Science of the Total Environment 650 (2019) 2641–2647

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Ambient air pollution and fetal growth restriction: Physician diagnosis of fetal growth restriction versus population-based small-for-gestational age

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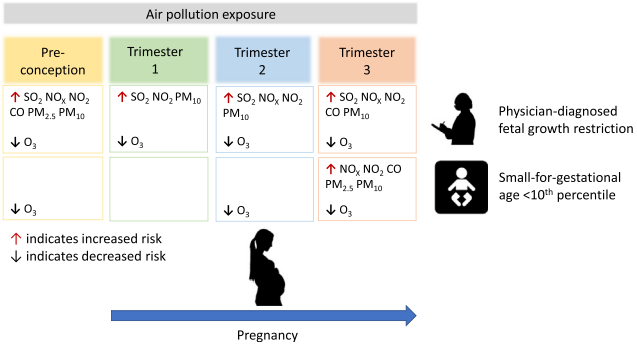
HIGHLIGHTS

- Small-for-gestational age (SGA) is a common proxy of fetal growth restriction (FGR).
- We found air pollution increased the risk for physician-diagnosed FGR.
- However, SGA was generally not associated with air pollution.
- Diagnosed FGR was a more sensitive indicator of risk associated with air pollution.
- Studies incorporating SGA may miss risks to fetal growth related to air pollution.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 17 May 2018
Received in revised form 24 August 2018
Accepted 28 September 2018
Available online 03 October 2018

Editor: Wei Huang

Keywords:
Ambient air pollution
Fetal growth restriction
Small-for-gestational age

ABSTRACT

Background: Ambient air pollution may affect fetal growth restriction (FGR) through several mechanisms. However, prior studies of air pollution and small-for-gestational age (SGA), a common proxy for FGR, have reported inconsistent findings.
Objective: We assessed air pollution in relation to physician-diagnosed FGR and population-based SGA in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Consecutive Pregnancy Study (2002−2010).
Methods: Among 50,005 women (112,203 singleton births), FGR was captured from medical records and ICD-9 codes, and SGA determined by population standards for birthweight <10th, <5th and <3rd percentile. Community Multiscale Air Quality models estimated ambient levels of seven criteria pollutants for whole pregnancy, 3-months preconception, and 1st, 2nd and 3rd trimesters. Generalized estimating equations with robust standard errors accounted for interdependency of pregnancies within participant. Models adjusted for maternal age, race/ethnicity, pre-pregnancy body mass index, smoking, alcohol, parity, insurance, marital status, asthma and temperature.

Abbreviations: FGR, fetal growth restriction; SGA, small-for-gestational age; LBW, low birthweight; ICD9, International Classification of Diseases-9; CMAQ, Community Multiscale Air Quality Model; SO_2, sulfur dioxide; O_3, ozone; NO_X, nitrogen oxides; NO_2, nitrogen dioxide; CO, carbon monoxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; IQR, interquartile range; RR, relative risk; CI, confidence interval.

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https://doi.org/10.1016/j.scitotenv.2018.09.362
0048-9697/

Results: FGR was diagnosed in 1.5% of infants, and 6.7% were <10th, 2.7% <5th and 1.5% <3rd percentile for SGA. Positive associations of SO_2, NO_2 and PM_{10} and negative associations of O_3 with FGR were observed throughout preconception and pregnancy. For example, an interquartile increase in whole pregnancy SO_2 was associated with 16% (95% CI 8%, 25%) increased FGR risk, 17% for NO_2 (95% CI 9%, 26%) and 12% for PM_{10} (95% CI 6%, 19%). Associations with SGA were less clear.
Conclusions: Chronic exposure to air pollution may be associated with FGR but not SGA in this low-risk population.

1. Introduction

Fetal growth restriction (FGR), the failure of a fetus to reach its full growth potential, is a condition of pregnancy associated with both short- and long-term morbidity (American College of Obstetricians and Gynecologists, 2013). It can occur when the fetus does not receive adequate nutrients and oxygen from maternal circulation. The exact pathology leading to growth restriction from placenta origin is not exactly known, although it may be associated with inadequate trophoblast invasion and subsequent impaired uterine-placental perfusion as evidenced by growth restriction associated with hypertensive disorders of pregnancy (Mifsud and Sebire, 2014; Salafia et al., 2006). Growth-restriction is associated with a higher risk of stillbirth (Pilliod et al., 2017) and neonatal complications (Pallotto and Kilbride, 2006), as well as long-term outcomes including cognitive delays during childhood (Murray et al., 2015) and development of obesity, type 2 diabetes and cardiovascular disease in adulthood (Crispi et al., 2018; Eriksson et al., 2003). In epidemiologic and clinical research, FGR is often estimated based on small-for-gestational age (SGA), defined as falling below the 10th percentile for birthweight dependent on gestational age. Although FGR and SGA are frequently used interchangeably, they have different meanings. SGA includes constitutionally small but healthy infants and not all infants with FGR will meet criteria for SGA. Distinguishing FGR from SGA remains a pressing challenge in both research and clinical practice (Zhang et al., 2010).

In clinical practice, initial screening for FGR can be accomplished non-invasively using fundal height, the distance from top of the uterus to the pelvic bone, which maps closely with gestational age (American College of Obstetricians and Gynecologists, 2013). When there is a discrepancy in fundal height of >3 cm, estimated fetal weight < 10th percentile based on ultrasound can be used to determine the need for additional screening and management (American College of Obstetricians and Gynecologists, 2013). Fetal growth is also typically monitored with serial ultrasounds in pregnancies at high risk for FGR. Although growth restriction during pregnancy can be managed through early delivery in cases where the intrauterine environment may cause more harm than prematurity (American College of Obstetricians and Gynecologists, 2013; McCowan et al., 2018), there are currently no validated treatment options to improve the flow of nutrients and oxygen to the fetus after diagnosis (Groom and David, 2018). Primary prevention is therefore key to reducing the health effects associated with FGR.

Exposure to ambient air pollution has been associated with both adverse pregnancy events (Pedersen et al., 2014; Siddika et al., 2016) and potential mechanisms underlying the pathology of fetal growth restriction. As air pollution exposure leads to increases in systemic inflammation and oxidative stress, it may affect fetal growth through various mechanisms including changes in placental volume and blood flow (Hettfleisch et al., 2017), induction of epigenetic changes in placental and fetal tissue (Cai et al., 2017; Kingsley et al., 2016) and alteration of placental mitochondrial content (Janssen et al., 2012).

Prior epidemiologic research evaluating the association of air pollution with growth restriction has been inconsistent. Most studies have employed surrogate assessments for fetal growth, using either SGA or low birthweight (LBW), which may incorrectly classify infants with FGR. While several studies have found an association between ambient air pollution and smaller birthweight (Le et al., 2012; Li et al., 2017; Smith et al., 2017), several other studies have not (Hannam et al., 2014; Lavigne et al., 2016), with little discernable differences in methodologic approaches or magnitude of air pollution exposure. One factor that may contribute to this inconsistency in findings is misclassification of FGR infants by categorizing infants as SGA and/or LBW. To address this potential source of misclassification in prior research, we evaluated the association of air pollution with physician diagnosis of FGR, as well as the consistency of these findings with the association of air pollution with SGA.

2. Methods

The Consecutive Pregnancy Study included 51,086 mothers with two or more deliveries at ≥20 weeks gestation between 2002 and 2010 in one of the 20 hospitals within Utah's Intermountain Health Care system. Details of the study have been described elsewhere (Laughon et al., 2014). Briefly, information on demographics, reproductive and prenatal history, current pregnancy and labor and delivery outcomes were abstracted from the antepartum and labor and delivery summary electronic medical records. Each delivery was linked to International Classification of Diseases-9 (ICD9) codes from maternal and newborn discharge summaries. We excluded multiple pregnancies and participants who did not deliver at least two singleton pregnancies.

2.1. Air pollution assessment

Air pollution was assessed for each hospital referral region using modified Community Multiscale Air Quality (CMAQ) models (Foley et al., 2010). Inputs included meteorologic data derived from the Weather Research and Forecasting model, emission data generated from the United States Environmental Protection Agency National Emissions Inventory and photochemical properties of pollutants. Hourly air pollution levels were estimated for seven criteria air pollutants: sulfur dioxide (SO_2), ozone (O_3), nitrogen oxides (NO_X), nitrogen dioxide (NO_2), carbon monoxide (CO), particulate matter <10 μm (PM_{10}) and particulate matter <2.5 μm ($PM_{2.5}$) and output for 12 × 12 kilometer grid cells. For grid cells that had monitor data available, CMAQ estimates were fused with inverse-distance weighted monitor data to correct for potential measurement misclassification. To improve precision, merged estimates were weighted to reflect population density within the hospital referral region. Incorporation of inverse-distance weighted monitoring data and weighting for population density significantly improved model performance, with details on model performance published elsewhere (Chen et al., 2014). Briefly, the CMAQ models, which do not incorporate monitoring data, provide air pollution estimates across the continental United States, even in areas where monitoring was sparse. In model validation, it was found that for several air pollutants, including CO, SO_2 and $PM_{2.5}$, that CMAQ modeled estimates and averaged ambient air estimates from nearby monitoring stations were different, with fused estimates leading to significant improvements in model performance.

Air pollution estimates were averaged over five windows of exposure: 3-months preconception, whole pregnancy, first trimester, second trimester and third trimester. We additionally assessed a moving 6-week average exposure from 20 weeks gestation through delivery. Finally, to characterize change in air pollution level from the first to the