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Ozone and hypertensive disorders of pregnancy in Florida: Identifying critical windows of exposure

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ABSTRACT

Introduction: Ozone (O_3) has been linked to hypertensive disorders of pregnancy (HDP). However, inconsistent results have been reported, and no study has examined the critical exposure windows during pregnancy.

Materials and methods: We used Florida birth vital statistics records to investigate the association between HDP and O_3 exposure among 655,529 pregnancies with conception dates between 2005 and 2007. Individual O_3 exposure was assessed at mothers' home address at the time of delivery using the Hierarchical Bayesian space-time statistical model. We examined the association during three predefined exposure windows including trimester 1, trimester 2, and trimesters 1 & 2, as well as in each week of the first two trimesters using distributed lag models.

Results: Pregnancies with HDP had a higher mean exposure to O_3 (39.07 in trimester 1, 39.02 in trimester 2, and 39.06 in trimesters 1 & 2, unit: ppb) than those without HDP (38.65 in trimester 1, 38.57 in trimester 2, and 38.61 in trimesters 1 & 2, unit: ppb). In the adjusted logistic regression model, increased odds of HDP were observed for each 5 ppb increase in O_3 ($OR_{Trimester1}$=1.04, 95% CI: 1.03, 1.06; $OR_{Trimester2}$=1.03, 95% CI: 1.02, 1.04; $OR_{Trimester1\&2}$=1.07, 95% CI: 1.05, 1.08). In the distributed lag models, elevated odds of HDP were observed with increased O_3 exposure during the 1st to 24th weeks of gestation, with higher odds during early pregnancy.

Conclusions: O_3 exposure during pregnancy is related to increased odds of HDP, and early pregnancy appears to be a potentially critical window of exposure.

1. Introduction

Hypertensive disorders of pregnancy (HDP) are among the most common medical problems encountered during pregnancy, affecting up to 10% of all pregnancies (Duley, 2009; Miller and Carpenter, 2015). HDP is typically classified into four categories, including chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension (National High Blood Pressure Education Program, 2000). HDP is characterized by high blood pressure, usually after 20 weeks of gestation, as a result of higher cardiovascular burden caused by significant changes in blood volume and other physiologic characteristics during pregnancy (Yoder et al., 2009). It is considered a risk factor for neonatal and maternal morbidity and mortality (Allen et al., 2004; Bauer and Cleary, 2009; Bellamy et al., 2007; Duley, 2009; Lo et al., 2013; Wang et al., 2012; Wu et al., 2009). In the United States, preeclampsia alone contributes to about 25% of all medically indicated preterm deliveries (Ananth and Vintzileos, 2006; Goldenberg et al., 2008; Romero et al., 2014). Despite serious consequences, the biological mechanisms underlying HDP remain to be determined. Known risk factors for HDP include maternal characteristics such as nulliparity, obesity, advanced maternal age, adolescent pregnancy, pre-pregnancy hypertension or diabetes mellitus; and pregnancy-related factors such as multiple gestation, placental abnormalities, weight gain, gestational diabetes mellitus (GDM), family history of pre-eclampsia as well as African American race (Wolf et al., 2004). To reduce the continuously increasing incidence of HDP (Wallis et al., 2008), a better understanding of modifiable risk factors for HDP is needed to guide intervention efforts.

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Ambient air pollution has been linked to hypertension in the general population (Coogan et al., 2012; Dong et al., 2013; Foraster et al., 2014), and recent studies suggested a potential link between pregnancy air pollution exposure and HDP (Hu et al., 2014). Pregnant women experience higher cardiovascular burden given the fast and sudden change in blood volume (Ouzounian and Elkayam, 2012) as well as other physiologic characteristics, making them a potentially high-risk subpopulation. Furthermore, air pollution has been shown to have toxicological effects such as increasing circulating markers of oxidative stress, lipid peroxidation and inflammation (Ghio et al., 2012; Lee et al., 2011; Nagiah et al., 2015; Slama et al., 2008), all of which are associated with cardiovascular effects including hypertensive disorders of pregnancy (Fenzl et al., 2013; Sánchez-Aranguren et al., 2014; Zusterzeel et al., 2002). As a result, there are concerns that air pollution may also play a role in the development of HDP (Hu et al., 2014; Malmqvist et al., 2013).

Ozone (O_3) is the air pollutant of great concern to the state of Florida (Florida Department of Environmental Protection, 2012), and recent meta-analyses of existing studies on ozone and HDP suggest an overall positive association (Hu et al., 2014; Pedersen et al., 2014). However, results are still inconsistent among individual studies. Several important limitations exist from the current state of the literature. First, exposure assessment in many studies relied on sparsely located stationary air monitors (Mobasher et al., 2013; Olsson et al., 2013; van den Hooven et al., 2011; Vinikoor-Imler et al., 2012; Xu et al., 2013; Zhai et al., 2012). The poor spatial resolution resulting from this method limits the ability to adequately capture the spatial contrasts in O_3 levels, leading to increased exposure misclassification bias. In addition, participants living far away from these monitors are routinely excluded from the analyses leading to potential selection bias. Other studies used traffic density and distance from major roads as a proxy for exposure to pollution, which may also introduce substantial exposure misclassification bias (van den Hooven et al., 2009). Second, critical exposure windows to O_3 have not been established for HDP. Identification of such window is needed to improve the understanding of the underlying biological mechanisms between O_3 and HDP and to help inform the design and implementation of targeted and effective preventive strategies.

To address these limitations, we used the data from the EPA and CDC's National Environmental Public Health Tracking Network (U.S. EPA, 2014) to assess daily ambient O_3 levels, and linked it to the Florida Vital Statistics Birth Record dataset to investigate the association between HDP and O_3 among all eligible women residing in Florida with conception dates between January 1, 2005 and December 31, 2007. More importantly, we assessed potential critical pregnancy windows for O_3 exposure using a distributed lag model to reduce the influences of autocorrelation and collinearity in weekly O_3 exposure.

2. Methods

2.1. Study sample

Birth record data were obtained from the Bureau of Vital Statistics, Office of Health Statistics and Assessment, Florida Department of Health (http://www.floridahealth.gov/certificates/certificates/, Jacksonville, Florida). The data included all registered live births in Florida between January 1, 2005 and December 31, 2008 (n=917,788). Women with residential addresses outside Florida (n=4632) were excluded. Mother's residential address at delivery was initially geocoded by Florida Department of Health using ArcGIS v10.1, and 864,247 records (94.6%) were successfully geocoded. We further geocoded the addresses that failed to be geocoded by DOH using the Google Maps API (Application Programming Interface) by "ggmap" package in R, and a total of 913,048 records (99.9%) were successfully geocoded. Women whose residential address could not be geocoded after the second phase were excluded (n=108). To avoid fixed cohort bias (Strand et al., 2011), women were included based on their conception date instead of delivery date. Conception date was back calculated using delivery date and gestational age which was mainly determined by ultrasound. When ultrasound data was not available, clinical examination or last menstrual period was used to estimate gestational age. Among the 913,048 women who delivered during 2005–2008, a total of 691,011 women had the conception date between January 1, 2005 and December 31, 2007. In addition, women were excluded if they had non-singleton deliveries (n=21,609) or pre-pregnancy hypertension (n=10,590). Women whose births had a birthweight < 500 g or > 5000 g (n=621), or with a gestational age < 26 weeks (n=2662) were also excluded, leaving a total of 655,529 women in the final analyses.

2.2. Outcome assessment

During the collection of Vital Statistics Birth Record data, medical history of each woman was recorded, and diagnoses of pre-pregnancy hypertension, gestational hypertension or preeclampsia, and eclampsia were abstracted for analyses. Gestational hypertension was determined as onset of hypertension after 20 weeks of pregnancy, and preeclampsia was defined as the new onset of hypertension and proteinuria after 20 weeks of gestation. Eclampsia was determined by the presence of preeclampsia in addition to the onset of convulsions. Similar to previous environmental studies on HDP (Hu et al., 2014), the restricted definition of HDP was used, which included gestational hypertension, preeclampsia, or eclampsia. We assessed them aggregately as HDP for two reasons: 1) we were not able to distinguish between gestational hypertension and preeclampsia since the Florida Vital Statistics Birth Record data aggregated them together; and 2) potential differences in disease coding and diagnosis may exist since increased gestational hypertension and reduced mild preeclampsia and eclampsia are compensated more (Savitz et al., 2015).

2.3. Ozone exposure assessment

O3 data were obtained from the EPA and CDC's National Environmental Public Health Tracking Network (U.S. EPA, 2014), which were estimated using the hierarchical Bayesian space-time statistical model (HBM) during 2001–2008 with a daily temporal resolution and a spatial resolution of 12 km×12 km across the continental areas in the US (McMillan et al., 2010). The HBM approach combines the Air Quality System monitoring data with the Community Multiscale Air Quality modeled data, which includes emission, meteorology, and chemical modeling components, to predict air quality data for a specific time period and spatial scale (McMillan et al., 2010). Each woman's geocoded residential address at the time of delivery was spatially linked to the corresponding grid of the HBM data. Exposures were calculated as daily concentrations averaged over each of the first two trimesters (trimester 1: 1–13 weeks and trimester 2: 14–26 weeks) and over both the first and second trimesters (1–26 weeks) determined by gestational age and delivery date of each woman. In addition, weekly average levels of O_3 exposure during the first and second trimesters were calculated to assess the critical windows of exposure during pregnancy.

2.4. Covariates

Information on maternal characteristics such as age, race/ethnicity, education, marital status, pregnancy smoking status, pre-pregnancy body mass index (BMI), pre-pregnancy diabetes, parity, season and year of conception were obtained directly from the births records. Maternal age at delivery was categorized into six groups, with 5-year increments for women aged 20–40 years old as well as two additional groups for < 20 and ≥ 40 years old. Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, and others. In