Available online at www.sciencedirect.com
ScienceDirect
Environmental Research 105 (2007) 400–408
Environmental Research
www.elsevier.com/locate/envres

Does the effect of air pollution on pregnancy outcomes differ by gender? A systematic review ☆

Rakesh Ghosh*, Judith Rankin, Tanja Pless-Mulloli, Svetlana Glinianaia

Institute of Health and Society, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK

Received 22 November 2006; received in revised form 5 March 2007; accepted 23 March 2007
Available online 9 May 2007

Abstract

Gender is known to influence pregnancy outcomes. Recent studies have reported an association between air pollution exposure and adverse pregnancy outcomes, but gender differences have not been considered. In order to assess the current evidence of the interactive effects between gender and air pollution on pregnancy outcomes we undertook a systematic literature review. Using a comprehensive list of keywords, English language articles published between 1966 and 2005 were retrieved from major databases. Additional information on gender was obtained from the study authors. Studies were included if they contained well-defined measurements of ambient air pollutants, investigated pregnancy outcomes and reported estimates by gender. In total 11 studies were included. The quality of the studies was assessed using the framework in Systematic Reviews in Health Care Meta-analysis in context and Bracken's Guidelines. Of the 11 studies, four evaluated low birth weight (LBW); one each evaluated very low birth weight and fetal growth and six examined preterm birth (PTB). Females were at higher risk of LBW: adjusted odds ratios (AOR) ranged from 1.07 to 1.62. Males were at higher risk for PTB: AORs ranged from 1.11 to 1.20. In addition, there was some evidence to suggest that the effect of air pollution on LBW is differential by gender; however, the evidence was available only from four studies. This is the first systematic review to consider gender effect. Further high quality studies are needed to establish whether these findings prevail.

Keywords: Gender; Ambient air pollution; Low birth weight; Preterm birth; Systematic review

1. Introduction

For a number of adverse pregnancy outcomes, there is an observed difference according to the gender of the infant. A male excess has been reported in preterm birth (PTB) (MacGillivray and Davey, 1985; Cooperstock and Campbell, 1996; Zeitlin et al., 2002, 2004), congenital anomalies (Byron-Scott et al., 2005) and cerebral palsy (Jarvis et al., 2005). Male infants have consistently higher birth weight throughout gestation than females. Despite the weight advantage, newborn males experience higher perinatal mortality compared to females (Brothwood et al., 1986). Even in the extremely low birth weight and very low birth weight (VLBW) subgroups, male infants have poorer survival rates than females (Hoffman and Bennett, 1990; Stevenson et al., 2000). Growth of the male fetus is also more susceptible to certain extraneous factors e.g. smoking (Zaren et al., 2000) and caffeine consumption (Vik et al., 2003) than the female fetus.

Research on air pollution and pregnancy outcomes has gained momentum in the last two decades. Ritz et al. (2000) have reported that a 50 μg increase in particulate matter $<10\,\mu m$ (PM_{10}) exposure contributes to 20% increase in PTB. First trimester particulate matter $<2.5\,\mu m$ ($PM_{2.5}$) exposure of $>18.4\,\mu g/m^3$, increases the risk of small for gestational age (SGA) by 26% and a similar exposure during the second trimester increases the risk by 24% (Parker et al., 2004). Average three monthly carbon monoxide (CO) exposure of >5.5 ppm was found to increase the risk of low birth weight (LBW) by 22% (Ritz and Yu, 1999). Using a continuous scale, Maisonet and colleagues reported a 31% increased risk of LBW associated

☆ The review is a part of a PhD study which is funded by the Faculty of Public Health and BUPA Joint Research Fellowship, the Overseas Research Students Awards Scheme (ORSAS) and an International Postgraduate Bursary from Newcastle University.
*Corresponding author. Fax: +44 (0) 191 2228211.
E-mail address: rakesh.ghosh@ncl.ac.uk (R. Ghosh).

0013-9351/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.envres.2007.03.009

with 1ppm increase in CO (Maisonet et al., 2001), and Salam and colleagues reported that birth weight reduced by 22 g for an increase in 1.4 ppm CO exposure (Salam et al., 2005). Similar findings were also reported from other studies. In Brazil, a 10 $\mu g/m^3$ increase in PM_{10} and 1 ppm increase in CO exposure in the first trimester reduced birth weight by 14 and 23 g respectively (Gouveia et al., 2004). The risk of PTB was increased by 10% for each 100 $\mu g/m^3$ increase in total suspended particles (TSPs) and by 26% for each unit increase of sulphur dioxide (SO_2) in the logarithmic scale (Xu et al., 1995). In Lithuania the high tertile exposure of nitrogen dioxide (NO_2) increases the risk of PTB by 68% and that of LBW by 54% (Marozine and Grazuleviciene, 2002). Studies conducted in Vancouver (Liu et al., 2003), Taiwan (Lin et al., 2004), UK (Bobak et al., 2001), the Czech Republic (Bobak and Leon, 1999; Bobak, 2000) and South Korea (Ha et al., 2001; Lee et al., 2003) have reported similar associations. However, several contemporary studies have found no association between exposure to CO, SO_2, nitrogen oxides, petrochemical pollutants and risk of LBW (Alderman et al., 1987; Landgren, 1996; Dolk et al., 2000; Oliveira et al., 2002), as well as between CO, SO_2, NO_2, particulate matter, ozone (O_3), and risk of SGA (Woodruff et al., 2003).

Overall the evidence suggests an association between exposure to air pollution and adverse pregnancy outcomes, albeit small (Glinianaia et al., 2004; Maisonet et al., 2004; Sram et al., 2005). As gender differences exist in a number of pregnancy outcomes, the aim of this review is to investigate whether the effects of air pollution on pregnancy outcomes are different for males and females.

2. Materials and methods

2.1. Literature search and inclusion/exclusion criteria

This review was based on published English language articles and conducted following the guidelines in the Cochrane Reviewers Handbook 2004 (Alderson et al., 2004) and "Systematic Reviews in Health Care Meta-analysis in context" (Egger et al., 2004).

Criteria for inclusion of studies into this systematic review were the following: (1) use of well-defined exposure measurements (including personal monitoring, approximation from ambient levels, modelled estimates and proximity to pollution sources); (2) specification of pollutants (TSP, PM_{10}, $PM_{2.5}$, nitrogen oxides (NO_x), CO, SO_2, O_3, etc.); (3) investigated the effect of air pollution exposure on pregnancy outcomes; and (4) reported estimates of effect based on infant gender. Studies were excluded if they included multiple births and occupational or accidental exposures. Multiple births were not considered as plurality is an important risk factor that determines fetal growth (Vorherr, 1982). This review is aimed at studying the effects of prolonged ambient exposure to air pollutants, so accidental and occupational exposures were excluded.

Medline (1966–2005), Embase (1980–2005), Science citation index (1981–2005), CINAHL (1982–2005), Cochrane library and other environmental databases (Environmental Science and Pollution Management (1981–2005), Pollution Abstracts (1981–2005), Toxicology Abstracts (1981–2005), Toxline (1993–2005), Health and Safety Sciences abstracts (1981–2005)) were searched. Reference lists of relevant articles were also scanned.

With the help of a comprehensive set of keywords (Supplementary Box 1), we searched the databases listed above. Each of the keywords was first mapped to subject headings and then searched as keywords in the titles and abstracts. Articles that fulfilled the inclusion criteria were independently reviewed by at least two authors. Data from the individual studies were extracted using a data extraction tool from a previous review (Glinianaia et al., 2004).

Fig. 1 shows the sequence of study selection. After reviewing the full text, 24 studies were excluded. Of these, 11 did not consider gender as a covariate in the regression model, and 13 adjusted for gender in the model but did not report a gender-specific estimate. In total, we found 11 articles that fulfilled the inclusion criteria.

Additional information to investigate interaction was requested from the authors of the 11 articles. Authors were requested to provide contingency tables for which odds ratios (OR) were calculated for males and females for the highest (quartile, quintile, etc.) versus lowest exposure category (quartile, quintile, etc.) for each pollutant. We received additional information from four studies. Due to the heterogeneity in study design and the limited number of studies, we have summarised the results narratively.

2.2. Study quality

Study quality was assessed based on external validity (Greenhalgh, 1997) and internal validity (Alderson et al., 2004). A checklist was developed from the quality assessment framework in the Systematic Reviews in Health Care Meta-analysis in context (Juni et al., 2001) and Bracken's guidelines (Bracken, 1989) for observational studies, to assess the methodological quality and to summarise the validity of the selected studies. The checklist

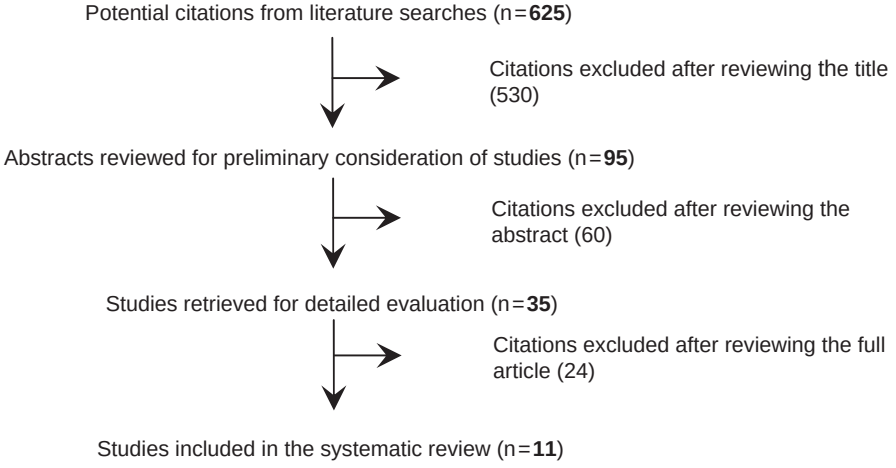

Fig. 1. Sequence of the search and review of studies.

was incorporated in the data extraction tool. The study domains considered are summarised in Table 1. Studies were graded as fully met, satisfactorily met and failed to meet the quality assessment criteria.

Study quality is summarised in Table 1. All but one study (Chen et al., 2002) stated the design. In the case-control studies, control selection was clearly explained with a reasonable logic. Universal outcome definitions and measurements were used giving external validity to the studies. However, wide varieties of covariates were adjusted for in the models. Missing data constituted only a small proportion of the sample except in the VLBW study (Rogers et al., 2000). Three studies (Rogers et al., 2000; Wilhelm and Ritz, 2003; Jedrychowski et al., 2004) adjusted for socio-economic status (SES) and three for maternal smoking (Rogers et al., 2000; Chen et al., 2002; Jedrychowski et al., 2004). We considered those studies which adjusted for SES and maternal smoking to fully meet the quality criteria. In the remaining studies residual confounding might have affected the results and therefore we considered the quality to be satisfactory.

2.3. Birth outcome definitions

In the studies LBW was defined as weight at birth less than 2500 g, VLBW as birth weight less than 1500 g and PTB as gestational age at birth less than 37 completed weeks.

3. Results

3.1. Study characteristics

Among the 11 studies (Table 2) included in the review, three were cohort studies (Wang et al., 1997; Chen et al., 2002; Jedrychowski et al., 2004) two case-control comparisons (Rogers et al., 2000; Wilhelm and Ritz, 2003) and six semi-individual (SI) studies (Lin et al., 2001a ,b; Tsai et al., 2003; Yang et al., 2003a, b, 2004). All of the studies used vital records to obtain the birth data. Additionally, two studies (Rogers et al., 2000; Jedrychowski et al., 2004) collected some primary data.

Table 1
Summary of the quality of studies by study domains

Study domain	Number of studies		
	Birth weight studies ($n = 5$)	Very low birth weight study ($n = 1$)	Pre-term birth studies ($n = 6$)
Design issues			
Study design clearly stated	4	1	6
Study group selection specified	5	1	6
Control selection process specified	3[a]	1	6
Exposure measurements			
Pollutants defined	5	1	1
Exposure duration clearly stated	5	1	6
Exposure measurement defined adequately	5	1	1
Outcome measurements			
Completeness of outcome measures	5	1	6
Missing data reported	5	1	6
Analysis			
Adequate adjustment for confounders[b]	3	1	1

[a]Remaining two were cohort studies.
[b]Adjustment was considered inadequate if socio-economic status and other important confounders were not considered in the analysis.

Two studies assessed birth weight as a continuous as well as a dichotomous variable (Wang et al., 1997; Chen et al., 2002); two assessed LBW (Lin et al., 2001b; Wilhelm and Ritz, 2003); one each assessed VLBW (Rogers et al., 2000); and fetal growth (Jedrychowski et al., 2004) and six examined PTB (Lin et al., 2001a; Tsai et al., 2003; Wilhelm and Ritz, 2003; Yang et al., 2003a, b, 2004).

Exposure measurements (Table 2) were estimated in four ways: (1) approximations from ambient monitoring; (2) statistical modelling using monitoring data; (3) personal monitoring and (4) comparison of pregnant women from polluted sites with those from relatively non-polluted sites.

3.2. Air pollution and adverse pregnancy outcomes

The risk of LBW reported across the studies ranged from OR 1.11 (CI 0.71–1.71) to 1.77 (CI 1.00–3.12) (Table 3). Jedrychowski et al. (2004) reported 140.3 g reduction in mean birth weight for an increase in $PM_{2.5}$ exposure from 10 to 50 $\mu g/m^3$.

The excess risk of PTB ranged from OR 1.08 (CI 1.01–1.15) to 1.41 (CI 1.08–1.82) across the studies (Table 3). These results have been discussed in detail in earlier reviews (Glinianaia et al., 2004; Maisonet et al., 2004; Lacasana et al., 2005; Sram et al., 2005).

3.3. Gender and adverse pregnancy outcomes

Gender differences in pregnancy outcomes were reported in the 11 studies after adjusting for covariates including the pollutants (Table 3). Three studies reported excess risk in females for LBW compared to males, adjusted ORs are 1.49 (CI 1.29–1.72) (Chen et al., 2002), 1.62 (CI 1.03–2.74) (Lin et al., 2001b), and 1.44 (CI 1.34–1.55) (Wilhelm and Ritz, 2003). In contrast, Wang and colleagues (Wang et al., 1997) reported that males were at 7–8% higher risk of LBW than females. In another study female infants showed an increasing trend towards VLBW compared to males, OR 1.23 (CI 0.75–1.43) (Rogers et al., 2000). The Polish study (Jedrychowski et al., 2004) reported a significantly lower mean birth weight (212.80 g) and smaller length and head circumference in females (lesser by 1.15 and 0.78 cm respectively).

Studies on PTB reported a reduced risk for females. A decrease in PTB in females compared to males was reported in six studies, and significant in four, ORs ranged from 0.83 (CI 0.74–0.93) to 0.88 (CI 0.82–0.96) (Table 3) (Lin et al., 2001a; Tsai et al., 2003; Wilhelm and Ritz, 2003; Yang et al., 2004). Three other studies (Table 3) reported risks of comparable magnitude (Lin et al., 2001a; Tsai et al., 2003;

Table 2
Study characteristics

First author (Year)	Location	Duration	Design	Pollutants	Exposure assessment	Pollutant values/study groups comparison
Chen et al. (2002)	USA	1991–1999	Cohort	CO, PM_{10}, O_3	24 h average of PM_{10}, 8 h average of CO and O_3 approximated from ambient levels	PM_{10}–31.53 μg/m^3 (22.32)[a] CO–0.98 ppm (0.55) O_3–27.23 ppb (10.62)
Lin et al. (2001b)	Taiwan	1993–1996	Semi-individual	SO_2, PM_{10}, NO_2	Approximation from ambient monitoring	SO_2–6.04 ppb (2.88)[b] PM_{10}–85.89 μg/m^3 (1.71) NO_2–12.09 ppb (2.23)
Wang et al. (1997)	China	1988–1991	Cohort	SO_2, TSP	Approximation from ambient monitoring	SO_2–9–308 μg/m^3[c] TSP–211–618 μg/m^3
Wilhelm and Ritz (2003)	USA	1994–1996	Case control	CO, PM_{10}, NO_2, O_3	Distance weighted traffic density measure and annual medians	CO–1.73 ppm[d] PM_{10}–41.11 ppm NO_2–4.35 pphm O_3–1.80 pphm
Jedrychowski et al. (2004)	Poland	Jan'01–Mar'03	Prospective Cohort	$PM_{2.5}$	Direct personal monitoring	$PM_{2.5}$–43 μg/m^3[a] $PM_{2.5}$–10.3–147.3 μg/m^3[c]
Rogers et al. (2000)	USA	Apr'86–Mar'88	Case control	SO_2, TSP	Statistical modelling from ambient monitoring estimates	TSP–5.93 μg/m^3[d] SO_2–3.80 μg/m^3 TSPSO_2–9.94 μg/m^3
Lin et al. (2001a)	Taiwan	1993–1996	Semi-individual	Petroleum refinery pollutants	Extreme point contrast	Births within petroleum municipalities were compared with those from the rest of Taiwan
Tsai et al. (2003)	Taiwan	1994–1997	Semi-individual	Pollutants from industrial and petrochemical sites	Extreme point contrast	Polluted area defined by a circle of 2 km around multiple sources, controls from the rest of Taiwan
Yang et al. (2003a)	Taiwan	1992–1997	Semi-individual	Pollutants from vehicular traffic on a freeway	Extreme point contrast	Births within 500 m from the freeway were compared with those within 500–1500 m
Yang et al. (2003b)	Taiwan	1992–1996	Semi-individual	Cement dust	Extreme point contrast	Births within 0–2 km from the freeway were compared with those within 2–4 km
Yang et al. (2004)	Taiwan	1994–1997	Semi-individual	Oil refinery pollutants	Extreme point contrast	Births within circles of 3 km radius from refineries with the rest of births in Taiwan

[a]Mean values (SD) of the pollutants.
[b]Geometric mean values (geometric SD) of the pollutants of the exposed area.
[c]Range of values of the pollutants.
[d]Annual medians of the pollutant.

Yang et al., 2004). Studies with different exposure such as traffic air pollution and cement air pollution also reported decreased risk for PTB in females OR 0.87 (CI 0.84–0.91) (Wilhelm and Ritz, 2003), 0.90 (CI 0.71–1.14) (Yang et al., 2003a), and OR 0.89 (CI 0.78–1.03) (Yang et al., 2003b). These estimates show that males are at higher risk for PTB.

3.4. Air pollution, gender and adverse pregnancy outcomes

Table 4 shows the interactive effects between air pollution and gender based on additional information obtained from the study authors. The OR for males in the VLBW study (Rogers et al., 2000) with TSP and SO_2 exposure was almost double that for females. The Chinese study (Wang et al., 1997) reported an adjusted OR for LBW in males which was 7–8% higher than for females for both SO_2 and TSP. In another study (Jedrychowski et al., 2004) there was no evidence of a significant difference in birth weight between the two genders for $PM_{2.5}$ exposure. In the traffic air pollution study (Wilhelm and Ritz, 2003) the OR was significant for NO_2 where males had 6% more risk of LBW than females and in the case of CO, the risk

Table 3
Summary of evidence on air pollution and pregnancy outcomes

First author (Year)	Sample size		Pollutants	OR (CI)[a]	OR (CI)[a]
	Study group	Controls		Air pollution	Gender (male as ref)
Low birth weight					
Chen et al. (2002)	36,305	—	PM_{10}	1.11 (0.71–1.71)	1.49 (1.29–1.72)
			CO	0.91 (0.56–1.46)	
			O_3	0.78 (0.51–1.21)	
Lin et al. (2001b)	1677	868	—	1.77 (1.00–3.12)	1.62 (1.03–2.74)
Wang et al. (1997)	74,671	—	SO_2	1.39 (1.22–1.60)	1.09 (0.97–1.22)
			TSP	1.24 (1.08–1.42)	1.07 (0.95–1.20)
Wilhelm and Ritz (2003)	3771	26,351	—	1.14 (1.00–1.29)	1.44 (1.34–1.55)
Birth weight (*continuous*)					
Jedrychowski et al. (2004)[b]	362		$PM_{2.5}$	−200.82 (−385.97 to −15.67)	−212.80 (−293.91 to −131.69)
Very low birth weight					
Rogers et al. (2000)	143	202	$TSPSO_2$	2.88 (1.16–7.13)	1.23 (0.75–1.43)
Preterm birth					
Lin et al. (2001a)	2027	49,673	—	1.41 (1.08–1.82)	0.83 (0.74–0.93)
Tsai et al. (2003)	14,545	49,670	—	1.11 (1.02–1.21)	0.88 (0.82–0.95)
Yang et al. (2003a)	3211	3040	—	1.30 (1.03–1.65)	0.90 (0.71–1.14)
Yang et al. (2003b)	3067	14,049	—	1.30 (1.09–1.54)	0.89 (0.78–1.03)
Wilhelm and Ritz (2003)	13,464	21,124	—	1.08 (1.01–1.15)	0.87 (0.84–0.91)
Yang et al. (2004)	7095	50,388	—	1.14 (1.01–1.28)	0.88 (0.82–0.96)

[a]Adjusted for other covariates in the model.
[b]Linear regression coefficients were reported for this study.

was higher by 4% in females. The differences in the risk of LBW for the two genders in the studies possibly suggests interaction between air pollution effects and gender (Wang et al., 1997; Rogers et al., 2000; Wilhelm and Ritz, 2003).

4. Discussion

Over the past decade a number of studies on air pollution and pregnancy outcomes have been published. Recent systematic reviews are suggestive of an association between air pollution and adverse pregnancy outcomes (Glinianaia et al., 2004; Maisonet et al., 2004; Sram et al., 2005). Existing studies have not adequately addressed whether fetal gender, a known factor influencing pregnancy outcomes, plays a role. In this systematic review, the first to investigate gender effects, we found that a possible differential effect of air pollution on pregnancy outcomes may exist.

The mean birth weight of female infants is generally lower than males. Consequently, a higher proportion of females tend to be LBW. Female gender and air pollution are two known risk factors for LBW (Table 3). In this review there is some evidence of interaction when the highest and lowest exposure groups were compared by gender. The risk of LBW was found to be higher in males in the presence of high levels of air pollution. Male infants are generally less mature than females at term, and also at earlier gestational ages (Torday et al., 1981; Leader et al., 1982; Catlin et al., 1990). The relatively less mature status may make them more vulnerable to extraneous factors such as air pollution than females. However, our results were based on four studies and with the limited data a proper test of interaction could not be undertaken.

Table 4
Odds ratios for air pollution and LBW/PTB by gender and pollutants[a]

Author	Pollutant	Male (CI)	Female (CI)
Low birth weight			
Rogers et al. (2000)	$TSPSO_2$	3.00 (0.95–9.67)	1.89 (0.48–7.47)
Wang et al. (1997)[b]	SO_2	1.16 (1.02–1.32)	1.09 (0.97–1.22)
Wang et al. (1997)[b]	TSP	1.15 (1.01–1.32)	1.07 (0.95–1.20)
Jedrychowski et al. (2004)	$PM_{2.5}$	$p = 0.09$[c]	0.86 (0.13–5.48)
Wilhelm and Ritz (2003)	PM_{10}	1.01 (0.92–1.11)	0.95 (0.87–1.04)
Wilhelm and Ritz (2003)	CO	1.05 (0.94–1.16)	1.09 (0.98–1.20)
Wilhelm and Ritz (2003)	O_3	0.94 (0.86–1.04)	0.93 (0.84–1.02)
Wilhelm and Ritz (2003)	NO_2	1.14 (1.04–1.25)	1.08 (0.99–1.19)
Preterm birth			
Wilhelm and Ritz (2003)	PM_{10}	1.04 (0.96–1.14)	1.03 (0.95–1.13)
Wilhelm and Ritz (2003)	CO	1.11 (1.01–1.22)	1.06 (0.96–1.18)
Wilhelm and Ritz (2003)	O_3	0.86 (0.79–0.94)	0.90 (0.82–0.98)
Wilhelm and Ritz (2003)	NO_2	1.19 (1.09–1.29)	1.11 (1.02–1.21)

[a]ORs were calculated from the additional data provided by the study authors.
[b]Adjusted OR in this study and unadjusted OR in the rest.
[c]p value was reported from Fisher's exact test.

Evidence of the differential nature of chemical insults on the growing fetus is available from recent studies. Tang and colleagues reported differential associations between cord blood polycyclic aromatic hydrocarbon (PAH)-DNA adduct levels and head circumference in males and females

(Tang et al., 2006). Prenatal exposure to organochlorines was reported to have a differential effect on sex hormones in males and females (Kraemer et al., 2006). Animal studies also support differential effects of chemical exposure by gender (Bunn et al., 2001; Silva et al., 2005).

Some previous air pollution and pregnancy outcome studies have reported investigation of interaction but found them to be non-significant. It is well known that a study requires sufficient power to obtain statistically significant interaction. Tang et al. (2006) did not find a significant interaction ($n = 150$) but stratified analysis yielded differential results for males and females. Moreover, statistical interaction is sensitive to both the scale and estimate used to measure interaction. An interaction that is not apparent when using a multiplicative scale with OR/RR measures, can become apparent when an additive scale with risk difference measure is used (Rothman, 2002) and vice-versa. Specialised estimates like relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index (SI) have been suggested to measure interaction (Rothman, 1976; Skrondal, 2003) and with birth weight (outcome), interaction can be measured in additive (linear) and LBW in multiplicative scale (logistic model).

The interactive effects of air pollution, pregnancy outcomes and gender should be considered in light of known limitations such as exposure misclassification, bias and confounding.

4.1. Exposure misclassification

The potential for bias in air pollution studies arises when the surrogate measures misclassify true personal exposures. Short term personal monitoring may also not be representative of the entire pregnancy especially in the presence of seasonality. A study in this review (Jedrychowski et al., 2004) that used personal monitoring repeated the measurements on a small percentage of the sample in each trimester, and found exposure to be stable over the duration of pregnancy. On the other hand, approximations from ambient levels provide exposure information for longer periods. The six semi-individual studies included in this review measured exposure at the ecological level; thereby increasing the potential for misclassification. None of the studies in this review investigated indoor air pollution. Only the Chinese study (Wang et al., 1997) reported similar indoor and outdoor trends in particulate concentrations and concluded that lack of control for indoor air pollution would not alter the nature of the association but it might reduce the power to detect significance (Xu et al., 1995). Nonetheless, bias from exposure misclassification potentially exists in the reviewed studies.

4.2. Other sources of bias

Almost all of the studies were population based and control selection in the case-control studies was appropriate, hence selection bias is less of a concern. Performance and detection bias do not directly apply as the essence of blinding existed in all the studies.

Attrition bias is not relevant in the reviewed studies, as drop outs were at the analysis stage due to missing data. Moreover, missing data comprised a very small percentage of the total sample except in one study (Rogers et al., 2000) where one-fifth of the cases and one-tenth of the controls were lost.

Studies that reported a gender based estimate were those that reported a positive association between air pollution and adverse pregnancy outcomes. None of the studies that reported negative associations explored gender effects. Thus publication bias may be relevant here.

4.3. Confounding

Potential confounders associated with LBW (Kramer, 1987a) and PTB (Berkowitz and Papiernik, 1993; Berkowitz et al., 1998) are gestational age, maternal weight gain, SES, reproductive history, medical risks of the index pregnancy and behavioural (smoking) and environmental factors. Of these the most important is gestational age (Thomas et al., 2000). Three of the five birth weight studies (Rogers et al., 2000; Chen et al., 2002; Jedrychowski et al., 2004) adjusted for gestational age in the analysis while the other two (Lin et al., 2001b; Wilhelm and Ritz, 2003) adjusted for it in the study design by restricting the sample to term and preterm LBW. The Chinese and Taiwanese studies were restricted to first parity pregnant women. Three studies (Rogers et al., 2000; Chen et al., 2002; Wilhelm and Ritz, 2003) adjusted for SES and three for maternal smoking (Rogers et al., 2000; Chen et al., 2002; Jedrychowski et al., 2004). Given the importance of SES (Kramer, 1987b; Basso et al., 1997) and maternal smoking status (Kramer, 1987b; Zaren et al., 2000) in fetal growth and development, studies that did not control for these variables might have been affected by residual confounding.

4.4. Biological plausibility

CO is the only pollutant for which the biological mechanism on the fetus is known. CO binds with haemoglobin and crosses the placenta by passive diffusion thereby reducing oxygen availability to the fetus (Longo, 1977). The higher affinity of fetal haemoglobin to CO compared to adults results in higher concentrations of stable carboxyhaemoglobin in the fetal blood than in the mother's (Gabrielli and Layon, 1995; Aubard and Magne, 2000). Male fetuses have been reported to have a higher growth rate and greater demands for blood circulation than female fetuses (Parker et al., 1984; Spinillo et al., 1994; Thomas et al., 2000). One possible explanation could be that owing to the higher rate of growth male fetuses require more oxygen, and carboxyhaemoglobin makes oxygen less available, which may be further aggravated by the

relatively immature status of male compared to female fetuses at a given gestational age. Our suggestion of the possible differential effect of CO on male fetal growth can be supported by findings from recent research on maternal smoking. Maternal smoking is shown to have a differential negative effect on growth of male and female fetuses, being more pronounced for male fetuses (Wertelecki et al., 1987; Spinillo et al., 1994; Zaren et al., 2000) and CO is known to be a major constituent of tobacco smoke (Longo, 1977; Walsh, 1994).

The biological mechanisms of the effect of other pollutants, including particulates, on the fetus are poorly understood, so gender-specific considerations can be at best speculative. The effect of any pollutants may be mediated through maternal conditions causing placental dysfunction and consequently affecting fetal growth; alternatively, the toxic components in the maternal circulation can cross the placenta and directly affect the fetus. The association between PM_{10} and respiratory diseases have been reported in many studies (Pope and Dockery, 2006). Evidence of biological causality between PM_{10} and respiratory conditions suggests that PM_{10} may increase maternal susceptibility to infections during pregnancy, including intrauterine infections. Male fetuses may be particularly vulnerable to intrauterine infections because their amniotic membranes are more prone to infection due to slower immunologic development compared to female fetuses (Hall and Carr-Hill, 1982; Perni et al., 2005). Moreover, exposure to PM_{10} increases blood viscosity in adults (Zondervan et al., 1987; Knottnerus et al., 1990), which in turn may reduce placental perfusion. One can speculate that increased blood viscosity may have a more pronounced effect on the placenta of the male fetus because placental dysfunction is more frequently observed in male than female births (Edwards et al., 2000; Ghidini and Salafia, 2005). In addition, particulates may directly interfere sometimes forming adducts (PAH-DNA), affecting fetal growth (Perera et al., 1998; Dejmek et al., 2000). There is no direct evidence of susceptibility of male fetuses to particulates leading to LBW. However, male fetuses are more prone to slower lung maturation than females (Torday et al., 1981; Catlin et al., 1990), while particulates are known to cause oxidative stress and increase permeability of the lung epithelium (Carter et al., 1997; Donaldson et al., 2001), which may result in a higher susceptibility for the male fetus.

In summary, the adjusted estimates from the air pollution and pregnancy outcome studies provided evidence consistent with existing knowledge that female infants are at an increased risk of LBW and males are at an increased risk of PTB. In addition, there was some evidence to suggest that air pollution effects on LBW may be differential by gender. Males were found to be at a higher risk of LBW in the presence of high levels of air pollution. However, the evidence was limited and inconclusive. Further investigation to ascertain interaction is required in high-powered datasets across different populations.

Acknowledgments

We are grateful to the study authors Prof. W. Jedrychowski, Dr. J. F. Rogers and Dr. M. Wilhelm who sent additional information on their studies.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2007.03.009.

References

Alderman, B.W., Baron, A.E., Savitz, D.A., 1987. Maternal exposure to neighborhood carbon monoxide and risk of low infant birth weight. Public Health Rep. 102, 410–414.

Alderson, P., Green, S., Higgins, J.P.T., 2004. Cochrane Reviewers' Handbook, 4.2.2. Wiley, Chichester, UK.

Aubard, Y., Magne, I., 2000. Carbon monoxide poisoning in pregnancy. Br. J. Obstet. Gynaecol. 107, 833–838.

Basso, O., Olsen, J., Johansen, A.M.T., Christensen, K., 1997. Change in social status and risk of low birth weight in Denmark: population based cohort study. Br. Med. J. 315, 1498–1502.

Berkowitz, G.S., Papiernik, E., 1993. Epidemiology of preterm birth. Epidemiol. Rev. 15, 414–443.

Berkowitz, G.S., Blackmore-Prince, C., Lapinski, R.H., Savitz, D.A., 1998. Risk factors for preterm birth subtypes. Epidemiology 9, 279–285.

Bobak, M., 2000. Outdoor air pollution, low birth weight, and prematurity. Environ. Health Perspect. 108, 173–176.

Bobak, M., Leon, D.A., 1999. Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986–8. Occup. Environ. Med. 56, 539–543.

Bobak, M., Richards, M., Wadsworth, M., 2001. Air pollution and birth weight in Britain in 1946. Epidemiology 12, 210.

Bracken, M., 1989. Reporting observational studies. Br. J. Obstet. Gynaecol. 96, 383–388.

Brothwood, M., Wolke, D., Gamsu, H., Benson, J., Cooper, D., 1986. Prognosis of the very low birthweight baby in relation to gender. Arch. Dis. Child. Fetal Neonatal Ed. 61, 559–564.

Bunn, T.L., Parsons, P.J., Kao, E., Dietert, R.R., 2001. Exposure to lead during critical windows of embryonic development: differential immunotoxic outcome based on stage of exposure and gender. Toxicol. Sci. 64, 57–66.

Byron-Scott, R., Sharpe, P., Hasler, C., Cundy, P., Hirte, C., Chan, A., et al., 2005. A South Australian population-based study of congenital talipes equinovarus. Paediatr. Perinat. Epidemiol. 19, 227–237.

Carter, J., Ghio, A., Samet, J., Devlin, R., 1997. Cytokine production by human airway epithelial cells after exposure to an air pollution particle is metal-dependent. Toxicol. Appl. Pharmacol. 146, 180–188.

Catlin, E.A., Powell, S.M., Manganaro, T.F., Hudson, P.L., Ragin, R.C., Epstein, J., et al., 1990. Sex-specific fetal lung development and mullerian inhibiting substance. Am. Rev. Respir. Dis. 141, 466–470.

Chen, L., Yang, W., Jennison, B.L., Goodrich, A., Omaye, S.T., 2002. Air pollution and birth weight in northern Nevada, 1991–1999. Inhal. Toxicol. 14, 141–157.

Cooperstock, M., Campbell, J., 1996. Excess males in preterm birth: interactions with gestational age, race, and multiple birth. Obstet. Gynecol. 88, 189–193.

Dejmek, J., Solansky, I., Benes, I., Lenicek, J., Sram, R.J., 2000. The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. Environ. Health Perspect. 108, 1159–1164.

Dolk, H., Pattenden, S., Vrijheid, M., Thakrar, B., Armstrong, B., 2000. Perinatal and infant mortality and low birth weight among residents near cokeworks in Great Britain. Arch. Environ. Health. 55, 26–30.

Donaldson, K., Stone, V., Seaton, A., MacNee, W., 2001. Ambient particle inhalation and the cardiovascular system: potential mechanisms. Environ. Health Perspect. 109 (Suppl. 4), 523–527.

Edwards, A., Megens, A., Peek, M., Wallace, E.M., 2000. Sexual origins of placental dysfunction. Lancet 355, 203–204.

Egger, M., Smith, G.D., Altman, D.G., 2004. Systematic Reviews in Health Care Meta-Analysis in Context. BMJ Books, London.

Gabrielli, A., Layon, A.J., 1995. Carbon monoxide intoxication during pregnancy: a case presentation and pathophysiologic discussion, with emphasis on molecular mechanisms. J. Clin. Anesth. 7, 82–87.

Ghidini, A., Salafia, C., 2005. Gender differences of placental dysfunction in severe prematurity. Br. J. Obstet. Gynaecol. 112, 140–144.

Glinianaia, S.V., Rankin, J., Bell, R., Pless-Mulloli, T., Howel, D., 2004. Particulate air pollution and fetal health a systematic review of the epidemiologic evidence. Epidemiology 15, 36–45.

Gouveia, N., Bremner, S.A., Novaes, H.M., 2004. Association between ambient air pollution and birth weight in Sao Paulo, Brazil. J. Epidemiol. Commun. Health 58, 11–17.

Greenhalgh, T., 1997. How to read a paper: papers that summarise other papers (systematic review and meta-analysis). Br. Med. J. 315, 672–675.

Ha, E.H., Hong, Y.C., Lee, B.E., Woo, B.H., Schwartz, J., Christiani, D.C., 2001. Is air pollution a risk factor for low birth weight in Seoul? Epidemiology 12, 643–648.

Hall, M.H., Carr-Hill, R., 1982. Impact of sex ratio on onset and management of labour. Br. Med. J. Clin. Res. Ed. 285, 401–403.

Hoffman, E.L., Bennett, F.C., 1990. Birth weight less than 800 grams: changing outcomes and influences of gender and gestation number. Pediatrics 86, 27–34.

Jarvis, S., Glinianaia, S.V., Arnaud, C., Fauconnier, J., Johnson, A., McManus, V., et al., 2005. Case gender and severity in cerebral palsy varies with intrauterine growth. Arch. Dis. Child. Fetal Neonatal Ed. 90, 474–479.

Jedrychowski, W., Bendkowska, I., Flak, E., Penar, A., Jacek, R., Kaim, I., et al., 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, 1398–1402.

Juni, P., Altman, D.G., Egger, M., 2001. Assessing the quality of randomised controlled trials. In: Egger, M., Smith, G.D., Altman, D.G. (Eds.), Systematic Reviews in Health Care Meta-Analysis in Context. BMJ Books, UK, pp. 87–102.

Knottnerus, J.A., Delgado, L.R., Knipschild, P.G., Essed, G.G., Smits, F., 1990. Haematologic parameters and pregnancy outcome. A prospective cohort study in the third trimester. J. Clin. Epidemiol. 43, 461–466.

Kraemer, U., Cao, Y., Winneke, G., Wittsiepe, J., Imoehl, M., Eberwein, H.G., et al., 2006. Prenatal exposure to organochlorine chemicals at environmental levels has a negative impact on sex steroids in newborns. International Conference on Environmental Epidemiology and Exposure, Paris. Epidemiology 17, S192.

Kramer, M.S., 1987a. Determinants of low birth weight: methodological assessment and meta-analysis. Bull. World Health Organiz. 65, 663–737.

Kramer, M.S., 1987b. Intrauterine growth and gestational duration determinants. Pediatrics 80, 502–511.

Lacasana, M., Esplugues, A., Ballester, F., 2005. Exposure to ambient air pollution and prenatal and early childhood health effects. Eur. J. Epidemiol. 20, 183–199.

Landgren, O., 1996. Environmental pollution and delivery outcome in southern Sweden: a study with central registries. Acta Paediatr. 85, 1361–1364.

Leader, L.R., Baillie, P., Martin, B., Vermeulen, E., 1982. The assessment and significance of habituation to a repeated stimulus by the human fetus. Early Hum. Dev. 7, 211–219.

Lee, B.E., Ha, E.H., Park, H.S., Kim, Y.J., Hong, Y.C., Kim, H., et al., 2003. Exposure to air pollution during different gestational phases contributes to risks of low birth weight. Hum. Reprod. 18, 638–643.

Lin, M.C., Chiu, H.F., Yu, H.S., Tsai, S.S., Cheng, B.H., Wu, T.N., et al., 2001a. Increased risk of preterm delivery in areas with air pollution from a petroleum refinery plant in Taiwan. J. Toxicol. Environ. Health 64, 637–644.

Lin, M.C., Yu, H.S., Tsai, S.S., Cheng, B.H., Hsu, T.Y., Wu, T.N., et al., 2001b. Adverse pregnancy outcome in a petrochemical polluted area in Taiwan. J. Toxicol. Environ. Health 63, 565–574.

Lin, C.M., Li, C.Y., Yang, G.Y., Mao, I.F., 2004. Association between maternal exposure to elevated ambient sulfur dioxide during pregnancy and term low birth weight. Environ. Res. 96, 41–50.

Liu, S.L., Krewski, D., Shi, Y.L., Chen, Y., Burnett, R.T., 2003. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ. Health Perspect. 111, 1773–1778.

Longo, L.D., 1977. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am. J. Obstet. Gynecol. 129, 69–103.

MacGillivray, I., Davey, D.A., 1985. The influence of fetal sex on rupture of the membranes and preterm labor. Am. J. Obstet. Gynecol. 153, 814–815.

Maisonet, M., Bush, T.J., Correa, A., Jaakkola, J.J., 2001. Relation between ambient air pollution and low birth weight in the Northeastern United States. Environ. Health Perspect. 109, 351–356.

Maisonet, M., Correa, A., Misra, D., Jaakkola, J.J.K., 2004. A review of the literature on the effects of ambient air pollution on fetal growth. Environ. Res. 95, 106–115.

Marozine, L., Grazuleviciene, R., 2002. Maternal exposure to low-level air pollution and pregnancy outcomes: a population based study. Environ Health: Global Access Sci. Source 1, doi:10.1186/1476-1069X-1181-1186.

Oliveira, L.M., Stein, N., Sanseverino, M.T., Vargas, V.M., Fachel, J.M., Schuler, L., 2002. Reproductive outcomes in an area adjacent to a petrochemical plant in southern Brazil. Rev. Saude Publica. 36, 81–87.

Parker, A.J., Davies, P., Mayho, A.M., Newton, J.R., 1984. The ultrasound estimation of sex-related variations of intrauterine growth. Am. J. Obstet. Gynecol. 149, 665–669.

Parker, J.D., Woodruff, T.J., Basu, R., Schoendorf, K.C., 2004. Air pollution and birth weight among term infants in California. Pediatrics 115, 121–128.

Perera, F.P., Whyatt, R.M., Jedrychowski, W., Rauh, V., Manchester, D., Santella, R.M., et al., 1998. Recent developments in molecular epidemiology: a study of the effects of environmental polycyclic aromatic hydrocarbons on birth outcomes in Poland. Am. J. Epidemiol. 147, 309–314.

Perni, S.C., Vardhana, S., Kalish, R., Chasen, S., Witkin, S.S., 2005. Clara cell protein 16 concentration in mid-trimester amniotic fluid: association with fetal gender, fetal G> A+ 38 CC16 gene polymorphism and pregnancy outcome. J. Reprod. Immunol. 68, 85–90.

Pope III, C.A., Dockery, D.W., 2006. Health effects of fine particulate air pollution: lines that connect. J. Air Waste Manag. Assoc. 56, 709–742.

Ritz, B., Yu, F., 1999. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ. Health Perspect. 107, 17–25.

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. Epidemiology 11, 502–511.

Rogers, J.F., Thompson, S.J., Addy, C.L., McKeown, R.E., Cowen, D.J., Decoufle, P., 2000. Association of very low birth weight with exposures to environmental sulfur dioxide and total suspended particulates. Am. J. Epidemiol. 151, 602–613.

Rothman, K.J., 1976. The estimation of synergy or antagonism. Am. J. Epidemiol. 103, 506–511.

Rothman, K.J., 2002. Measuring interaction. In: Epidemiology an Introduction. OUP, Oxford.

Salam, M.T., Millstein, J., Li, Y., Lurmann, F.W., Margolis, H.G., Gilliland, F.D., 2005. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the children's health study. Environ. Health Perspect. 113, 1638–1644.

Silva, I.A., El Nabawi, M., Hoover, D., Silbergeld, E.K., 2005. Prenatal $HgCl_2$ exposure in BALB/c mice: gender-specific effects on the ontogeny of the immune system. Dev. Comp. Immunol. 29, 171–183.

Skrondal, A., 2003. Interaction as departure from additivity in case-control studies: a cautionary note. Am. J. Epidemiol. 158, 251–258.

Spinillo, A., Capuzzo, E., Nicola, S., Colonna, L., Lasci, A., Zara, C., 1994. Interaction between fetal gender and risk factors for fetal growth retardation. Am. J. Obstet. Gynecol. 171, 1273–1277.

Sram, R.J., Binkova, B., Dejmek, J., Bobak, M., 2005. Ambient air pollution and pregnancy outcomes: a review of literature. Environ. Health Perspect. 113, 375–382.

Stevenson, D.K., Verter, J., Fanaroff, A.A., Oh, W., Ehrenkranz, R.A., Shankaran, S., et al., 2000. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. Arch. Dis. Child. Fetal Neonatal Ed. 83, F182–F185.

Tang, D., Li, T., Liu, J.J., Chen, Y., Qu, L., Perera, F., 2006. PAH-DNA adducts in cord blood and fetal and child development in a Chinese cohort. Environ. Health Perspect. 114, 1297–1300.

Thomas, P., Peabody, J., Turnier, V., Clark, R.H., 2000. A new look at intrauterine growth and the impact of race, altitude, and gender. Pediatrics 106, E21.

Torday, J., Nielsen, H., Fencl Mde, M., Avery, M., 1981. Sex differences in fetal lung maturation. Am. Rev. Respir. Dis. 123, 205–208.

Tsai, S.S., Yu, H.S., Liu, C.C., Yang, C.Y., 2003. Increased incidence of preterm delivery in mothers residing in an industrialized area in Taiwan. J. Toxicol. Environ. Health 66, 987–994.

Vik, T., Bakketeig, L., Trygg, K., Lund-Larsen, K., Jacobsen, G., 2003. High caffeine consumption in the third trimester of pregnancy: gender-specific effects on fetal growth. Paediatr. Perinat. Epidemiol. 17, 324–331.

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

Walsh, R.A., 1994. Effects of maternal smoking on adverse pregnancy outcomes—examination of the criteria of causation. Hum. Biol. 66, 1059–1092.

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, 514–520.

Wertelecki, W., Hoff, C., Zansky, S., 1987. Maternal smoking: greater effect on males, fetal tobacco syndrome. Teratology 35, 317–320.

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

Woodruff, T.J., Parker, J.D., Kyle, A.D., Schoendorf, K.C., 2003. Disparities in exposure to air pollution during pregnancy. Environ. Health Perspect. 111, 942–946.

Xu, X., Ding, H., Wang, X., 1995. Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study. Arch. Environ. Health 50, 407–415.

Yang, C.Y., Chang, C.C., Chuang, H.Y., Ho, C.K., Wu, T.N., Tsai, S.S., 2003a. Evidence for increased risks of preterm delivery in a population residing near a freeway in Taiwan. Arch. Environ. Health. 58, 649–654.

Yang, C.Y., Chang, C.C., Tsai, S.S., Chuang, H.Y., Ho, C.K., Wu, T.N., et al., 2003b. Preterm delivery among people living around Portland cement plants. Environ. Res. 92, 64–68.

Yang, C.Y., Chang, C.C., Chuang, H.Y., Ho, C.K., Wu, T.N., Chang, P.Y., 2004. Increased risk of preterm delivery among people living near the three oil refineries in Taiwan. Environ. Int. 30, 337–342.

Zaren, B., Lindmark, G., Bakketeig, L., 2000. Maternal smoking affects fetal growth more in the male fetus. Paediatr. Perinat. Epidemiol. 14, 118–126.

Zeitlin, J., Saurel-Cubizolles, M.J., De Mouzon, J., Rivera, L., Ancel, P.Y., Blondel, B., et al., 2002. Fetal sex and preterm birth: are males at greater risk? Hum Reprod. 17, 2728–2762.

Zeitlin, J., Ancel, P.Y., Larroque, B., Kaminski, M., Study, E., 2004. Fetal sex and indicated very preterm birth: results of the EPIPAGE study. Am. J. Obstet. Gynecol. 190, 1322–1325.

Zondervan, H., Oosting, J., Hardeman, M., Smorenberg-Schoorl, M., Treffers, P., 1987. The influence of maternal whole blood viscosity on fetal growth. Eur. J. Obstet. Gynecol. Reprod. Biol. 25, 187–194.