as weight in grams including low birth weight, or small for gestational age (SGA).

In Table 2, we present a summary of the 17 articles studying the effect of NO_2 exposure on birth weight (Lacasana et al., 2005). The number is itself an indication of the growing interest in this issue. Ten out the 17 studies assessed the relationship of NO_2 with birth weight, also 10 examined the relationship with LBW, and 9 the relationship with SGA. Among the 10 studies analyzing birth weight, a significant association was found in four studies (Gouveia et al., 2004; Mannes et al; 2005; Bell et al., 2007; and Morello-Frosch et al., 2010). In two other studies, an association was clearer when some sub-analysis was made trying to improve exposure assessment by restricting either spatially, i.e. women living <2km away from a monitoring station in the French study in Nancy and Poitiers (Lepeule et al., 2010), or taking into account time activity, i.e. women spending <2hr/day in non-residential outdoor in a cohort of the Spanish INMA study (Aguilera et al., 2009). Of the 10 studies that considered LBW, only 4 found an association with NO_2 (Lee et al., 2003; Bell et al., 2007; Brauer et al., 2008, Morello-Frosch et al., 2010). On the other hand, six of the nine articles (Liu et al., 2003; Salam et al., 2005; Mannes et al., 2005; Liu et al., 2007; Brauer et al., 2008; Ballester et al., 2010) studying SGA found an association with NO_2. This discrepancy may be due to the number of cases of SGA is greater than that of LBW term. Moreover, the use of SGA, calculated for each week of gestation, enables the effect of gestational length to be more effectively controlled than LBW, which is done by simply selecting births that take place after a certain period of gestation (between weeks 37- 44 weeks). On the other hand, it

should be noted that all these studies found an association between LBW and exposure to other pollutants, mainly particulate matter, CO and SO_2.

Regarding studies focusing on **PM exposure**, the paper by Glinianaia et al. (2004) was the first work systematically reviewing the evidence on the association between air pollution and fetal health outcomes. Twelve articles published between 1996 and 2001 were identified that included PM as the exposure of interest. Limitations in design and lack of confounding factors were defined. Authors concluded that currently available evidence was compatible with either a small adverse effect of particulate air pollution on fetal growth or with no effect. In their recently published review, Bosetti et al. (2010) identified 17 articles including information on PM exposure and LBW or very low birth weight (i.e. weight at birth < 1500 g). In most of the reviewed studies (14/17), LBW was the outcome studied; 2 studies considered VLBW infants, and another one considered infants with a birth weight between 2,500 and 3,000 g (Slama et al., 2007). With reference to the pollutant investigated (Bosetti et al., 2010), 5 studies (the older ones) considered exposure to TSP, 12 exposure to PM_{10} , and only 3 considered exposure to $PM_{2.5}$ (Bell et al., 2007; Brauer et al., 2008; Slama et al., 2007). Besides limitations described in the Glinianaia et al. (2004) article, Bosetti et al. (2010) underscored poor exposure assessment and inconsistent reporting of findings, especially in relation to time windows of exposure-effect. The authors concluded in the same way of Glinianaia 6 years before (2004): the excess risk associated with exposure to particulates during pregnancy, if any, is small and it is unclear if it is causal or due to misclassification or residual confounding (Bosetti et al., 2010).

For **CO** exposure, in their recent review, Shah & Balkhair (2011) identified 13 studies reporting results for LBW and four SGA. Among them only three reported an increased risk of LBW, two associated with exposures during the third trimester (Maisonet et al., 2001; Ritz & Yu, 1999) and the other at first and second trimesters (Lee et al., 2003). Only one of the studies assessing SGA reported a significant higher risk (Liu et al., 2003).

In the same review (Shah & Balkhair 2011), 14 studies were summarized describing results from studies including **SO_2** and LBW, but only one examined the impact of SO_2 on SGA. Five studies reported increased odds of LBW births following SO_2 exposure and one reported significant association with Very LBW (Rogers et al., 2000).

Other pollutants such ozone (O_3) and benzene have also been included in studies evaluating the effects of air pollution in fetal growth According the review by Shah & Balkhair (2011), no significant effect of **O_3** on LBW or SGA was reported. Regarding **benzene** a significant association was found in the Spanish INMA cohort in Sabadell, especially among women spending more time in their residence (Aguilera et al., 2009). However, a recent combined analysis of four cohorts in the INMA study, including Sabadell, Valencia, Asturias and Gipuzkoa cohorts (Estarlich et al., 2011) confirmed the association between NO_2 exposure and reductions in both length and weight at birth but not as a result of benzene exposure.

To try to overcome the difficulties of synthesizing previous findings due to differences in study design, several multicenter international initiatives have been launched recently. One of them, previously cited, ICAPPO has recently published its first results (Parker et al., 2011). Another large multicenter international study is the European Study of Cohorts for Air Pollution Effects (ESCAPE) (http://www.escapeproject.eu), is currently working to develop uniform criteria for assessing air pollution effects on reproductive outcomes.. ESCAPE will include information on more than 70,000 mother-child pairs and air-pollution. The results from this project can provide strong evidence on existence of a risk in fetal growth retardation related with exposure to air pollution during pregnancy.

Study	Location (time period)	Design N° of births	Outcome(s)	Exposure				Res
				Assessment: -data source; -individual assignment	Mean (SD) NO_2 levels, in µg/m³	Pregnancy periods examined	NO_2 increase assessed	β (95% C OR (9
Lepeule et al., 2010	Poitiers and Nancy, France (2003-2006)	Cohort of pregnant women 776	Birth weight	2 methods: 1. AQMS: - 3 and 6 monitoring stations for each city, respectively - nearest station 2. TAG.:- 61, and 89 passive samplers in 9 and 10 campaigns for each city, respectively -residential prediction using LUR and temporal adjustment	AQMS: Poitiers: 24.9 Nancy: 31.2 TAG: Poitiers: 20.3 Nancy: 31.2	Trimester; Entire pregnancy	10 µg/m³ (5.3 ppb) increase among women living <1 ,<3, <5km from a monitoring station	-β for birth weig for women livin from a monitori -AQMS: –37 (–7 -TAG: –51 (–12
Gehring et al., 2011	Amsterdam, Holland (2003-2004)	Cohort of pregnant women 7610	Birth weight among born ≥37 <43 weeks SGA	-13 4-week measurements using passive samplers at 62 sites, and GIS; -residential prediction using LUR and-temporal adjustment using background monitors	P50 38.7 (IQR:35.3; 43.3)	Trimester; Entire pregnancy	Quintiles	No association b and birth weigh
Morello-Frosch et al., 2010	California, USA (1996-2006)	Birth register-based study 3,545,177	Birth weight LBW among born between 37-44 weeks	-residential estimation (at ZIP code) using timely geocoded levels by air quality networks	45.5 (17.9)	Trimester; Entire pregnancy	18.8 µg/m³ (10 ppb) increase among women living <3, <5, <10km from a monitoring station	-β for birth weig Entire pregnanc <3 km: -8.3 (-9.6 <5 km: -9.7 (-10. <10 km: -9.0 (-9. 1st trimester, sm associations (~-3 2nd trimester: no association 3rd trimester <3 km: -8.1 (-10. <5 km: -7.9 (-9.2 <10 km: -7.0 (-7. -OR for LBW Entire pregnanc <3 km: 1.03 (1.01 <5 km: 1.04 (1.03 <10 km: 1.03 (1.0

Study	Location (time period)	Design N° of births	Outcome(s)	Exposure				Res
				Assessment: -data source; -individual assignment	Mean (SD) NO_2 levels, in µg/m³	Pregnancy periods examined	NO_2 increase assessed	β (95% C OR (9
Madsen et al., 2010	Oslo, Norway (1999-2002)	Birth register-based study 25,229	Birth weight LBW excluded <37 wg SGA excluded <37 wg	-dispersion model based on GIS and background air pollution levels -monitoring station	29.8 (11.2) Q1 Q4 35.6 (4.2)	Entire pregnancy	Q4 (>38.0) vs Q1 (<20.3) µg/m³	No association b and birth weigh among all popu Higher effect an multiparious mo to 12.7)
Ballester et al., 2010	Valencia; Spain (2004-2006)	Cohort of pregnant women 785	Birth weight SGA	-4 campaigns using passive samplers at 93 sites, monitoring network, and GIS; -residential prediction using Kriging + LUR and temporal adjustment	36.9 (11.1)	Trimester; Entire pregnancy	10 µg/m³ (5.3 ppb)	-β for birth weig 1st trimester: -1 Entire pregnanc 13.8) -OR for SGA 2nd trimester: 1 Entire pregnanc 1.74)
Aguilera et al., 2009	Sabadell, Spain (2004-2006)	Cohort of pregnant women 570	Birth weight	-3 campaigns using passive samplers at 57 sites, monitoring network, and GIS; -residential prediction using LUR	32.17 (8.89)	Trimester; Entire pregnancy	IQR: 12.0 µg/m³	No association b and birth weigh population. Only significant women spendin non-residential β for birth weig -74.7 (-140.4 to -
Brauer et al., 2008 [34]	Vancouver, Canada (1999-2002)	Birth register-based study 70,249	SGA LBW excluded <37 wg	-Monitoring network and 2 campaigns using passive samplers at 116 sites; -nearest and inverse-distance weighting (IDW) area monitors, LUR temporally adjusted	32.5 (range:15.3; 53.6)	Month; Entire pregnancy	10 µg/m³ (5.3 ppb)	Entire pregnanc OR for SGA :1.1 OR for LBW:1.1
Slama et al., 2007 [12]	Munich, Germany (1998,1999)	Cohort of pregnant women 1,016	BW<3000 g among births>2500g and >37 <44 weeks	- 2 campaigns with passive samplers at 40 sites, and GIS; -residential prediction using LUR.	35.8 (P5th:28.3; P95th: 42.5)	Trimester; Entire pregnancy	10 µg/m³ (5.3 ppb) , Quartiles	PR 1st trimester: 0. 2nd trimester: 1. 3rd trimester: 1 Entire pregnanc 1.68) No significant a quartiles

Study	Location (time period)	Design N° of births	Outcome(s)	Exposure				Res β (95% C OR (9
				Assessment: -data source; -individual assignment	Mean (SD) NO_2 levels, in µg/m³	Pregnancy periods examined	NO_2 increase assessed	
Bell et al., 2007 [10]	Massachusetts and Connecticut , USA (1999-2002)	Birth register-based study 358,504	Birth weight LBW excluded <37 wg	Average county-level concentration from monitoring networks	32.7 (9.4)	Trimester; Entire pregnancy	9.0 µg/m³ (4.8 ppb)	β for birth weig 1st trimester: n Entire pregnanc 7.0) OR for LBW Entire pregnanc 1.051) Associations for were less consis
Hansen et al., 2007 [35]	Brisbane; Australia (2000-2003)	Birth register-based study 21,432	SGA	-4 monitoring stations; -average of measurements	16.5 (7.7)	Trimester ; Month	IQR: 11.1 µg/m³ (5.9 ppb) Quartiles	No association b and SGA
Liu et al., 2007 [32]	Calgary, Edmonton, and Montreal; Canada (1985-2000)	Birth register-based study 386,202	SGA among born between wg37-42	-2, 4, 8 monitoring stations in each city, respectively; -mean of measurements in the residential area	45.1 (IQR:32.9; 55.5)	Trimester ; Month	37.6 µg/m³ (20 ppb)	OR for Trimeste 1st : 1.16 (1.09-1. 2nd: 1.14 (1.06- 1 3rd : 1.16 (1.09- 1
Mannes et al., 2005 [31]	Sydney Australia(1998-2000)	Birth register-based study 138,056	Birth weight SGA	Average of the monitoring stations in the city	43.6 (13.9)	Trimester; one month before birth	1.88 µg/m³ (1 ppb) increase among women living <5km from a monitoring station	β for birth weig 1st trimester: -26 2nd trimester: -3 24.3) 3rd trimester: -3 22.5) Month before pr 27.8 to -11.5) OR for SGA 1st trimester: 1. 2nd trimester: 1. 3rd trimester: 1. Month before pr (1.00-1.14)

Table 2. Results from studies assessing NO_2 effect on birth weight published in the period 2003- 2010

Study	Location (time period)	Design N° of births	Outcome(s)	Exposure				R β (95% OR
				Assessment: -data source; -individual assignment	Mean (SD) NO_2 levels, in µg/m³	Pregnancy periods examined	NO_2 increase assessed	
Salam et al., 2005 [30]	California, USA (1975-1987)	Birth register-based study 3,901	Birth weight SGA <P15 born between wg 37-44 LBW born between wg 37-44	Spatial interpolation from the 3 nearest monitoring stations (in <50 km) When there are available stations in <5 km the nearest station data are assigned	67.9 (29.0)	Trimester Entire pregnancy	47 µg/m³ (25 ppb)	β for birth we Entire pregna 20.4) OR for SGA 1stTrimester : Entire pregna No associatio trimesters or I
Wilhelm and Ritz, 2005 [29]	Los Angeles County, CA, USA (1994-2000)	Birth register-based study 106,483	LBW at term Born between 90-320 days; excluded weight <500g or >5000g	15 monitoring stations for the county-level analysis 11 stations for the address-level analysis	73.5 (range:38.7-116.6	First month Trimester 6 weeks before birth Entire pregnancy	nr	Results from c models for NO provided. No associatio and LBW afte and/or PM10.
Gouveia et al., 2004 [28]	Sao Paulo, Brasil (1997)	Birth register-based study 179,460	Birth weight LBW at term; excluded <37wg or weight <1000g >5500g	Mean of the hourly maximum from between 4-12 NO_2 monitoring stations in the city	117.9 (51.2)	Trimester	10 µg/m³ (5.3 ppb)	β for birth we 1st trimester: No associatio and LBW
Lee et al.,2003 [27]	Seul, Korea (1996-1998)	Birth register-based study 388,105	LBW born between wg37-44	Daily mean of the 20 monitoring stations in the city	61.1 (19.2)	Month Trimester Entire pregnancy	IQR: 27.6 µg/m³ (14.7 ppb)	OR for LBW 1st trimester: 2nd trimester: 3rd trimester Entire pregna 1.08)
Liu et al., 2003 [26]	Vancouver (Canada) (1986-1998)	Birth register-based study 229,085	SGA born between wg 37-44 LBW excluded <500g or <22wg	Mean of the monitoring stations in the residential area of each mother	36.5(P5th:21.6; P95th: 60.0)	First Month Last month Trimester	18.8 µg/m³ (10 ppb)	OR for SGA First month: 1 Last month: 0. 1st trimester: 2nd trimester: 3rd trimester OR for LBW First month: 0 Last month: 0.

Table abbreviations: β (95% CI): regression coefficient for birth weight (in grams) and 95% confidence interval; OR: odds ratio; PR: prevalence ratio; SGA: small for gestational age: <10th percentile from population charts unless otherwise indicated in the table; LBW: birth weight <2500gr unless otherwise indicated in the table. LBW at term: LBW among those born ≥37 weeks of gestation; nr: not reported; wg: weeks of gestation; BSP: Black smoke particles; ppb: parts per billion. P5th: Percentile 5th. P95th: Percentile 95th ; IQR: Interquartile range; Q: quartile (i.e. Q1: first quartile); BTEX: benzene, toluene, ethylbenzene, xylene

[a] Covariates considered: 1: Gestational age 2: Maternal age; 3: Maternal pre-pregnancy weight; 4: Gestational weight gain; 5: Maternal height; 6: Maternal body mass index; 7: Parity; 8: Maternal education; 9: Maternal working status; 10: Maternal socio economic status; 11: Mother's country of origin; 12:Living with partner; 13: Maternal smoking during pregnancy; 14: Maternal environmental Tobacco Exposure at home; 15: Maternal environmental general tobacco exposure; 16: Maternal alcohol consumption; 17: Paternal height; 18: Infant sex; 19: Season; 20: Country of origin ; 21: Year of birth; 22: Income; 23: Prenatal care; 24: Type of delivery; 25: Birth order; 26: Weather; 27: Mother's ethnicity; 28: Marital status; 29: Previous abortions; 30: Location of residence; 31: Diabetes; 32:Time since last delivery; 33: Previous preterm; 34: Paternal education; 35: Neighbourhood SES measures; 36: Work stress during pregnancy; 37:Depression during pregnancy

Few studies have examined the relation between air pollution exposure during pregnancy and other anthropometric indicators at birth such as head circumference (HC). Studies in two cohorts of pregnant women have assessed the relationship between prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAH) and fetal growth (Choi et al., 2006). One of these cohorts was from Cracow (Poland) and the other was made up of predominantly African-American and Dominican women from New York City (US). PAH exposure was related to a reduction in birth weight, length and HC among babies from Cracow, where exposure levels were higher. Among the participants from New York, results indicated a greater effect on African-American women, with higher reductions in both birth weight and HC, showing some kind of susceptibility to PAH exposure. In another study Hansen et al. (2007) assessed birth length and HC among 26,617 term births in Brisbane, Australia. Exposures to the four pollutants studied (i.e. PM_{10}, black smoke, ozone and NO_2) were not significantly associated with a reduction in HC. However an interquartile range increase in NO_2, but not in other pollutants, during the third trimester was associated with a reduction in length: -0.15 cm (95%CI -0.25 to -0.05) for a 10 μg/m^3 increase in NO_2. In the French Eden cohort (Slama et al., 2006) a reduction of -0.31 cm (95%CI -0.73 to 0.10) in HC at birth was found when comparing NO_2 exposure in the highest tertile (>31.4 μg/m^3) to that in the lowest tertile. In a study in the Spanish INMA cohort in Valencia (Ballester et al., 2010) a reduction in birth length of -0.07 cm (95%CI -0.15 to 0.02) was associated with a 10 μg/m^3 increase in NO_2 during the first trimester. When exposure above 40 μg/m^3 was compared with exposure equal to or less than 40 μg/m^3, a reduction of -0.27 cm (95%CI -0.51 to -0.03) in birth length was found. In the combined analysis of four cohorts within the INMA study a (Estarlich et al., 2011) an increase of 10 μg/m^3 in NO_2 exposure during pregnancy was associated with a change in birth length of -0.09 cm (95% CI: -0.18 to -0.01). For the subset of women who spent ≥15 hr/day at home, the change in birth length was twice that.

Finally, regarding studies assessing fetal growth using ultrasound data instead of neonatal outcomes, we found only three studies. The first one was an Australian study that examined 15,623 scans at mid pregnancy and assigned air pollution data to each woman's residential postal code from the closest monitoring station (Hansen et al., 2008). The authors reported a negative impact of several air pollutants, but no impact of NO_2. They indicated as a possible

cause for inconsistent results the increase in the exposure measurement error with increasing distance from a monitor. The second study (Slama et al., 2009) examined three scans for 271 women at second and third trimesters and a personal assessment of maternal benzene exposure in a French pregnancy cohort. The authors found this exposure associated with a reduction of head dimensions during the second trimester. In the third one, Aguilera et al (2010) conducted a study with 1692 ultrasounds for 562 women within the Sabadell INMA-cohort. An adverse effect of NO_2 exposure on fetal growth measures during the second and third trimester was found, after restricting analyses to women with less mobility.

3.5 Congenital malformations

Among the environmental factors related to the risk of congenital anomalies, air pollution is among the most studied (Ritz 2010). Thus, studies conducted in California (Ritz et al., 2002) and Texas (Gilboa et al., 2005) showed a positive association between specific cardiac defects and various environmental pollutants measured at stations near the residence of mothers between weeks 3 and 8 of gestation, but the evidence was insufficient for other AC. However, Hwang et al (2008) identified associations between oral abnormalities and exposure to ozone during the first two months of pregnancy, but not with other air pollutants. In Atlanta, Strickland et al. (2009) studied exposure to PM_{10} during 3-7 weeks of gestation and found a small increased risk for one of 12 specific cardiac abnormalities. Hansen et al. (2009) in Brisbane, showed an association with exposure to ozone and SO_2 during 3-8 weeks of gestation and two different subgroups of heart defects (pulmonary artery and aorta) and oral defects. In the north of England, Rankin et al. (2009) described a weak positive association between airborne particles measured as black smoke and nervous system abnormalities, and a negative association between exposure to black smoke and SO_2 during the first trimester of pregnancy and cardiac abnormalities. Also in England, Dummer et al. (2003) found an increased risk of lethal congenital anomalies (spina bifida and heart defects) in relation to living near incinerators, and an increased risk of fetal death and anencephaly in relation to living near incinerators and crematoriums. Exposure to air pollutants from combustion (SO_2, NO_2 and PM_{10}) has been associated with tetralogy of Fallot (Dolk et al., 2010).

A systematic review and meta-analysis of epidemiological studies on ambient air pollution and congenital anomalies was recently published (Vrijheid et al., 2011). The authors conducted meta-analyses if at least four studies published risk estimates for the same pollutant and anomaly group. Summary risk estimates were calculated for risk at high versus low exposure level in each study, and risk per unit increase in continuous pollutant concentration.

An analysis of the data indicated that each individual study reported statistically significant increased risks for some combinations of air pollutants and congenital anomalies, among many combinations tested. In meta-analyses, NO_2 and SO_2 exposures were related to increased risk of coarctation of the aorta (OR per 10 ppb NO_2=1.17, 95%CI: 1.00-1.36; OR per 1 ppb SO_2=1.07, 95%CI: 1.01- 1.13) and tetralogy of Fallot (OR per 10ppb NO_2=1.20, 95%CI :1.02-1.42; OR per 1 ppb SO_2=1.03, 95%CI: 1.01-1.05), and PM_{10} exposure to an increased risk of atrial septal defects (OR per 10 $\mu g/m^3$=1.14, 95%CI: 1.01-1.28). Meta-analyses found no statistically significant increase in risk of other cardiac anomalies or oral clefts. The authors conclude that they found some evidence for an effect of ambient air pollutants on congenital

cardiac anomaly risk. Similar to reviews on other reproductive outcomes, the authors suggest that improvements in the areas of exposure assessment, outcome harmonization, assessment of other congenital anomalies, and mechanistic knowledge are needed to advance this field.

4. Discussion and conclusions

4.1 General overview

One general conclusion of such studies was that although there is evidence prenatal exposure to air pollutants has a detrimental effect on fetal development (Sram et al., 2005) and infant mortality (Lacasana et al., 2005), results are less consistent for other outcomes. Specifically, in studies that have examined the relationship between exposure to pollutants and preterm birth or congenital anomalies, the evidence is insufficient to suggest causality (Hackley et al., 2007) (Vrijheid et al., 2010). Even for findings related with fetal development, recent reviews point out substantial heterogeneity in the results, making it difficult to draw robust conclusions (Shah & Balkhair, 2011). In any case, associations are of small magnitude.
Among the issues that have been identified as crucial in comparing and interpreting the results on prenatal air pollution exposure and fetal development, the following have been highlighted (Slama et al., 2008; Ritz & Wilhelm, 2008; Woodruff et al., 2009; Shah & Balkhair, 2011): study design, exposure assessment (time activity and critical windows of exposure) and outcomes definition.

4.2 Biological mechanisms

Numerous biologic pathways have been identified whereby particulate air pollutants might impact the placenta and fetus. Kannan et al. (2006) performed a robust study on plausible fisiopathological mechanisms by which exposure to particulate matter may lead to adverse perinatal outcomes. They identified five mechanistic pathways including a) oxidative stress; b) pulmonary and placental inflammation; c) blood coagulation; d) alteration of endothelial function; and e) hemodynamic responses to particulate exposure. As Ritz & Wilhelm given attention (2008), these pathways may not act independently. For example, an increase in maternal blood pressure and an impaired trophoblast invasion of the spiral arteries may induce uteroplacental hypoperfusion and a state of relative hypoxia surrounding the trophoblast. Some experimental studies have added evidence, as in the study by Veras et al. (2009) where the researchers exposed female mice during pre-gestational and gestational periods to filtered or non-filtered air in exposure chambers in a garden near high density traffic. Then placentas were collected from near-term pregnancies and prepared for microscopical examination and alterations on placental functional morphology were found in placentas from those exposed to non-filtered air. Besides that, fetal weight declined in exposed group.
Polycyclic aromatic hydrocarbons (PAH), an important component of fine particulates from combustion sources, have been proposed as having a role in adverse reproductive outcomes. Experimental evidence showed that prenatal exposure of rats to maternal inhalation of benzo(a)pyrene (a PAH known for its potential toxicity) significantly compromised fetal survival rate and birth weight (Archibong et al., 2002). PAH exposure effects on fetal growth have been described in epidemiological studies in humans (Choi et al., 2006). Induction of apoptosis after DNA damage from PAH, endocrine disruption, and

binding to the aryl hydrocarbon receptor for placental growth factors, resulting in decreased exchange of oxygen and nutrients have been proposed as the mechanisms for PAH toxicity (Choi et al., 2006; Veras et al 2010; Dejmek et al., 2000). On the other hand, adult male exposure to inhaled PAH has also been found to affect fertility in male rates (Ramesh et al., 2008).

On the other hand, NO_2 is a potent oxidant and increased lipid peroxidation in the maternal and/or fetal compartment has been found in preterm birth (Moison et al., 1993). Tabacova et al. (1997) investigated the relationship between exposure to nitrogen-oxidizing species and pregnancy complications in an area in Bulgaria highly polluted by oxidized nitrogen compounds. Methemoglobin, a biomarker of individual exposure, was determined, and glutathione balance and lipid peroxide levels were measures of oxidant/antioxidant status. A high percentage of women suffered from pregnancy complications. The most common ones were anemia (67%), threatened abortion/premature labor (33%), and signs of preeclampsia (23%). Methemoglobin was significantly elevated in all three conditions, compared with normal pregnancies. Reduced total glutathione, an indicator of maternal antioxidant reserves, decreased, whereas cell-damaging lipid peroxide levels increased. Mohoroviz found similar results for methemoglobin in a polluted area of Croatia (Mohorovic, 2004). These results suggest that maternal exposure to environmental oxidants can increase the risk of pregnancy complications through stimulation of the formation methemoglobin, which may lead to hypoxia and hypoxemia in pregnant women and has an important influence on maternal health as well as placental and fetal development. The study in Croatia also described the impact of early exposures (first two months), as this is the time of greatest susceptibility in human gestation. It remains unclear if NO_2 is just a marker of air pollution from traffic or other combustions (i.e. PM, PAH or volatile organic compounds VOC), or it is a pollutant playing an important role on .

Another studied pollutant, carbon monoxide (CO) is known to induce fetal hypoxia by forming carboxyhemoglobin at the expense of oxyhemoglobin, thus resulting in an increased risk of fetal underdevelopment and neonatal mortality (Veras et al., 2010). These effects, however, have been described in relation to high CO concentrations related with tobacco exposure, some times higher than those present in ambient air. This fact raises the issue of whether CO may be reflective of the action of other toxins as PAH, metals or VOC (Ritz & Wilhelm, 2008)

Finally, the role of genetic polymorphisms, mainly as effect modifiers, on the relation between maternal air pollution exposure and reproductive outcomes should be considered. Some preliminary studies have reported how some genotypes as GSTM1 and CYP1A1*2A modified the effect of environmental exposure on birth weight and prematurity (Sram et al., 2006).

4.3 Public health implications

Air pollution is still an important public health problem. Exposure to elevated levels of air pollution can cause a variety of adverse health outcomes, including reproductive outcomes, yet being respiratory and cardiovascular diseases the two groups of causes where higher burden is borne. Air quality in developed countries has been generally improved over the last three decades. However, many recent epidemiological studies have consistently shown positive associations between low-level exposure to air pollution and adverse health outcomes. Thus, adverse health effects of air pollution, even at relatively low levels, remain a public concern and strategies to improve air quality around the world are being defined (EU 2005).

Fetuses are very susceptible to environmental exposures and disruption of their development may have an impact on child and adult health. Exposure to ambient air pollution is ubiquitous and even if increased risks of adverse reproductive outcomes are small, they can have a big impact measured as number of attributable cases at the population level (Slama et al., 2008). Two examples can illustrate this. One cost-benefit analysis of air pollution regulations in the USA (Wong et al., 2004), examined the child-specific health impacts derived from the U.S. Clean Air Act (CAA). It was estimated that from 1990-2010, CAA regulations would prevent 10,000 fewer low birth weight infants, which represented an estimated savings of 230 million U.S. dollars in health care costs. A recent health impact assessment in Korea (Seo et al., 2010) estimated that population-attributable risk of low birthweight related to PM_{10} pollution ranged between 5% and 19% in seven Korean cities, indicating that a large proportion of LBW could be prevented if air pollution was reduced.

Fetal and child health are a clearly identifiable topic adding argues to need to reinforce international, national and local efforts to improve air quality around the world, as well as providing health professional and the population, especially pregnant women indications and recommendations to prevent hazardous exposures during pregnancy

4.4 Next steps: future research

Fairly all the reviews and methodological papers on this topic published recently agree that current evidence suggests that air pollution may play some role in adverse pregnancy outcomes (Slama et al., 2008; Ritz & Wilhellm, 2008; Woodroof et al., 2009). Also, it is widely shared that owing the importance on the study and prevention of potential environmental insults during pregnancy this is a clear developing field in epidemiology and biomedical research. Besides that a number of limitations in former studies and some opportunities for better advance in the knowledge on the issue have been identified, leading to proposal of a series of recommendations including the following:

- Develop collaborations to establish large international cohorts with high availability and quality of exposure and potentially confounding factors, with enough sample size and avoiding as much as possible selection bias.
- Expand, clearly defined, new outcomes to be considered in studies, including subfertility, fetal loss, pregnancy complications (i.e. preeclampsia, hypertension), as well as measured characteristics after birth (i.e. placental weight, sexual differentiation, perinatal neurological scores).
- Improve exposure assessment by using models allowing for spatial and temporal resolution and also taking into account time-activity patterns, allowing for identification time-windows of susceptibility during pregnancy.
- Include biomarkers of exposure to air pollution as well as those of susceptibility (i.e. genetic polymorphisms).
- Report extensively cohort characteristics as well as information on outcomes, exposure and covariables.
- Develop experimental studies to help identify relevant biological mechanisms (Slama et al., 2008)

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6. References

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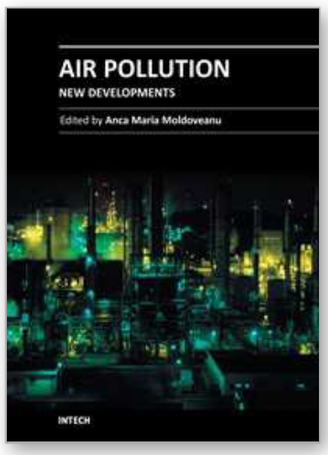

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Today, an important issue is environmental pollution, especially air pollution. Due to pollutants present in air, human health as well as animal health and vegetation may suffer. The book can be divided in two parts. The first half presents how the environmental modifications induced by air pollution can have an impact on human health by inducing modifications in different organs and systems and leading to human pathology. This part also presents how environmental modifications induced by air pollution can influence human health during pregnancy. The second half of the book presents the influence of environmental pollution on animal health and vegetation and how this impact can be assessed (the use of the micronucleus tests on TRADESCANTIA to evaluate the genotoxic effects of air pollution, the use of transplanted lichen PSEUDEVERNIA FURFURACEA for biomonitoring the presence of heavy metals, the monitoring of epiphytic lichen biodiversity to detect environmental quality and air pollution, etc). The book is recommended to professionals interested in health and environmental issues.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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