Environmental Research 137 (2015) 316–322

Contents lists available at ScienceDirect

Environmental Research

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

Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus

Candace A. Robledo [a], Pauline Mendola [a,*], Edwina Yeung [a], Tuija Männistö [a], Rajeshwari Sundaram [b], Danping Liu [b], Qi Ying [c], Seth Sherman [d], Katherine L. Grantz [a]

[a] *Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Division of Intramural Population Health Research, Epidemiology Branch, Rockville, MD 20892, USA*
[b] *Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Division of Intramural Population Health Research, Biostatistics and Bioinformatics Branch, Rockville, MD 20892, USA*
[c] *Texas A&M University, Zachary Department of Civil Engineering, College Station, TX 77845, USA*
[d] *The EMMES Corporation, Rockville, MD 20852, USA*

ARTICLE INFO

Article history:
Received 29 August 2014
Received in revised form
23 December 2014
Accepted 24 December 2014

Keywords:
Preconception
Pregnancy
Air pollution
Gestational diabetes

ABSTRACT

Background: Air pollution has been linked to gestational diabetes mellitus (GDM) but no studies have evaluated impact of preconception and early pregnancy air pollution exposures on GDM risk.

Methods: Electronic medical records provided data on 219,952 singleton deliveries to mothers with (n=11,334) and without GDM (n=208,618). Average maternal exposures to particulate matter (PM) $\leq$ 2.5 µm ($PM_{2.5}$) and $PM_{2.5}$ constituents, PM $\leq$ 10 µm (PM_{10}), nitrogen oxides (NO_x), carbon monoxide, sulfur dioxide (SO_2) and ozone (O_3) were estimated for the 3-month preconception window, first trimester, and gestational weeks 1–24 based on modified Community Multiscale Air Quality models for delivery hospital referral regions. Binary regression models with robust standard errors estimated relative risks (RR) for GDM per interquartile range (IQR) increase in pollutant concentrations adjusted for study site, maternal age and race/ethnicity.

Results: Preconception maternal exposure to NO_X (RR=1.09, 95% CI: 1.04, 1.13) and SO_2 (RR=1.05, 1.01, 1.09) were associated with increased risk of subsequent GDM and risk estimates remained elevated for first trimester exposure. Preconception O_3 was associated with lower risk of subsequent GDM (RR=0.93, 0.90, 0.96) but risks increased later in pregnancy.

Conclusion: Maternal exposures to NO_x and SO_2 preconception and during the first few weeks of pregnancy were associated with increased GDM risk. O_3 appeared to increase GDM risk in association with mid-pregnancy exposure but not in earlier time windows. These common exposures merit further investigation.

Published by Elsevier Inc.

1. Introduction

Exposure to air pollution during pregnancy has been shown to adversely impact birth outcomes (Shah and Balkhair, 2011; Sram et al., 2005) and may also affect maternal health during pregnancy and over the life course (Kampa and Castanas, 2008; Basile and Bloch, 2012). Epidemiological studies have linked air pollution to type 2 diabetes prevalence,(Brook et al., 2008) incidence (Kramer et al., 2010; Coogan et al., 2012) and mortality in non-pregnant women (Raaschou-Nielsen et al., 2013). Type 2 diabetes and GDM share some common risk factors and both are characterized by insulin resistance and impaired insulin secretion (Ben-Haroush et al., 2004). Approximately 50% of women experiencing GDM will develop type 2 diabetes within 5 years of the affected pregnancy, with pregnancy thought to unmask underlying beta cell dysfunction in susceptible women (American Diabetes Association, 2003). Although the biologic mechanisms that link air pollution to the development of diabetes are still unclear, one pathway may be systemic inflammation that results in metabolic dysfunction (Rajagopalan and Brook, 2012). Furthermore, obesity and overnutrition, risk factors for the development of diabetes, may render

---

Abbreviations: AQRH, Air Quality and Reproductive Health Study; BMI, body mass index; CI, confidence interval; CMAQ, Community Multi-scale Air Quality Model; CO, carbon monoxide; CSL, Consortium on Safe Labor Study; EPA, US Environmental Protection Agency; GDM, gestational diabetes mellitus; LMP, last menstrual period; PM10, particulate matter $\leq$ 10 µm; PM2.5, fine particulate matter $\leq$ 2.5 µm; RR, relative risk; O_3, ozone; NO_X, nitrogen oxides; SO_2, sulfur dioxides

[*] Correspondence to: Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Blvd, Room 7B13E, Rockville, MD 20852, USA. Fax: +301 402 2084.
E-mail address: pauline.mendola@mail.nih.gov (P. Mendola).

http://dx.doi.org/10.1016/j.envres.2014.12.020
0013-9351/Published by Elsevier Inc.

women more susceptible to the effects of air pollution (Sun et al., 2009) and also promote the development of GDM during pregnancy.

Recent studies have linked air pollutants to GDM (Malmqvist et al., 2013) and abnormal glucose tolerance during pregnancy (Fleisch et al., 2014) but exposure assessments were limited to one or two pollutants occurring during the first and/or second trimester of pregnancy. The objectives of the present study were to investigate the association between criteria air pollutants regulated by the US Environmental Protection Agency (EPA) and the risk of GDM in a contemporary obstetric cohort in the US. Exposure estimates were based on modified Community Multiscale Air Quality models that allowed for complete coverage of the study areas (Chen et al., 2014). Since GDM is typically diagnosed in the mid-late second trimester and may be a function of underlying maternal vulnerability, we chose to expand the time windows studied to include the 3 months prior to conception, the first and second trimesters and each gestational week of pregnancy from 1 to 24 in order to identify critical windows of exposure for GDM risk.

2. Methods

2.1. Study design, participants and outcome measurement

The Consortium on Safe Labor (CSL) was a retrospective cohort study of labor and delivery in the US conducted between 2002 and 2008 based in 12 clinical centers (with 19 hospitals) across 15 hospital referral regions. The study design and characteristics of subjects have been previously described in detail (Zhang et al., 2010). The names and locations of centers can be found in the acknowledgments. Briefly, participating hospitals had obstetric electronic medical records (EMRs) by design that allowed clinical data to be captured into pre-specified fields. This allowed uniform data collection strategies across study sites. Unlike administrative data, the use of EMRs in this study were a direct source of data rich in clinical and demographic details. Institutional review board approval was obtained from all participating institutions.

Data from EMRs of mothers and infants were obtained for 228,562 deliveries among 208,695 women and linked to hospital discharge records. The present analysis was restricted to singleton pregnancies without pregestational diabetes ($n=220{,}264$). Data were obtained on maternal characteristics including age, race/ethnicity, parity, marital status, type of insurance and pre-pregnancy body mass index (BMI). Since age was retained in the final model, we excluded women with missing data ($n=302$). Ten singleton pregnancies with preconception time windows prior to 2002 were also excluded because exposure models only covered the main study years. Analyzes were conducted using data on the remaining singleton pregnancies ($n=219{,}952$) among 201,015 women.

While the information captured does not contain specific glucose screening methods, in the US, a 1 h/50 g oral glucose challenge test is routinely administered between 24 and 28 weeks gestation to screen pregnant women for GDM (American Diabetes Association, 2003). If blood glucose is found to be between 135 and 199 mg/dl, women undergo a 3 h/100 g oral glucose challenge test for diagnosis of GDM (Metzger and Coustan, 1998). GDM was recorded in the medical record or in discharge records (code 648.8) using the International Classification of Diseases, Ninth Revision.

2.2. Air pollution measurements

The Air Quality and Reproductive Health (AQRH) study linked pregnancies from the CSL to air pollutant exposures estimated using a modified Community Multi-scale Air Quality Model (CMAQ) version 4.7.1 (Community Multiscale Air Quality Overview, 2013; Foley et al., 2009). Since the CSL data are anonymous, maternal exposures are based on the average air pollutant levels for her delivery hospital referral region during each of the defined exposure windows (The Dartmouth Atlas of Health Care, 2013). The size of hospital referral regions ranged from 415 to 312,644 km^2. Observed data from air quality monitors in the EPA Air Quality System were used to correct estimates predicted with the CMAQ using an inverse distance weighting technique. Average hourly exposure estimates for each hospital referral region were weighted for population density to discount exposure in places where women were unlikely to live or work. This technique for generating average pollutant concentrations for the study population is described in detail elsewhere (Chen et al., 2014). Briefly, the CMAQ is a three-dimensional multi-pollutant air quality model developed by the EPA. The CMAQ predicts ambient pollutant levels using emissions and meteorological data (including temperature, relative humidity and wind characteristics) from the National Emission Inventories and from the Weather Research and Forecasting Model, respectively. Our final pollution prediction model was compared with four other exposure assessment methods, including observed data only, and found to best account for the spatial variation in pollutant concentrations and population density across hospital referral regions (Chen et al., 2014).

Hourly exposure estimates for each pollutant were averaged across the pregnancy exposure windows for each woman based on her last menstrual period (LMP). Since routine screening for GDM generally occurs in the second trimester (24–28 weeks) and preliminary analyzes showed no association between mean levels of air pollutants across the whole second trimester average and GDM risk (data not shown), we focused on exposure windows prior to this time period. This analysis includes a preconception period window (91 days prior to last menstrual period (LMP), a first trimester average (LMP through 13 weeks of gestation) and weekly averages for gestational weeks 1 through 24. Criteria air pollutants, particulate matter (PM) with aerodynamic diameter ≤ 2.5 μm in μg/m^3 (PM$_{2.5}$) and ≤ 10 μm in μg/m^3 (PM$_{10}$), nitrogen oxides (NO$_x$ in parts per billion (ppb)), carbon monoxide (CO in ppm), sulfur dioxide (SO$_2$ in ppb) and ozone (O$_3$ in ppb) were estimated in each exposure window. Modeled ambient levels of PM$_{2.5}$ constituents (μg/m^3) were also estimated and included elemental carbon, organic compounds, ammonium ion, sulfate, nitrate and dust components.

2.3. Statistical analyses

Descriptive statistics summarized demographic characteristics and air pollution exposure for the analytic cohort of pregnancies with ($n=11{,}334$) and without GDM ($n=208{,}618$). Examination of the association between air pollution exposure quartiles on GDM risk in regression models suggested a linear relationship. Therefore, in regression models the pollutant concentrations were modeled in their original scale for ease of interpretation. Spearman rank correlations between each of the pollutants were calculated (Supplemental Table 1). Binary regression models with the log link function were fitted to estimate relative risks (RR) for GDM per interquartile range (IQR) increase for each air pollutant. The 95% confidence intervals (CI) were calculated using robust standard errors. A first order autoregressive covariance structure was used to account for within-cluster correlation for women with more than one singleton pregnancy during the study period. Separate models were created for air pollutants during each exposure window, including each gestational week from 1 to 24.

Models for constituents of fine particulate matter were