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Multiple pregnancies and air pollution in moderately polluted cities: Is there an association between air pollution and fetal growth?

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ABSTRACT

Background: Multiple pregnancies (where more than one fetus develops simultaneously in the womb) are systematically excluded from studies of the impact of air pollution on pregnancy outcomes. This study aims to analyze, in a population of multiple pregnancies, the relationship between fetal growth restriction (FGR), small for gestational age (SGA) and exposure to air pollution in moderately polluted cities.
Methods: All women with multiple pregnancies living in the city of Besançon or in the urban area of Dijon and who delivered at a university hospital between 2005 and 2009 were included. FGR and SGA were obtained from medical records. Outdoor residential nitrogen dioxide (NO_2) exposure was assessed using the mother's address, considering a 50 m radius buffer over the following defined pregnancy periods: each trimester, entire pregnancy and two months before delivery. Logistic regression analyses were performed.
Results: This study included 249 multiple pregnancies with 506 newborns. The median of NO_2 concentration considering a 50 m radius buffer during entire pregnancy was 23.1 μg/m^3 (minimum at 10.1 μg/m^3 and maximum at 46.7 μg/m^3). No association was observed between NO_2 and SGA whatever the pregnancy period (the odds ratio (OR) range 0.78 to 0.88). Regarding FGR, the OR associated with an increase of 10 μg/m^3 of NO_2 exposure during entire pregnancy was 1.52 (95% Confidence Interval (CI): 1.02–2.26). Similar results were observed for NO_2 exposure during the various pregnancy periods.
Conclusions: These results are in line with an association between NO_2 and fetal growth in multiple pregnancies for an exposure mostly below the threshold set out in European legislation.

1. Introduction

Multiple pregnancies present all the complications of singletons, but at higher rates, especially for preterm delivery and fetal growth abnormalities (Oepkes and Sueters, 2017; Santana et al., 2016). Fetal growth abnormalities are associated with perinatal morbidity, neonatal death and stillbirth (Figueras and Gardosi, 2011; Gardosi and Francis, 2009; Kady and Gardosi, 2004; Sharma et al., 2016a), and they increase

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the prevalence of long-term neurodevelopmental, cardiovascular, and endocrinological consequences (Barker et al., 1993; Figueras and Gratacos, 2017; Jacobsson et al., 2008; Sharma et al., 2016a). Fetal growth abnormalities may be caused by four types of factors: maternal (extreme age, disadvantaged socioeconomic status, hypertensive disorders, cytomegalovirus-maternal infection), placental (abnormal uteroplacental vasculature, single umbilical artery), fetal or genetic (major congenital anomalies of the fetus) (CNGOF, 2013; Sharma et al., 2016a; Sharma et al., 2016b).

Among the many indicators of fetal growth abnormalities, small for gestational age (SGA) and fetal growth restriction (FGR) seem to be the most relevant in multiple pregnancies. SGA is defined as a weight lower than the 10th centile of weight for gestational age and sex. FGR is defined as a halt or decline in growth due to placental insufficiency on two antenatal measurements taken two to three weeks apart (ACOG, 2013; CNGOF, 2013; Ego, 2013; Figueras and Gratacos, 2017; Lausman et al., 2013; RCOG, 2013). FGR is therefore more difficult to diagnose retrospectively than SGA and is rarely used as an outcome in environmental epidemiological studies.

In a meta-analysis of 12 European cohorts of singleton births, Pedersen et al. found that increased ambient air pollutants and traffic density are associated with reduced fetal growth represented by term low birth weight (term LBW i.e. birth weight under 2500 g for birth after 36 weeks of gestational age), birth weight and birth head circumference (Pedersen et al., 2013). In France, Lepeule et al. reported that increased NO_2 exposure was associated with reduced fetal growth represented by birth weight (Lepeule et al., 2010). However, the results are discordant for several atmospheric pollutants, and between adjustments, periods of pregnancy or subgroups. For example, in 2011 Malmqvist et al. reported both an increased risk of SGA with increased nitrogen oxides (NOx) exposure and no association; the two analyses differ on the adjustment factors used in the models (Malmqvist et al., 2011). In 2017, the same authors also found an association between increased NOx exposure and reduced fetal growth estimated by antenatal echography (Malmqvist et al., 2017). In a birth cohort in UK, Vinikoor-Imler et al. found that increased particulate matter with an aerodynamic diameter ≤ 2.5 µm ($PM_{2.5}$) exposure was associated with increased fetal growth represented by SGA in the three trimesters, and with increased fetal growth represented by term LBW in the third trimester only. They found that increased ozone exposure was associated with reduced fetal growth represented by SGA in the first and third trimesters, and that increased ozone exposure was associated with reduced fetal growth represented by term LBW in the third trimester. Conversely, they found that increased ozone exposure was associated with increased fetal growth represented by term LBW in the first and second trimesters (Vinikoor-Imler et al., 2014). In Canada, Stieb et al. reported that increased NO_2 exposure was associated with reduced fetal growth represented by SGA, term LBW and term birth weight (Stieb et al., 2016). In London, Smith et al. found that increased NO_2 or $PM_{2.5}$ exposure was associated with reduced fetal growth represented by term LBW, term SGA and term birth weight, but the association disappeared in two air pollutant models (Smith et al., 2017). These studies all used data from single pregnancies. Today, only one published study has investigated the effect of air pollution exposure in multiple pregnancies. Bijnens et al. found that increased NO_2 and PM_{10} exposures were associated with reduced fetal growth represented by birth weight and SGA in moderate to late preterm twins (32–36 weeks of gestation) but not in term born twins (Bijnens et al., 2016). Although multiple pregnancies are a risk factor for fetal growth abnormalities, the occurrence of FGR and SGA in multiple pregnancies may be increased by NO_2 exposure.

The objective of this study was to analyze, in a population of multiple pregnancies, the relationship between FGR, SGA and chronic environmental exposure to air pollution in medium-sized French cities.

2. Material and methods

2.1. Population

For this retrospective study, we included all multiple pregnancies in women residing in Besançon or in the urban area of Dijon who delivered at the Besançon or Dijon university hospital between 1st January 2005 and 31st December 2009. The Besançon and Dijon university hospitals are level 3 maternities (i.e. with a neonatal intensive care unit). Stillborns and live newborns, whose births occurred after 22 completed weeks of gestation and/or with birth weight > 500 g, were included. When a woman had several multiple pregnancies in the study period, only one pregnancy was included after random selection. Hence, the number of women and the number of multiple pregnancies included in the analysis population is the same. Furthermore, for some sensitivity analyses, triplets and same-sex twins were excluded in order to eliminate potential bias due to the major effects of triple pregnancies or of twin-twin transfusion syndrome.

This work is part of the PRECEE program (PREgnancy and Combined Environmental Exposure) and complements results published by Barba-Vasseur et al. in 2017 on preterm delivery, which focused on preterm birth in single pregnancy (Barba-Vasseur et al., 2017).

2.2. Outcomes

Birth weight and fetal growth restriction (FGR) were extracted from the Besançon computerized medical records (DIAMM® software developed by the Association of Computerized Users in Pediatrics, Obstetrics and Gynecology (Audipog®)) and from the Burgundy perinatal network records and paper medical records for Dijon. Births were classified as SGA if birth weight was < 10th centile for gestational age and sex in one or more newborns of the pregnancy. The threshold for the 10th centile of birth weight was estimated in a population of French newborns from single and multiple pregnancies by gestational age and sex (Audipog®). In order to test for a classification effect, SGA was also defined according to three other birth weight standards for gestational age and sex: one standard with intrauterine standards estimated with data from the 2010 perinatal study (Ego et al., 2016), and two standards with birth weight standards estimated from Burgundy perinatal network data with two statistical methods (Ferdynus et al., 2009; Rousseau et al., 2017). According to French, British, and Canadian recommendations, FGR was defined as a defect in fetal growth on two antenatal measurements taken two to three weeks apart (CNGOF, 2013; Lausman et al., 2013; RCOG, 2013). FGR was retained according to the ICD10 codes in medical records (O36.5, P05.0, P05.1).

2.3. Covariables

All variables available in the medical records were analyzed to detect potential confounders: maternal socioeconomic characteristics, obstetrical history (including parity), pregnancy complications (including gestational hypertension and diabetes) and characteristics of the newborns.

Maternal age was calculated at delivery and dichotomized with a threshold of 35 years old. Maternal smoking during pregnancy was coded as “present” if active smoking was ticked in the medical records. Malnutrition was defined by pre-pregnancy body mass index lower than 18.5 or by the presence of an ICD10 code of malnutrition in medical records (O25, E43, E44). Major infant congenital abnormalities represented any major congenital anomalies according to the European network of population-based registries for the epidemiologic surveillance of congenital anomalies (EUROCAT, 2005). Infant congenital abnormalities considered for this study were determined before birth or at birth.

The neighborhood socioeconomic level was estimated with a collective socioeconomic index calculated at the geographical scale of the

French sub-municipal census block groups defined by the National Institute of Statistic and Economics Studies (approximately 2000 inhabitants). Variables related to family and household, immigration and mobility, employment and income, education and housing were extracted from the 2008 population census database. From among these variables, 39 were selected because of their occurrence in the literature (Lalloué et al., 2013; Messer et al., 2006; Pornet et al., 2012). The first component of a principal component analysis (PCA) was used to calculate a standardized socio-economic index following a reduction step. The socioeconomic index was calculated using the R package *SesIndexCreatoR* (Lalloué et al., 2013). A value of the socioeconomic index in the last decile was considered as low neighborhood socioeconomic level.

2.4. NO_2 exposure

The participants' addresses at the date of delivery were extracted from CPAGE® software using the personal identification number and the date of delivery. This address identified the residential building. Two NO_2 exposure assessments were calculated at each mother's building: considering a 50 m radius buffer centered on the building centroid ($NO_{2,50m}$) and considering the 6 m perimeter around the façades of the building ($NO_{2,6m}$) (Barba-Vasseur et al., 2017; Tenailleau et al., 2015; Tenailleau et al., 2016). The NO_2 levels were calculated using a two-step emission and diffusion modeling. NO_2 emissions were calculated from road traffic data using CIRCUL'AIR software, developed and used by all approved French Air Quality Monitoring Agencies (AASQA) (COPERT IV European standard methodology). AASQA's pollution emission inventory was used to assess NO_2 emissions related to heating, industries and long-range sources. NO_2 concentration was estimated 2 m above ground on a 25 m grid with reinforced gridding around the axes of emission, using the ADMS-Urban© software (CERC) for diffusion modeling. ESRI arcGIS© software (V10.1) was used for spatial interpolation to increase the spatial resolution of the ADMS output. NO_2 concentration expressed in micrograms per cubic meter (μg/m^3) was thus calculated at a 4 m^2 (2 m × 2 m) raster. The validity of the 2 m result was estimated on the basis of data from four, two-week-long measurement campaigns carried out during autumn and winter 2010 as well as spring and summer 2011. Measurements were based on 863 passive samplers and the nine AASQA air pollution measurement stations (ATMO Franche-Comté and Atmosf'Air Bourgogne). Validation statistics (r^2) range from 0.64 to 0.69. Monthly maps of NO_2 concentration were established from January 2004 to December 2009 using hourly meteorological data to account for the seasonal variations in NO_2 concentrations. Using the monthly maps, time-weighted average NO_2 exposure was assessed over the following defined pregnancy periods: first, second and third trimester, entire pregnancy and two months before delivery.

2.5. Statistics

The association between NO_2 exposure and SGA or FGR was estimated by univariable and multivariable logistic regression analyses, where SGA or FGR were taken as binary outcomes in the models. A pregnancy was categorized as SGA (or FGR) if at least one fetus was SGA (or FGR). Departure from the assumption of linearity was tested by introducing a polynomial function of the NO_2 exposure variables into the models. The OR were adjusted for: maternal age older than 35 years at delivery, low neighborhood socioeconomic level, maternal smoking during pregnancy, malnutrition, nulliparity, gestational hypertension and diabetes. Because of the non-random distribution of missing data, a missing data class was attributed to participants for whom no value for potential confounding variables was available. Only two adjustment factors of the model had missing data: malnutrition (n = 20) and maternal smoking during pregnancy (n = 16), affecting only 8% of pregnancies. Sensitivity analyses were conducted using different criteria to define NO_2 exposure and SGA outcome. First, NO_2 concentration considering the 6 m perimeter around the façades of the building, instead of considering a 50 m radius buffer was considered. Second, three other birth weight standards were used to define SGA as an outcome variable (Ego et al., 2016; Ferdynus et al., 2009; Rousseau et al., 2017). Furthermore, for some sensitivity analyses, triplets and same-sex twins were excluded. Indeed twin-to-twin transfusion syndrome is a risk factor for fetal growth abnormalities in monochorionic twins. Because data concerning chorionicity was not available for our study, we did a sensitivity analysis on twins of different sex, who are necessarily dichorionic twins. A multilevel model was used to explore a potential hierarchical data structure. Maternal age at delivery was also considered for adjustment in continuous form, or with a second or third order polynomial. Finally, we adjusted the analyses for a supplementary fetal characteristic: the presence of major infant congenital abnormalities in at least one fetus of the pregnancy. SAS 9.4 software (SAS Institute, Cary, NC) and MLwiN 2.27 (University of Bristol, UK) were used.

2.6. Ethics

This study was approved by the French National Advisory Committee for the Treatment of Information in Health Research (CCTIRS) (registration number 15.292, 2015 April 9th) and by the French data protection authority (CNIL) (registration number DR-2015-736, 2015 December 24th). A letter of information was sent to each participant included, and only one eligible family refused to participate.

3. Results

Among the 10,905 deliveries which occurred in the Besançon or Dijon university hospital from women living in the defined study area, 249 multiple pregnancies with 506 newborns were included in the study; eight pregnancies were triple. One multiple pregnancy was excluded due to repeated multiple pregnancies for the same woman over the study period, three due to incorrect address (wrong or unrecognizable recorded street names) and one because the family opposed the use of their medical data. The number of women included (249) is the same as the number of multiple pregnancies as a result of the subject selection criteria.

Among the 249 multiple pregnancies, 64 had FGR and 94 had SGA in one or more fetus. Forty-eight (51%) pregnancies with at least one SGA fetus did not have FGR; and 18 (28%) of pregnancies with at least one FGR fetus did not have SGA. SGA and FGR were significantly associated (p-value < 0.0001, Chi-square test). Among the 41 pregnancies with a maternal age older than 35 years, 10 (24.4%) had SGA and 8 (19.5%) had FGR in one or more fetus. Among the 34 pregnancies of women with a low neighborhood socioeconomic level, 16 (47.1%) had SGA and 12 (35.3%) had FGR in one or more fetus. Among the 13 pregnancies of women who lived alone, 4 (30.8%) had SGA and 6 (46.2%) had FGR in one or more fetus. The pregnancy and newborn characteristics are presented in Table 1.

The median of NO_2 concentration considering a 50 m radius buffer during the entire pregnancy was 23.1 μg/m^3 with a minimum exposure of 10.1 μg/m^3 and a maximum exposure of 46.7 μg/m^3 (Fig. 1).

For SGA, the OR associated with a 10 μg/m^3 increase of NO_2 exposure during the first, the second and the third trimester were 0.78 (95% CI: 0.55–1.12), 0.83 (95% CI: 0.58–1.19), and 0.88 (95% CI: 0.62–1.25), respectively (Table 2). Sensitivity analyses were conducted using the birth weight standards of Ego, Ferdynus and Rousseau (Cf. Material and methods). The proportion of pregnancies with at least one SGA fetus was 57%, 34% and 52% respectively. Sensitivity analyses led to the same conclusion of no association.

When considering FGR, the OR associated with a 10 μg/m^3 increase of NO_2 exposure during the first, the second and the third trimester were 1.42 (95% CI: 0.97–2.08), 1.55 (95% CI: 1.06–2.27), 1.35 (95%

Table 1
Pregnancy and newborn characteristics according to fetal growth restriction and small for gestational age status, 2005–2009 (N = 249 pregnancies and 506 newborns).

	Total	Small for gestational age[a]		Fetal growth restriction	
		Yes	No	Yes	No
	N (%)	N (%)	N (%)	N (%)	N (%)
Pregnancies	N = 249	N = 94	N = 155	N = 64	N = 185
Maternal age at delivery > 35 years old	41 (16.5)	10 (10.6)	31 (20.0)	8 (12.5)	33 (17.8)
Low neighborhood socioeconomic level	34 (13.7)	16 (17.0)	18 (11.6)	12 (18.8)	22 (11.9)
Living status[b]					
- Living alone	13 (5.6)	4 (4.4)	9 (6.3)	6 (10.0)	7 (4.1)
- Married, cohabitation, other	220 (94.4)	86 (95.6)	134 (93.7)	54 (90.0)	166 (95.9)
Maternal employment during pregnancy[b]	167 (72.0)	65 (71.4)	102 (72.3)	48 (78.7)	119 (69.6)
Maternal smoking during pregnancy[b]	29 (12.5)	14 (15.1)	15 (10.7)	11 (17.5)	18 (10.1)
Pre-pregnancy body mass index (kg/m^2)[b]					
- < 25	155 (67.7)	60 (70.6)	95 (66.0)	44 (75.9)	111 (64.9)
- 25–30	47 (20.5)	14 (16.5)	33 (22.9)	6 (10.3)	41 (24.0)
- > 30	27 (11.8)	11 (12.9)	16 (11.1)	8 (13.8)	19 (11.1)
Malnutrition[b]	20 (8.7)	10 (11.8)	10 (6.9)	10 (17.2)	10 (5.9)
Nulliparity	139 (55.8)	58 (61.7)	82 (52.9)	44 (68.8)	95 (51.4)
Gestational hypertension	30 (12.1)	12 (12.8)	18 (11.6)	9 (14.1)	21 (11.4)
Placental Abruption	3 (1.2)	1 (1.1)	2 (1.3)	1 (1.6)	2 (1.1)
Placenta praevia	2 (0.8)	1 (1.1)	1 (0.7)	1 (1.6)	1 (0.5)
Infection	48 (19.3)	15 (16.0)	33 (21.3)	12 (18.8)	36 (19.5)
Infection of amniotic fluid	14 (5.6)	3 (3.2)	11 (7.1)	3 (4.7)	11 (6.0)
Genitourinary infection	27 (10.8)	9 (9.6)	18 (11.6)	8 (12.5)	19 (10.3)
Diabetes	23 (9.2)	4 (4.3)	19 (12.3)	4 (6.3)	19 (10.3)
Hydramnios	10 (4.0)	6 (6.4)	4 (2.6)	2 (3.1)	8 (4.3)
Prematurity	152 (61.0)	43 (45.7)	109 (70.3)	41 (64.1)	111 (60.0)
Newborns	N = 506	N = 126	N = 377	N = 132	N = 374
Status					
- Living	471 (93.1)	114 (90.5)	355 (94.2)	128 (97.0)	343 (91.7)
- Still born	21 (4.1)	10 (7.9)	10 (2.6)	1 (0.7)	20 (5.3)
- Deceased shortly after birth	14 (2.8)	2 (1.6)	12 (3.2)	3 (2.3)	11 (3.0)
Sex					
- Male	267 (52.8)	76 (60.3)	190 (50.4)	65 (49.2)	202 (54.0)
- Female	239 (47.2)	50 (39.7)	187 (49.6)	67 (50.7)	172 (46.0)
Birth weight (g)[b]	2129 (663)	1924 (602)	2197 (669)	1917 (565)	2204 (680)
Major infant congenital abnormalities	40 (7.9)	7 (5.6)	33 (8.8)	20 (15.2)	20 (5.4)
Apgar score at 5 min = 10[b]	356 (77.4)	94 (79.7)	262 (77.1)	90 (72.6)	266 (79.2)

N: number; N (%): number (percentage) except for birth weight which is described by mean (standard deviation).
[a] Lower than 10th centile of birth weight for gestational age.
[b] Missing data: living status (n = 16), maternal employment during pregnancy (n = 17), maternal smoking during pregnancy (n = 16), pre-pregnancy BMI (n = 20), malnutrition (n = 20), birth weight (n = 3), term low birth weight (n = 1), Apgar score at 5 min (n = 46).

CI: 0.92–1.98), respectively (Table 2). The OR associated with a 10 μg/m^3 increase of NO_2 exposure during the entire pregnancy and during the two last months before delivery were 1.52 (95% CI: 1.02–2.26) and 1.53 (95% CI: 1.04–2.25), respectively. When analysis was restricted to the 79 pregnancies with twins of different sex, the OR associated with a 10 μg/m^3 increase of NO_2 exposure during the first, second and third trimester were 2.43 (95% CI: 1.31–4.54), 3.13 (95% CI: 1.53–6.41), and 3.06 (95% CI: 1.46–6.45), respectively (Supplementary Table in Appendix).

Sensitivity analyses with $NO_{2,6m}$ indicators led to similar results. For SGA, the OR associated with a 10 μg/m^3 increase of NO_2 exposure considering the 6 m perimeter around the façades of the building during the first, the second and the third trimester were 0.83 (95% CI: 0.58–1.18), 0.88 (95% CI: 0.62–1.24), and 0.92 (95% CI: 0.65–1.30), respectively. And for FGR, the OR associated with a 10 μg/m^3 increase of NO_2 exposure during the first, the second and the third trimester were 1.38 (95% CI: 0.94–2.02), 1.51 (95% CI: 1.04–2.20), and 1.32 (95% CI: 0.90–1.92), respectively. Sensitivity analyses with multi-level analyses or with maternal age in three other forms (continuous form, or with a second or third order polynomial) or with adjustment on major infant congenital abnormalities led to similar results.

4. Discussion

To our knowledge this is the first study to analyze the potential influence of air pollution on fetal growth restriction in multiple pregnancies. We included all multiple pregnancies (n = 249) from a large database of > 10,000 deliveries over a 5-year period. Environmental exposure to NO_2 was associated with FGR in multiple pregnancies, especially during the second trimester and the two months before delivery. However, no association between NO_2 exposure and SGA was identified.

4.1. Different results between SGA and FGR

Our results differed for SGA and FGR. SGA could be less specifically a disorder of fetal growth than FGR. Indeed, the size and weight of newborns are strongly influenced by those of their parents. SGA is defined by birth weight and does not take into account the growth trajectory. SGA is therefore associated with the measurements of the parents. Conversely, FGR is a dynamic measure of growth regardless of the measured weight value. Therefore, SGA seems less appropriate for identifying an association between fetal growth disorders and environmental exposure than FGR, particularly in a context of moderate exposure and multiple pregnancies. Most published studies which have analyzed the association between NO_2 and the same definition of SGA,

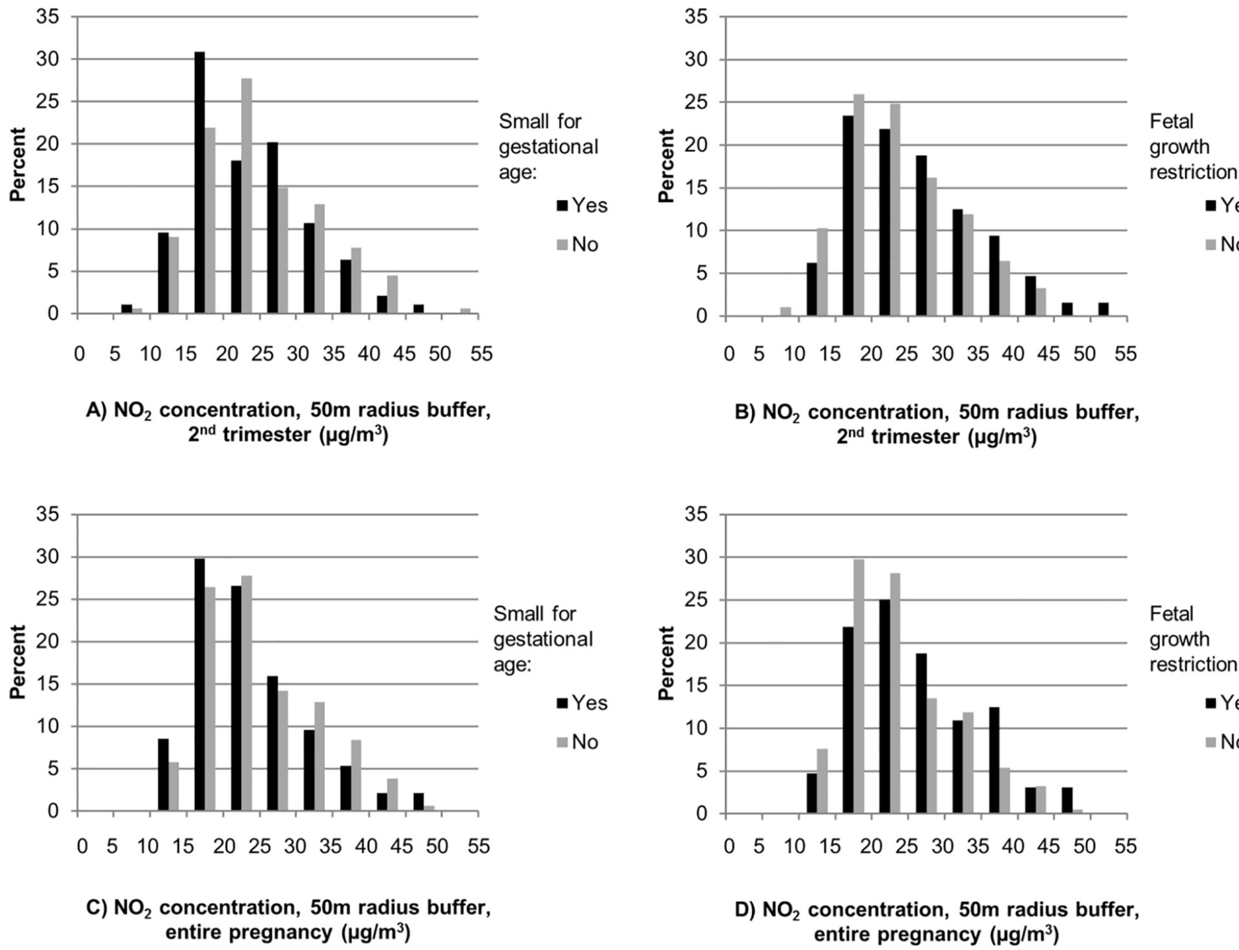

Fig. 1. NO_2 exposure, considering a 50 m radius buffer, in multiple pregnancies, during the second trimester and entire pregnancy, according to fetal growth restriction and small for gestational age status, 2005–2009 (N = 249).

Table 2
Relationship between NO_2 exposure during pregnancy and small for gestational age or fetal growth restriction, 2005–2009 (N = 249 pregnancies and 506 newborns).

	Outcome		Crude OR [95% CI] for an increase of 10 µg/m^3	*p*-Value[a]	Adjusted[b] OR [95% CI] for an increase of 10 µg/m^3	*p*-Value[a]
	Yes *µ (SD)*	No *µ (SD)*				
Small for gestational age	N = 94	N = 155	N = 249		N = 249	
NO_2 concentration, 50 m radius buffer (µg/m^3)						
- First trimester	23.7 (7.8)	25.1 (8.1)	0.79 [0.57; 1.10]	0.161	0.78 [0.55; 1.12]	0.181
- Second trimester	23.6 (7.8)	24.7 (8.2)	0.84 [0.61; 1.17]	0.301	0.83 [0.58; 1.19]	0.307
- Third trimester[c]	23.5 (8.5)	24.3 (8.0)	0.88 [0.63; 1.22]	0.431	0.88 [0.62; 1.25]	0.471
- Entire pregnancy	23.6 (7.6)	24.8 (7.8)	0.82 [0.58; 1.15]	0.246	0.81 [0.56; 1.17]	0.256
- The two months before delivery	23.7 (8.0)	24.4 (7.9)	0.90 [0.65; 1.24]	0.507	0.88 [0.62; 1.25]	0.477
Fetal growth restriction	N = 64	N = 185	N = 249		N = 249	
NO_2 concentration, 50 m radius buffer (µg/m^3)						
- First trimester	26.1 (8.8)	24.0 (7.7)	1.37 [0.90; 1.95]	0.074	1.42 [0.97; 2.08]	0.076
- Second trimester	26.3 (8.7)	23.6 (7.7)	1.50 [1.06; 2.12]	0.023	1.55 [1.06; 2.27]	0.024
- Third trimester[c]	25.3 (7.9)	23.6 (8.3)	1.30 [0.92; 1.84]	0.144	1.35 [0.92; 1.98]	0.122
- Entire pregnancy	26.1 (8.3)	23.8 (7.5)	1.47 [1.02; 2.10]	0.038	1.52 [1.02; 2.26]	0.038
- The two months before delivery	26.0 (8.0)	23.5 (7.8)	1.48 [1.04; 2.11]	0.029	1.53 [1.04; 2.25]	0.033

A pregnancy was coded as SGA (or FGR) if at least one fetus of the pregnancy was coded as SGA (or FGR).
N: number; µ (SD): NO_2 exposure average (standard deviation); OR: odds ratio; CI: confidence interval.
[a] Wald Chi-square test.
[b] Adjusted for maternal age above 35 years at delivery, low neighborhood socioeconomic level, maternal smoking during pregnancy, malnutrition, nulliparity, gestational hypertension and diabetes. The adjustment for major infant congenital abnormalities in addition to the 7 previous factors led to the same results.
[c] Missing data for delivery before 29 weeks of gestational age (n = 11).

found similar results (Capobussi et al., 2016; Dadvand et al., 2014; Gehring et al., 2011; Hannam et al., 2014; Poirier et al., 2015). On the other hand, two studies reported an association in single pregnancies and one in twins. Liu et al. found an association between NO_2 exposure and SGA with OR for a 10 μg/m^3 increase of NO_2 in the first, second, and third trimesters: 1.04, 1.03, and 1.04 (after conversion from ppb to μg/m^3), respectively and Ballester et al. found an OR of 1.37 during the second trimester (Ballester et al., 2010; Liu et al., 2007). Bijnens et al., in Belgium, found an association between NO_2 exposure and SGA in moderate to late preterm twins only (32–36 weeks of gestation) with OR for a 10 μg/m^3 increase of NO_2 in the second trimester, third trimester, and last month of pregnancy of 1.49, 1.51, and 1.59, respectively (Bijnens et al., 2016). In the present study, FGR was associated with NO_2 exposure in multiple pregnancies: the OR ranged from 1.35 to 1.55 for an increase of 10 μg/m^3 of NO_2 concentration depending on the period of pregnancy. Such an association in multiple pregnancies was not reported in other studies. The absence of association between NO_2 in the third trimester and FGR could be due to a lack of power, seeing as 11 women delivered before 29 weeks of gestational age.

4.2. Physiopathology

The physiopathology of the effect of NO_2 on fetal growth remains unclear. The exposure to air pollution has been suspected of increasing oxidative stress and systemic inflammation (Ghio et al., 2012; Ha et al., 2017; Møller et al., 2014), and, during pregnancy, air pollution exposure may decrease uterine blood flow, placental fetal exchange and, therefore, slow fetal growth (Biberoglu et al., 2016; Browne et al., 2015; Figueras and Gratacos, 2017; Ha et al., 2017; Prada and Tsang, 1998; Slama et al., 2008).

4.3. Outcome definitions

Many indicators of fetal growth are used in the literature: birth weight, birth length and birth head circumference, LBW (birth weight under than 2500 g), term birth weight, term LBW, SGA, term SGA, FGR, and antenatal measurements, such as biparietal diameter, femur length, abdominal diameter and estimated fetal weight measured in late pregnancy (Dadvand et al., 2013; Lepeule et al., 2010; Malmqvist et al., 2011; Malmqvist et al., 2017; Pedersen et al., 2013; Stieb et al., 2016; Vinikoor-Imler et al., 2014; Westergaard et al., 2017). Because of the high prevalence of preterm birth and LBW in multiple pregnancies due to prematurity, measures "at term" and LBW seemed to be less relevant. Conversely, SGA and FGR are determined in relation to gestational age; they are also associated with a number of diseases in childhood and adulthood (Barker et al., 1993; Figueras and Gardosi, 2011; Figueras and Gratacos, 2017; Jacobsson et al., 2008; Kady and Gardosi, 2004; Sharma et al., 2016a). Adverse growth outcomes were defined differently for SGA and FGR. SGA was objectively determined from the French perinatal network reference of birth weight for sex and gestational age (Audipog®) and compared with three other references; the association between NO_2 exposure and SGA was maintained. The definition of FGR requires further discussion. FGR was established from the ICD10 codes listed in medical records. Since 2013, FGR is defined as a defect in fetal growth on two antenatal measurements two to three weeks apart according to French, British, and Canadian recommendations (CNGOF, 2013; Lausman et al., 2013; RCOG, 2013). Our study was conducted before these recommendations were published. Even if the two antenatal measurements were performed, the diagnostic criteria may have been slightly different between operators. To confirm FGR retrospectively, we had to find two antenatal measurements with a two-week interval. However, as multiple pregnancies are also monitored outside the hospital, it is not possible to reconstruct obstetrical follow-up in full. Because FGR implies a dynamic evaluation of fetal growth during pregnancy by obstetricians, a coding effect cannot be ruled out. The multicentric quality of this study allowed for a reduction of this potential coding effect. Finally, twin-to-twin transfusion syndrome is a complication resulting from disproportionate blood supply and can result in fetal growth abnormalities. It can affect monochorionic multiples, i.e. multiple pregnancies where two or more fetuses share a chorion and a single placenta. Information for chorionicity was not available in our study. Same-sex twins can come from the same egg and share the same placenta. Twins of different sex always come from two different eggs and each has its placenta; the pregnancy is necessarily dichorionic and twin-to-twin transfusion syndrome is impossible. Moreover, the more fetuses in the uterus, the more growth is affected, so triplets are at higher risk of SGA and FGR than twins. Therefore, triplets and same-sex twins were excluded from the sensitivity analysis. The results of this analysis were not influenced by triple pregnancies or twin-to-twin transfusion syndrome, and we found a greater association between NO_2 exposure and FGR in this subgroup.

4.4. Study limits

Our study presents several limits. Compared to the multiple pregnancies recorded in the 2010 French perinatal study, this study population presented more adverse outcomes for preterm births (61.0% vs 41.7%, respectively) and LBW (69.1% birth weights < 2500 g vs 50.1%), fewer newborns with an Apgar score at 10 (77.4% of newborns vs 85.0%), fewer caesarians before labor (16.8% vs 34.1%), and less labor induction (13.3% vs 26.8%) (Blondel and Kermarrec, 2011).

Complicated multiple pregnancies are more closely monitored in public hospitals and particularly in level 3 maternity units. The two public university hospitals included in the study are also obstetrical primary care hospitals. Because of their immediate proximity for women living in the studied urban areas, the effect of the reference status of the two maternities is limited. In France, women can choose to deliver in a public or private hospital. Socioeconomic conditions, which could influence the choice between public and private hospital, are also related to environmental exposure (Goodman et al., 2011; Gray et al., 2013). However, the choice between public and private hospital status seemed more related to the risk of adverse pregnancy outcomes than to the socioeconomic conditions of the mother. In fact, in a previous study of single pregnancies without comorbidities, we did not find any difference between our study and the 2010 perinatal study, especially for maternal age and preterm birth rate (Barba-Vasseur et al., 2017; Blondel and Kermarrec, 2011).

Because of the retrospective design of the study, specific attention was paid to the data collection from medical records. Missing data occurred only for two adjustment factors of the model (malnutrition and maternal smoking during pregnancy) and affected only 8% of pregnancies. The use of a missing data class for these two factors in the principal analysis slightly decreased the OR value from 0.05 to 0.1 but did not change the significance of the OR. Another limit was the absence of information about a potential move during pregnancy – we used the mother's address at delivery, which was recorded in the hospital information system upon admission, for geocoding.

Individuals spend about 80% of the time in indoor environments (European Commission, 2004) and French women spend 16/24 h (67% of the time) inside their dwelling (Zeghnoun and Dor, 2010), but we did not use indoor air measurements for our study. Due to the retrospective design of this study, NO_2 exposure was assessed using modelled outdoor exposure. A good agreement between indoor air measurements and outdoor values obtained by modeling has been shown in a study in Vancouver, Canada (Nethery et al., 2008a, 2008b); and a retrospective modeling of exposure allows a repeatable exposure assessment. Particular attention was paid to calculate NO_2 exposure closest to the home (considering the building perimeter or in the immediate neighborhood). In fact, maternity leave for multiple pregnancies in France is at least 12 weeks before term, and time spent at home increases during maternity leave.

5. Conclusions

The study results are in favor of a negative association between environmental exposure to air pollution and fetal growth in multiple pregnancies. These results needs to be confirmed in prospective studies with antenatal measurements of fetal growth using customized birth weight standards according to maternal and fetal characteristics. The influence of environmental exposures in multiple pregnancies is rarely taken into consideration even though these pregnancies are already at high risk of complications.

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Conflicts of interest

Authors ASM, FM, SP, GT, DR, MB, JD, HH, ALP, MVB, EB, CQ and NB do not declare any conflict of interest. Author PS received funding from the following commercial companies: Merck Serono, Finox Biotech, Ferring, MSD France SAS, Teva Santé SAS, Allergan France, Gedeon Richter France, Effik SA, Karl Storz Endoscopie France, GE Medical Systems SCS, Laboratoires Genevrier, HAC Pharma, and Ipsen. The authors confirm that none of this funding was used to support the research in this study. There are no patents, products in development or marketed products to declare. This does not alter the authors' adherence to all the ICMJE policies on sharing data and materials.

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