Preterm birth and air pollution: Critical windows of exposure for women with asthma

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Background: Ambient air pollutants may increase preterm birth (PTB) risk, but critical exposure windows are uncertain. The interaction of asthma and pollutant exposure is rarely studied.

Objective: We sought to assess the interaction of maternal asthma and air pollutant exposures in relation to PTB risk.

Methods: Electronic medical records for 223,502 US deliveries were linked with modified Community Multiscale Air Quality model outputs. Logistic regression with generalized estimating equations estimated the odds ratio and 95% CIs for PTB on the basis of the interaction of maternal asthma and particulate matter with aerodynamic diameter of less than 2.5 microns and particulate matter with aerodynamic diameter of less than 10 microns, ozone (O_3), nitrogen oxides (NO_x), sulfur dioxide (SO_2), and carbon monoxide (CO) per interquartile range. For each gestational week 23 to 36, exposures among women who delivered were compared with those remaining pregnant. Three-month preconception, whole pregnancy, weeks 1 to 28, and the last 6 weeks of gestation averages were also evaluated.

Results: On assessing PTB by gestational week, we found that significant asthma interactions were sporadic before 30 weeks but more common during weeks 34 to 36, with higher risk among mothers with asthma for NO_x, CO, and SO_2 exposure and an inverse association with O_3 in week 34. Odds of PTB were significantly higher among women with asthma for CO and NO_x exposure preconception and early in pregnancy. In the last 6 weeks of pregnancy, PTB risk associated with particulate matter with aerodynamic diameter of less than 10 microns was higher among women with asthma.

Conclusions: Mothers with asthma may experience a higher risk for PTB after exposure to traffic-related pollutants such as CO and NO_x, particularly for exposures 3-months preconception and in the early weeks of pregnancy. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

***Key words:** Asthma, pregnancy, preterm birth, air pollution*

Environmental factors that contribute to adverse pregnancy outcomes have received considerable attention, and the current literature regarding the risk of preterm birth at less than 37 weeks' gestation is well summarized in several recent review articles.[1-5] Overall, the evidence for higher preterm birth risk associated with ambient air pollution is mixed, but third-trimester exposure to carbon monoxide (CO) and particulate matter with aerodynamic diameter of <10 microns (PM_{10}) was significantly associated with a higher preterm birth risk in a recent meta-analysis.[2] Other summaries and pooled estimates suggested significantly higher risks associated with a range of exposure windows for particulate matter with aerodynamic diameter of less than 2.5 microns ($PM_{2.5}$)[3,4] and sulfur dioxide (SO_2).[3] Air toxics, particularly polycyclic aromatic hydrocarbons, may also be related to early delivery.[1]

Despite the effort in this area,[6] no etiologically relevant critical exposure time-window for ambient air to influence preterm birth risk has been determined and the varied time windows make comparisons between studies more difficult. A wide range of air pollution exposure estimates have been used, ranging from whole pregnancy averages,[7-9] trimester-specific results[8-12] to months[13] or weeks[14-16] before delivery. Several studies evaluated multiple windows[9,17-19] and in some early studies, the relevant windows were unclear.[7] Heterogeneity in study design and exposure metrics may be part of the issue behind the lack of consistency in findings across studies.[20,21]

Further adding to the complexity is the likelihood that pregnant women are not uniformly susceptible to the impact of air pollutants and women with asthma may be particularly vulnerable. Asthma exacerbation and perhaps incidence are related to poor air quality.[22] Asthma prevalence is estimated to be more than 9% among American women,[23] and maternal asthma is a well-known risk factor for preterm birth,[24] a finding also observed in our data.[25] A study of birth records from 1988 to 2006, conducted in Stockholm, Sweden, found significant preterm birth risks for mothers with and without asthma associated with first-trimester ozone (O_3) exposure, but observed no main effect or interaction with asthma for first-trimester nitrogen oxides (NO_x) exposure.[26] Other susceptible subpopulations such as the elderly or diabetic persons appear to respond differentially to exposure,[27] but air

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This research was supported by the Intramural Research Program of the National Institutes of Health, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), including funding for the Consortium on Safe Labor (Contract No. HHSN267200603425C) and the Air Quality and Reproductive Health Study (Contract No. HHSN2752008000021, Task Order No. HHSN27500008). This article has been cleared for publication by the NICHD, but the funding source had no role in the design, analysis, interpretation, or writing of the manuscript.

Disclosure of potential conflict of interest: T. Männistö has received grants from Laboratoriolääketieteen edistämissäätiö and Paulo Foundation.

Received for publication June 8, 2015; revised November 13, 2015; accepted for publication December 1, 2015.

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0091-6749
http://dx.doi.org/10.1016/j.jaci.2015.12.1309

Abbreviations used
CO: Carbon monoxide
NO_x: Nitrogen oxides
O_3: Ozone
PM_{10}: Particulate matter with aerodynamic diameter of less than 10 microns
$PM_{2.5}$: Particulate matter with aerodynamic diameter of less than 2.5 microns
SO_2: Sulfur dioxide

pollution effects have also been muted among individuals with preexisting disease.[28] Given that the worldwide impact of asthma on the lives of young women continues to increase[29] and challenges to control air pollution remain, whether pregnant women with asthma are also a susceptible subpopulation is an important avenue for investigation.

To address these data gaps, we evaluated the impact of exposure to criteria air pollutants on the week-by-week risk of preterm birth and for a range of exposure windows in a large, contemporary US obstetric cohort of women with and without asthma.

METHODS

Study population

Gestational age, maternal demographics, medical, reproductive, and prenatal history, and a summary of labor and delivery information were ascertained in the Consortium on Safe Labor (2002-2008).[30] This retrospective cohort of births at 23 weeks' gestation or more was assembled using electronic medical records from 12 centers (19 hospitals) across the United States (Fig 1). The cohort included 228,562 deliveries with 233,736 newborns, with 87% of births occurring during 2005 to 2007. We excluded multifetal pregnancies (n = 5,050) and pregnancies missing air quality data (n = 10), resulting in an analytic sample of 223,502 singleton pregnancies among 204,175 women. Most women (185,785 [91.0%]) contributed only 1 pregnancy. The Consortium on Safe Labor was approved by the institutional review boards of all participating institutions. Data collection and validation have been previously described.[30]

Outcome and covariates

All outcome and covariate data were derived from electronic delivery records and supplemented with International Classification of Diseases, 9th Revision codes in the hospital discharge summaries. Preterm birth was defined using the best clinical gestational age recorded in the medical record. Births at each week from 23 to 36 weeks of gestation were compared to ongoing pregnancies. We also examined preterm birth as a dichotomous variable with 2 cutoff points: preterm birth (<37 weeks' gestation) and early preterm birth (<34 weeks' gestation). Asthma diagnosis was recorded in the medical record and/or in the discharge summary (International Classification of Diseases, 9th Revision code 493.0-493.9). Adjusted models include maternal age in years (<20, 20-24, 25-29, 30-34, ≥35 y, and unknown); race/ethnicity (white, black, Hispanic, Asian/Pacific Islander, other race, and unknown), pre-pregnancy body mass index (kg/m^2) (<18.5, underweight; 18.5-24.9, normal weight; 25-29.9, overweight; ≥30 obese; and unknown), smoking and alcohol use (both yes/no), study site, parity (nulliparous, primiparous, and multiparous), insurance status (private, public/government, self-pay/other, and unknown), marital status (married, divorced/widowed, single, and unknown), and maternal comorbidities (chronic hypertension, diabetes, thyroid disease, and HIV). Covariates were selected *a priori* on the basis of earlier analyses of preterm birth in association with maternal asthma.[25,31]

Exposure

Ambient air pollutant concentrations were estimated using a modified version of the Community Multiscale Air Quality model,[32] a 3-dimensional, regional air quality model developed by the US Environmental Protection Agency. Meteorology inputs for model simulations were generated using the Weather Research and Forecasting model, including inputs for hourly temperature, relative humidity, and wind characteristics. Air pollutant emissions were generated using US Environmental Protection Agency National Emission Inventories. Hourly concentrations of ambient air pollutants for the ground-level layer (approximately 30 m high) over the entire continental United States for years 2001 to 2009 were calculated in the Air Quality and Reproductive Health study. Because the Consortium on Safe Labor data are anonymized, these hourly concentrations were averaged to estimate mean daily levels within each of the 15 distinct delivery hospital referral regions,[33] which were then averaged to obtain weekly and whole pregnancy exposure estimates. The size of hospital referral regions ranged from 415 to 312,644 km^2. Estimates were weighted for population density to discount exposure in areas in which women were unlikely to live or work. Modeled data were fused with observed monitor data retrieved from the US Environmental Protection Agency Air Quality System, where available, and estimates were adjusted using inverse distance weighting for criteria air pollutants: $PM_{2.5}$ and PM_{10}, O_3, NO_x, SO_2, and CO. Our final model results were compared with pollutant-level estimates obtained with 4 other commonly used strategies, including one based on monitors alone. Our fused, population-weighted model performed very well with better coverage for particles, SO_2, and O_3 than for monitors alone and with stronger agreement with measured exposure for both gas-phase and particle-phase species than raw Community Multiscale Air Quality models.[34] Risk models are based on interquartile range (the difference between the 25th and 75th percentiles) changes in exposure (see Table E1 in this article's Online Repository at www.jacionline.org).

Statistical analyses

Each observed pregnancy was included in the analysis, and pregnancy was the unit of analysis in all statistical testing. Pregnancies to the same woman were accounted for with generalized estimating equations and robust variance estimates to adjust for their lack of independence. Descriptive statistics were calculated by preterm status, but no significance testing was conducted. To study the acute effect of air pollution on preterm birth, we performed a conditional logistic regression for each gestational week from 23 to 36, conditioning on women being at risk for delivery at that week (ie, not previously delivered). We then compared exposure among deliveries at that week versus the same gestational week of exposure for all ongoing pregnancies. This is akin to a fetuses-at-risk approach that uses the idea of discrete-time survival analysis, but we fit saturated regression models by fully stratifying on the weeks of delivery. For these analyses, the risk estimate is interpreted as the odds of preterm delivery in a particular gestational week when exposure to the pollutant increases by 1 interquartile range during that week. This interpretation is analogous to an "instantaneous risk ratio" in a survival analysis.

We also conducted analyses to examine the marginal probability of preterm birth (both <34 and <37 weeks) in association with ambient concentrations of each air pollutant for longer, more chronic exposure periods. Preliminary results of analyses of each gestational week from 1 to 28 suggested a change in risk over time that was well captured with equal division of the first 2 trimesters into 7-week increments (1 to 7, 8 to 14, 15 to 21, and 22 to 28). We also examined a 3-month preconception window, the last 6 weeks of pregnancy, and the total pregnancy. In contrast to the fetus-at-risk type of analyses, these logistic regressions estimated the marginal increase in the odds of preterm birth (or early preterm birth), per interquartile range increase in air pollution within a specific exposure window. As sensitivity analyses, risks associated with peak weekly concentration during each of the 7-week windows were also estimated.

Odds ratios and 95% CIs for each week of gestation 23 to 36 and for dichotomous preterm birth outcomes (<34 weeks, <37 weeks) were estimated using logistic regression. Robust standard errors and generalized estimating equations were used to account for multiple births by the same women. Crude,