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Exposure to ambient air pollution during pregnancy and preterm birth: A Spanish multicenter birth cohort study

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ABSTRACT

Background and objective: Preterm birth is a major determinant of infant mortality and morbidity. Air pollution has been suggested as a risk factor for preterm delivery; however, the scientific evidence on this impact remains inconsistent. We assessed the association between residential exposure to air pollution during pregnancy and preterm birth (gestational age at delivery <37 weeks) in Spain.
Methods: This study was based on 2409 pregnant women participating in the INMA birth cohorts in Asturias, Gipuzkoa, Sabadell and Valencia. Ambient levels of nitrogen dioxide (NO_2) and benzene were estimated for each woman's residence for each trimester and for the whole pregnancy, using temporally adjusted land-use regression models. The association between air pollution exposure and preterm birth was assessed for each cohort separately by means of logistic regression models controlling for potential confounders, under single- and two-pollutant models, for all the women in the study and for those spending more than 15 h/day at home. Combined estimates of the association across cohorts were obtained through meta-analysis.
Results: Throughout the whole sample, suggestive but no statistically significant associations were found between exposure and preterm birth. For pregnant women spending more time at home significant associations were found for both pollutants, under single- and two-pollutant models. Under the last ones, NO_2 exposure during the second trimester and the whole pregnancy was associated with a higher risk of preterm delivery (OR=1.58, (95%CI: 1.04–2.42) per 10 $\mu g/m^3$ increase). Benzene exposure during the third trimester was also associated with preterm birth in that subsample (OR=1.45, (95%CI: 1.00–2.09) per 1 $\mu g/m^3$ increase).
Conclusion: We found suggestive associations between NO_2 and benzene exposure during pregnancy and preterm birth. Estimates of the association were higher among women who spent more time at home, probably reflecting a better exposure assessment in this group.

1. Introduction

Preterm birth is a major determinant of infant mortality and morbidity. Blencowe et al. (2012) estimated that, in 2010, approximately 15 million babies were born preterm (<37 weeks of gestation) accounting for 11.1% of all live births worldwide. Preterm birth is estimated to be responsible for one-third of the global neonatal deaths and the second most common cause of death after pneumonia in children younger than 5 years (Liu et al., 2012). In addition, preterm infants who survive remain at risk of developing a large number of complications, not only during infancy but also later in life, including neurodevelopmental,

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respiratory, cardiovascular and metabolic disorders (Behrman and Butler, 2006). Besides its impact on health outcomes, preterm birth also has consequences on the quality of life and psychosocial status and represents an important economic burden for families and societies (Saigal and Doyle, 2008).

A wide range of risk factors have been suggested as being related with preterm birth (Goldenberg et al., 2008) including exposure to environmental contaminants (Wigle et al., 2008). Maternal exposure to air pollution has been adversely associated with several birth outcomes including birth weight and preterm birth, birth weight being far more widely studied (Lacasaña et al., 2005; Srám et al., 2005; Shah and Balkhair, 2011; Stieb et al., 2012). Reviews on the topic suggest an association but find no conclusive evidence for a relationship between preterm delivery and maternal exposure to air pollution. Differences in study design, sample size, exposure assessment, levels of exposure, outcome frequency, and adjustment for potential confounders could partly explain differences.

To date, most of the studies reporting on the impact of air pollution on pregnancy outcomes have mainly focused on criteria air pollutants, and the available evidence for a similar impact of non-criteria air pollutants such as benzene has remained very limited (Protano et al., 2012; Ferguson et al., 2013). The major sources of outdoor benzene exposure for the general population are automobile service stations, exhaust from motor vehicles, and industrial emissions (ATSDR, 2007). Further research on the possible negative effects of benzene on pregnancy is required (Protano et al., 2012).

The INMA (INfancia y Medio Ambiente – Childhood and Environment) project is a network that follows seven population-based birth cohorts in Spain and it was established to evaluate the role of the environment on fetal and childhood health (Guxens et al., 2012). The four 'de novo' cohorts within INMA (Asturias, Gipuzkoa, Sabadell, and Valencia) share a common protocol that includes assessment of air pollution starting at the beginning of pregnancy. The relation between prenatal exposure to air pollution and reproductive outcomes in these four cohorts has been examined in several works within the INMA project, including anthropometric measures at birth and fetal growth (Estarlich et al., 2011; Iñiguez et al., 2015). The relation with preterm birth has been assessed only in the Valencia cohort (Llop et al., 2010), suggesting a higher risk of preterm birth in association with maternal exposure to traffic-related air pollution. The aim of this study is to assess the association between residential ambient levels of NO_2 and benzene during pregnancy and preterm birth in the four INMA cohorts with diverse air pollution levels, as well as different sociodemographic characteristics.

2. Methods

2.1. Study population

A total of 2644 pregnant women who fulfilled the inclusion criteria (i.e. ≥ 16 years of age, intention to deliver at the reference hospital, no problems of communication, singleton pregnancy, and no assisted conception) were recruited between November 2003 and February 2008 at their first routine specialized antenatal care visit (10–13 weeks of gestation) in the main public hospital or reference health center in four study areas: Asturias, Gipuzkoa, Sabadell, and Valencia (Supplementary Fig. S1). After excluding the women who withdrew, were lost to follow-up, or underwent induced or spontaneous abortions or fetal deaths, a sample of 2505 women were monitored until delivery, from May 2004 to August 2008. The final population in this study consisted of 2409 women who delivered a live newborn and had an assigned air pollution exposure. Exposure assignment was performed for all women with home addresses capable of being geocoded and who had been living within the study area for at least seven months of the gestation period. The study was approved by the ethical committees of the centers involved in the study, and written informed consent was obtained from all the participating pregnant women.

2.2. Air pollution exposure assessment

Exposure to ambient NO_2 and benzene was estimated for each woman for different periods of her pregnancy. A complete description of the methodology on exposure modeling has been reported previously (Estarlich et al., 2011; Iñiguez et al., 2009). Briefly, ambient concentrations of nitrogen dioxide (NO_2) and benzene were repeatedly measured with passive samplers distributed over the study areas. The number of samplers for each pollutant ranged from 57 in Sabadell to 93 in Valencia. The samplers measured the levels of pollutants using radial symmetry (Radiello®, Fondazione Salvatore Maugeri, Padua, Italy), and remained exposed during various sampling periods of seven days each. Land-use regression (LUR) was employed to predict NO_2 and benzene levels at the women's residential addresses using the information from kriging with empirical measures and Geographical Information Systems data (altitude, distance to roads, traffic, and uses of land). The R^2 for these LUR models ranged between 0.51 and 0.75 for NO_2 and between 0.44 and 0.73 for benzene (Supplementary Table S1).

NO_2 spatial estimations were temporally adjusted using daily background NO_2 levels measured by monitoring stations in each area. Benzene was not continuously measured in all the monitoring stations. Temporal correlations of benzene with other ambient air pollutants are variable and depend on each location (Beckerman et al., 2008). So for temporal adjustment of benzene levels, the available air pollutant that best correlated with it was used. Resulting daily estimates of NO_2 and benzene for the geocoded home address of each study participant were averaged to assess exposure during each trimester as well as throughout the whole pregnancy. Changes in residential address during pregnancy were taken into consideration when they accounted for a relevant fraction ($>2/9$), which occurred in 1–6% of cases, depending on the cohort.

2.3. Birth outcome

Preterm birth was considered as occurring when delivery was before completed 37th week of gestation. Gestational age was based on the reported last menstrual period. An early ultrasound of the crown-rump length was also available and was used for gestational dating when the difference with the last menstrual period was equal to or greater than 7 days (12% of the participants).

2.4. Covariates

Potential confounders, as well as determinants of preterm birth were selected based on previous scientific findings. Information on parental socio-demographic characteristics, environmental exposures, time-activity patterns, and life style variables was obtained through detailed questionnaires administered twice during their pregnancy (around weeks 12 and 32). In addition to variables obtained from the questionnaires, infant's sex, season of delivery, and zone of residence (urban, rural) were also included in the analyses. Socio-economic status (SES) was defined according to the most privileged occupation during pregnancy of the mother or the father using a widely used Spanish adaptation of the international ISCO88 coding system (Domingo-Salvany et al., 2000) and