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The use of ultrasound measurements in environmental epidemiological studies of air pollution and fetal growth

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Abstract

Purpose of review—Recently, several international research groups have suggested that studies about environmental contaminants and adverse pregnancy outcomes should be designed to elucidate potential underlying biological mechanisms. The purpose of this review is to examine the epidemiological studies addressing maternal exposure to air pollutants and fetal growth during gestation as assessed by ultrasound measurements.

Recent findings—The six studies published to date found that exposure to certain ambient air pollutants during pregnancy is negatively associated with the growth rates and average attained size of fetal parameters belonging to the growth profile. Fetal parameters may respond to maternal air pollution exposures uniquely, and this response may vary by pollutant and timing of gestational exposure. Current literature suggests that mean changes in head circumference, abdominal circumference, femur length, and biparietal diameter are negatively associated with early-pregnancy exposures to ambient and vehicle-related air pollution.

Summary—The use of more longitudinal studies, employing ultrasound measures to assess fetal outcomes, may assist with the better understanding of mechanisms responsible for air pollution-related pregnancy outcomes.

Keywords

air pollution; fetal growth; ultrasound measures

INTRODUCTION

Maternal exposures to environmental contaminants during pregnancy are a global public health concern. Previous literature has reviewed studies on the relationship between air

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pollutants and pregnancy outcomes including low birth weight, small for gestational age (SGA), and preterm birth [1–4]. These studies contribute to current understanding of the adverse effects of air pollution exposure during pregnancy.

However, these studies commonly lack an assessment of how these exposures affect fetal growth over the course of the pregnancy, and whether certain times in gestation are particularly critical. Fetal growth outcomes studied include weight and anthropometric measurements of abdominal circumference or head circumference, collected at the time of birth. However, assessment of fetal health at birth does not fully capture the timing of changes to fetal growth and development during gestation. Birth weight is not an adequate single predictor of fetal health as birth weight varies by factors such as race and sex [5–7]. Also, low birth weight can result from both growth restriction and preterm birth [8,9], so determining if growth restriction, preterm birth, or a combination played a role is difficult when weight and dimensions of the baby are assessed only at birth.

ESTIMATION OF MATERNAL EXPOSURE TO AIR POLLUTION DURING PREGNANCY

Air pollution is a heterogeneous mixture of particles and gases. People can be exposed to air pollution inside their homes or other buildings (from indoor sources and/or infiltration of outdoor pollutants), in the workplace, outdoors, and commuting. Effects of air pollution exposure on respiratory and cardiovascular health, and more recently on birth outcomes, are well documented [10,11,12▪]. Many studies obtain daily concentrations of air pollutants from outdoor monitors and match them to the dates of the pregnancy, creating overall pregnancy or trimester-specific exposure estimates. Commonly measured outdoor pollutants include ozone (O_3), particulate matter less than 10 and 2.5 micrometers in aerodynamic diameter (PM_{10} and $PM_{2.5}$), carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). Other pollutants of concern include volatile organic compounds and specific components of particles (metals, organics). As an alternative or supplement to pollutant concentrations from outdoor monitors, pollutant exposure during pregnancy can be estimated based on personal or indoor monitoring of the study participants [13]. Other studies evaluate ‘biomarkers’ of pollutant exposure, such as oxidative stress markers in urine or DNA adducts in blood [14,15].

Mechanisms hypothesized for how air pollutant exposure may cause preterm birth or reduce fetal growth include oxidative stress, endocrine disruption, pulmonary and placental inflammation, blood viscosity, and hemodynamic responses [10,16]. During gestation, physiological changes may make the expecting woman more susceptible to air pollution exposures. Compared with a nonpregnant woman, pregnant women experience an approximately 50% increase in alveolar ventilation rate [17]. This allows increased uptake of inhaled pollutants, including fine particulates. Some particulate matter constituents can enter the blood stream. Common gestational complications include development of hemodilutional anemia. This could result in decreased oxygen binding capacity. As CO is a common air pollutant, with higher binding affinity to hemoglobin than oxygen, an increase in CO exposures among pregnant women could reduce the amount of oxygen delivered to the developing fetus. DNA damage and oxidative stress are other potential mechanisms.

Polycyclic aromatic hydrocarbons (PAHs) are a class of compounds related to vehicle emissions that are known carcinogens and DNA damaging agents. Markers of PAH exposure (formation of PAH DNA-adducts in maternal and cord blood) have been studied in relation to adverse birth outcomes [15,18].

ULTRASOUND MEASURES OF FETAL GROWTH

Previous epidemiology literature has relied on birth registry data to assess pregnancy outcomes associated with maternal exposure to air pollutants [3,4,19]. Although this may be useful for evaluating birth weight and preterm birth, a late assessment of growth restriction could potentially introduce bias. Classifying infants as growth-restricted at birth may result in biased effect estimates as a result of misclassification for two major reasons. First, clinical literature specifies that being growth-restricted and small for gestational age are not synonymous [20▪,21]. Second, birth weight as a proxy for fetal growth may not be the best endpoint, as recent literature has shown that birth weight poorly reflects intrauterine growth restriction (IUGR) during the first two trimesters and ignores the possibility that growth impairment affecting long-term health could occur during one time period, but the fetus could continue to grow and achieve population growth standards by birth [5,22].

Recent reviews suggest that reducing the time between exposure and outcome assessment may result in more accurate classifications of growth restriction *in utero* [5,23]. Ultrasound technology is a classic clinical methodology that can be used for assessment of fetal growth during pregnancy. Ultrasonography is widely used in prenatal care to estimate gestational age, assess fetal growth, and determine physical abnormalities and various other vital assessments. In clinical settings, IUGR can be diagnosed with the use of the fetal growth profile, that is, measurements of head circumference, abdominal circumference, femur length, and biparietal diameter (BPD) by ultrasound scans [24]. Identifying growth restriction *in utero* could potentially elucidate specific mechanisms explaining growth restriction related to environmental exposures.

STUDIES OF AIR POLLUTION AND IUGR

To identify epidemiology studies addressing the link between air pollution and IUGR, keyword and reference lists searches using *PubMed* were conducted using the key words ‘air pollution, fetal growth, and ultrasound’. This search identified eight studies examining growth restrictions associated with maternal air pollution exposures during gestation. Six studies, summarized in Table 1 [25–28,29▪▪,30▪▪], covered two categories of outdoor air pollution: ambient, and vehicle-related. Two other studies primarily focused on environmental tobacco smoke [31▪,32] and are not discussed here.

Ambient air pollution and IUGR

The first published study to employ ultrasound scans to measure fetal growth in association with maternal exposure to ambient air pollution was set in France in the prenatal and early postnatal determinants of the child’s development and health study [25]. Maternal exposure to atmospheric NO_2 was examined in relation to changes of in-utero measurements of head circumference. Study participants were recruited from two French maternity hospitals at less

than 24 weeks of gestation. Individual NO_2 exposures were estimated from time of fertilization to the date of each ultrasound exam for 366 women residing within 2 kilometers from the nearest monitor. Adjusted linear and logistic regression models were used to determine head circumference reductions and odds of head circumference reduction at various time periods. Head circumference measurements decreased 3.8 and 3.1 mm between 30 and 34 weeks and at birth, respectively, comparing the highest tertile of NO_2 exposure (NO_2 >31.4 μg/m^3) with the lowest.

In another study in France, 271 nonsmoking pregnant women were recruited from two maternity hospitals at less than 20 weeks of gestation to examine associations between IUGR and airborne benzene exposures [27]. The benzene exposures were estimated with measures from personal diffusive samplers worn for 1 week during the 27th gestational week. Fetal parameters measured during gestation and at birth included head circumference and BPD; BPD being the only parameter measured in each trimester. Adjusted linear regression models showed reductions in mean head circumference during each stage of pregnancy in association with elevated levels of log-transformed benzene exposures, with the greatest reported reduction of 1.9 mm at third trimester and at birth.

In a Brisbane, Australia cohort, associations between fetal ultrasound measurements during mid-pregnancy and ambient air pollution exposure during the first trimester were evaluated. This retrospective study collected 15 623 ultrasound scans from 14 734 Australian pregnancies [26]. The scans were originally collected to create a population specific growth curve, so 84% of the pregnancies had one scan, 13% had two scans, and 3% had three ultrasound scans performed during pregnancy. The final analysis included only the scans of women living within 2 kilometers of pollutant monitors and only scans captured during gestational weeks 13–26; resulting in a varying total of scans (120–510) depending on the pollutant model. Exposure during pregnancy was estimated using air pollution and meteorological data from the Air Services Unit, Queensland Environmental Protection Agency. Utilizing five temperature monitors and 18 ambient air monitors, most within a 30 kilometer radius from Brisbane, hourly concentration readings were obtained for O_3, NO_2, SO_2, and PM_{10}. Daily averages were calculated for PM_{10}, NO_2, and SO_2, whereas an 8 h average was calculated for O_3 and temperature. Ultrasound and air pollutant data were analyzed in a four-stage regression model using generalized estimating equations. Reductions were reported for all parameters among exposed women, with abdominal circumference being associated with most pollutants and reporting the highest decreases (−1.67 mm). Statistically significant reductions in head circumference, BPD, and abdominal circumference associated with NO_2 exposures were seen only in models restricted to women who spent at least 15 h per day at home.

Vehicle-related air pollution and IUGR

The INMA (Environment and Childhood) study in Sabadell, Spain performed a total of 1692 ultrasound examinations measuring all four growth parameters for 562 pregnancies. The majority of the scans were one per woman; however, 3% of the women received three to six ultrasounds [28]. This study measured NO_2 and benzene, toluene, ethylbenzene, *m/p*-xylene, and *o*-xylene (BTEX) as markers of motor vehicle exhaust. Exposure metrics were

calculated using geospatial information systems techniques and land regression modeling to account for intraurban variations in air pollution. The 57 monitoring sites used passive samplers to take 1-week measurements, in three campaigns for NO_2 and four campaigns for BTEX. Pollutant averages were calculated as a proxy for annual mean concentrations. Land cover, topography, population density, roads, and distance to local sources of pollution were used as predictor variables in models estimating outdoor air pollution levels associated with home addresses of the study participants. The models were adjusted for the daily variances in NO_2 concentrations observed at the stationary monitors. Mixed-effect models were used to estimate five windows of fetal exposure: from last menstrual period (LMP) to 12, 20, and 32 weeks of gestation; and average exposures during 12–20 and 20–32 weeks. With these windows of exposure and the exposure models, average cumulative exposures were calculated for each woman during pregnancy. BTEX and NO_2 exposures during weeks 1–12 were associated with unadjusted mean reduction in BPD growth between 20–32 weeks: −0.124 and −0.075 mm per week, respectively. Results were similar for attained fetal size at 32 weeks of gestation.

The INMA study has several cohorts across Spain, including in Valencia. This cohort recruited 855 women; data from 785 were used to examine the association between growth parameters and outdoor NO_2 exposures [30▪▪]. The study design was similar to the Sabadell cohort. However, linear-mixed models fitted to the data revealed associations between higher NO_2 exposures and reductions in fetal parameter attained size at 32 weeks of 9% for all parameters except femur length (6%). Length and head circumference at birth were reduced by 6% among mothers exposed to NO_2 levels above the median (38 $\mu g/m^3$).

The Generation R cohort in the Netherlands consisted of 8880 pregnant mothers followed from years 2001 to 2005. The analysis sample consisted of 7772 women with varying total ultrasound measurements [29▪▪]. Fetal femur length and head circumference were the only ultrasound parameters measured in the Netherlands Generation R study. Femur length was a proxy for total body length and head circumference represented fetal development. Parameters were measured in each trimester. The number of scans per trimester differed because first trimester measurements were restricted to mothers with a normal (28 days) menstrual cycle and a known LMP. This Dutch study assessed individual exposures to PM_{10} and NO_2 at the home addresses of expecting mothers, combining continuous monitoring data and dispersion modeling techniques. Continuous outdoor monitor data was collected using standard methods set by the Netherlands Ministry of Infrastructure and Environment. Multiple linear regression and mixed-effect models were used to assess the relationship between fetal parameters and pollution exposures, both cross-sectionally and longitudinally. A statistically significant reduction of 1.74 mm in third trimester head circumference was associated with the highest quartile PM_{10} exposures. Risk of preterm birth and SGA was also reported.

CONCLUSION

Understanding potential mechanisms by which fetal growth parameters may be negatively associated with air pollutant exposures is critical. The six existing studies estimated exposure to air pollution using data from personal and ambient monitors and other

information. Although some associations between maternal pollution exposure and restricted fetal growth were observed, features of these studies, including examination of different pollutants using different statistical models, hinder comparison of results. Furthermore, the number of studies is limited, thus preventing general conclusions at this stage. We next make comments that may help guide design of future research.

The approach for collection and analysis of ultrasound measurements in these epidemiological studies varied, as did the choice of fetal growth parameters examined. Ultrasound images, like most imaging methods, are prone to measurement error, especially when images taken by multiple ultrasound technicians are used without accounting for possible systematic differences in technique between individuals. Evaluating the potential magnitude and existence of such measurement error is possible with statistical models and by correlation methods. Intrareliability and interreliability assessments should be performed to produce intraclass correlations that measure the agreement of two or more observers measuring the same fetal growth parameters [33–35]. The use of mixed-effect models could also adjust for measurement error, by including an indicator variable for each technician, when reliability is unable to be assessed separately by different technicians measuring the same fetus at the same visit.

A key feature of this research is the hypothesized critical windows of exposure, during which a given pollutant can affect target organs in the developing fetus. Although some authors selected critical windows *a priori*, windows were often simply the periods of gestation in which routine ultrasound scans were taken within that population. Although this is a logical approach, current literature suggests other methods to statistically study windows of susceptibility based on timing of exposure and outcome variables [36].

Accurate assessment of fetal growth, that is, growth rate versus fetal size, is important. When examining changes in fetal growth, repeated ultrasound measurements should be collected for each developing fetus. This may better indicate the rate of change in these parameters and could potentially identify critical windows of exposure. With advanced statistical models, the change in attained size of fetal parameters may also be evaluated at given periods of gestation, so fetal measures should ideally be taken during suspected time windows of particular developmental relevance. The current studies utilizing ultrasound data had repeated measures for 3% or less of their population.

Statistical models used to test associations and which potential confounders were adjusted for varied by study. Common covariates across the studies in Table 1 included maternal age, smoking, prepregnancy weight or BMI, socioeconomic variables, gestational age, and fetal sex. Some models included nutritional measures [29▪▪,30▪▪]. Additional exposure variables included pesticides, paints, noise, temperature, and seasonality [26,27,29▪▪].

Although the studies reviewed here were unable to provide clear linkages between slowed growth in the parameters and specific mechanisms, clinical literature suggests that the reductions in the growth rates of fetal parameters are associated with increased risks of prenatal morbidity and mortality [37]. Further research using repeated ultrasound measures

of fetal parameters is needed to assess changes in fetal growth in response to air pollutant exposures.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 283).

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KEY POINTS

- Maternal exposure to air pollutants can adversely affect pregnancy outcomes.
- Mechanisms explaining air pollution and fetal growth are not accurately illustrated by assessing outcomes only at birth.
- The use of repeated ultrasound measurements to examine fetal growth in association with air pollution exposure during pregnancy can shed light on such mechanisms.

Table 1

Epidemiological studies of associations between air pollution exposure during pregnancy and ultrasound measures of fetal parameters

Reference	Study location	Number of women	Number of ultrasound measurements	Time period of ultrasound measurements	Fetal parameters evaluated[a]	Air pollutants[b]	Air pollutant exposure windows	Summary of key results	Additional covariates[c]
[25]	France	366	2 per pregnancy	Second and third trimester	HC	NO_2	Fertilization – trimester ultrasound exam	Decreases in HC were associated with the highest tertile of NO_2 exposure	Parity, gestational diabetes, and maternity center
[26]	Australia	14 734	1–3 per pregnancy	13–26 weeks of gestation	HC, AC, FL, and BPD	O_3, NO_2, SO_2, and PM_{10}	Monthly; first 4 months of pregnancy	Negative associations between early exposures to pollutants and mean changes in growth parameters during mid-gestation (13–26 weeks)	Concurrent temperature exposures, and seasonality and long-term trend
[27]	France	271	2–3 per pregnancy	Second and third trimester	HC and BPD	Benzene	7 day sampling period	Reductions in BPD and HC associated with log transformed exposures of benzene in second and third trimesters	Urinary cotinine levels, birth order, occupational exposure to paints or pesticides, month of conception, maternal age at end of studies, and center
[28]	Sabadell, Spain	562	1 per pregnancy	12, 20, and 32 weeks of gestation	HC, AC, and BPD	NO_2 and BTEX	LMP until 12, 20, and 32 weeks; 12–20 and 20–32 week averages	Exposure during weeks 1–12 was negatively associated with BPD growth in weeks 20–32	Season of conception, parity

Reference	Study location	Number of women	Number of ultrasound measurements	Time period of ultrasound measurements	Fetal parameters evaluated[a]	Air pollutants[b]	Air pollutant exposure windows	Summary of key results	Additional covariates[c]
[29▪▪]	Netherlands	7772	3 per pregnancy	First, second and third trimester	HC and FL	NO_2 and PM_{10}	Conception – trimester ultrasound exam	NO_2 and PM_{10} exposures during pregnancy were inversely associated with HC and FL at various stages of gestation.	Parity, folic acid supplementation use, alcohol consumption, paternal height, and road traffic noise exposure
[30▪▪]	Valencia, Spain	785	3 per pregnancy	12, 20, and 32 weeks of gestation	BPD, AC, and FL	NO_2	0–12, 12–20, 20–32, 32–delivery; 0–20 and 0–32 week avg.	Adverse effects on fetal parameters were higher in association with NO_2 exposure in earlier stages of pregnancy	Maternal gestational weight gain, country of origin, zone of residence, parity, alcohol, caffeine, vegetable, fruit and energy intake and season of conception

LMP, last menstrual period.

[a] Fetal parameters: head circumference (HC), abdominal circumference (AC), femur length (FL), and biparietal diameter (BPD).

[b] Air pollutants: nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), particulate matter less than 10 μm aerodynamic diameter (PM_{10}), and benzene, toluene, ethylbenzene, *m*/*p*-xylene, and *o*-xylene compounds (BTEX).

[c] Common covariates included maternal age, smoking, SES measures, weight/BMI, and fetal sex.