

# Fetal Growth and Maternal Exposure to Particulate Matter during Pregnancy

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Prior studies reported an association between ambient air concentrations of total suspended particles and SO<sub>2</sub> during pregnancy and adverse pregnancy outcomes. We examined the possible impact of particulate matter up to 10 µm (PM<sub>10</sub>) and up to 2.5 µm (PM<sub>2.5</sub>) in size on intrauterine growth retardation (IUGR) risk in a highly polluted area of Northern Bohemia (Teplice District). The study group includes all singleton full-term births of European origin over a 2-year period in the Teplice District. Information on reproductive history, health, and lifestyle was obtained from maternal questionnaires. The mean concentrations of pollutants for each month of gestation were calculated using continuous monitoring data. Three intervals (low, medium, and high) were constructed for each pollutant (tertiles). Odds ratios (ORs) for IUGR for PM<sub>10</sub> and PM<sub>2.5</sub> levels were generated using logistic regression for each month of gestation after adjustment for potential confounding factors. Adjusted ORs for IUGR related to ambient PM<sub>10</sub> levels in the first gestational month increased along the concentration intervals: medium 1.62 [95% confidence interval (CI), 1.07–2.46], high 2.64 (CI, 1.48–4.71). ORs for PM<sub>2.5</sub> were 1.26 (CI, 0.81–1.95) and 2.11 (CI, 1.20–3.70), respectively. No other associations of IUGR risk with particulate matter were found. Influence of particles or other associated air pollutants on fetal growth in early gestation is one of several possible explanations of these results. Timing of this effect is compatible with a current hypothesis of IUGR pathogenesis. Seasonal factors, one of the other possible explanations, is less probable. More investigation is required to examine these findings and alternative explanations. *Key words:* air pollution, environmental exposure, fetal growth, intrauterine growth retardation, particulate matter, PM<sub>2.5</sub>, PM<sub>10</sub>, reproductive effects. *Environ Health Perspect* 107:475–480 (1999). [Online 4 May 1999] <http://ehpnet1.niehs.nih.gov/docs/1999/107p475-480dejmek/abstract.html>

The Teplice Program, an international research project, was developed to evaluate health consequences of extremely elevated air pollution levels in Teplice, a district in the Northern Bohemia brown coal basin. Typically, air pollution in this area is composed of a high concentration of fine particles dominated by acid sulfates, polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides, and toxic trace elements (1). The levels are especially high during meteorological inversions, which occur frequently during the fall and winter months. Changes in industry profiles, technological improvement of large power plants, and a rapid conversion of local heating systems from coal to gas, along with increasing traffic density, have resulted in changes in the pollutant levels and composition. With changes occurring after the political changes in the Czech Republic in 1989, a continual decrease of sulfur dioxide (SO<sub>2</sub>) and particulate matter has been observed over the last several years. In the meantime, this area presented an opportunity to study the health effects while relatively high pollutant levels exist.

One key interest in the Teplice area has been the possible effects of these pollutants on growth and development. To examine this, intrauterine growth retardation (IUGR) and measures of air pollution were examined.

Reduced fetal growth is one of the most important predictors of neonatal morbidity and mortality (2–4). Recent studies have also shown a relationship between some serious adult risks (namely noninsulin-dependent diabetes, hypertension, and coronary heart disease) and impaired growth in the prenatal and early postnatal period (5–7).

Preliminary analyses of the data collected during the first 18 months of the study resulted in two general observations: *a*) pollutant levels in this region [namely SO<sub>2</sub>, particulate matter ≤ 10 µm in size (PM<sub>10</sub>), and PAHs] were highest during the winter and lower in the summer, as measured by continuous air monitoring (8); and *b*) the prevalence of IUGR was greater for infants conceived during winter months than for those conceived in the summer (1). These preliminary observations are consistent with recent hypotheses for the etiology of IUGR—that initial changes leading to fetal growth retardation may be triggered in early pregnancy, around the time of implantation (9,10).

Other preliminary examinations of these data analyzed IUGR prevalence with selected air pollutants in early pregnancy. No association was observed for nitrogen oxides (NO<sub>x</sub>). SO<sub>2</sub> and PM<sub>10</sub> levels in early pregnancy were significantly associated

with IUGR (11,12); the relationship of PM<sub>10</sub> to IUGR was confirmed in subsequent analyses in a more complete data set enlarged by additional 1996 data (12).

Particulate matter has been associated with acute cardio-respiratory morbidity and mortality in recent studies (13,14). Two common measures of particulate matter are PM<sub>10</sub> and particulate matter up to 2.5 µm in size (PM<sub>2.5</sub>). The chemical composition of particles and of associated organics may vary by region, and is important to the understanding of potential toxicity (8).

The present study examines whether parental exposure to particulate matter in outdoor air during pregnancy is associated with IUGR. This evaluation uses ambient PM<sub>10</sub> and PM<sub>2.5</sub> measurements to examine this issue.

## Materials and Methods

The study group included all full-term singleton births of European origin in Teplice District from April 1994 through March 1996 to women with at least 1 year of residence in the district. All deliveries in Teplice District are hospitalized, allowing enrollment in the study during the hospital stay. The group was further restricted to the mother's first delivery during the study period. Preterm births (< 37 weeks gestation) were excluded from this analysis because of the

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differences in factors affecting fetal growth (15). Only mothers who completed the written informed consent were enrolled in the study.

Approximately 14% of births in the Teplice District are not of European ancestry. Most of these are Gypsies (95.2%) ethnically originating from India; the few remaining are of Asian origins (Chinese or Vietnamese). Because mature Gypsy infants are generally lighter than those of European origin (16), standards for fetal growth evaluation based on European birth data are unsuitable for evaluation of the growth of Gypsy babies. Therefore, Gypsy births, along with other births of non-European origin, were excluded from the present analyses.

Personal and lifestyle data were obtained via self-administered maternal

questionnaires and medical records. These data included occupational and other exposures, smoking and consumption of alcohol, past reproductive history, health status, and use of medication. Questionnaires were completed in the hospital after delivery, with the assistance of a specially trained nurse. Because the women reported their partners' information, more data are missing for paternal characteristics. These characteristics were examined in more detail among the married couples, where proportionately more complete paternal data were available. In addition to the maternal questionnaire data, the hospital staff used standardized forms created for this project to collect medical and health care data on the course and outcome of the pregnancy.

An IUGR birth was defined as one whose birth weight fell below the 10th

percentile, by gender and gestational week, for live births in the Czech Republic (1991–1993) (17). The gestational age (GA) in weeks was estimated by gynecologists using each woman's prenatal history log (her maternity card), which included her reported last menstrual period (LMP) plus data on prenatal visits, ultrasound measurements, etc. Prenatal care began early for most women: 93% began prenatal care and had an ultrasound examination in the first trimester of pregnancy. The estimated date of conception (EDC) was calculated using the GA and correcting from the LMP (decreasing the GA by 2 weeks).

The concentrations of PM<sub>10</sub> and PM<sub>2.5</sub> were continuously measured in Teplice from July 1993 through March 1996, using a versatile air pollution sampler (VAPS) (18) and methods developed by

**Table 1.** Demographic and lifestyle characteristics of study group.

	Intrauterine growth retardation			Others		
	Mean ± SD	Range	No. (%)	Mean ± SD	Range	No. (%)
Total			190 (9.8)			1,753 (90.2)
Mother's characteristics						
Age at delivery	24.7 ± 5.0	16–42		24.7 ± 4.7	15–44	
Years of education*	11.0 ± 2.0	7–18		11.5 ± 1.9	6–19	
Completed high school <sup>a</sup> *			128 (67.4)			1,448 (82.6)
Height (cm)*	163.9 ± 6.8	144–185		166.3 ± 6.3	148–187	
Prepregnancy weight (kg)*	58.4 ± 11.4	40–120		62.3 ± 12.0	38–131	
Number of live births (including current)	1.7 ± 1.0	1–7		1.7 ± 0.9	1–9	
Primiparous			104 (54.7)			866 (49.4)
Currently married*			119 (62.6)			1,343 (76.6)
Worked during pregnancy			105 (55.3)			1,058 (60.4)
Smokers						
Before pregnancy*			91 (47.9)			642 (36.6)
Cigarettes/day among smokers*	12.8 ± 6.2	2–30		11.2 ± 6.2	1–40	
Trimester 1*			64 (33.7)			393 (22.4)
Cigarettes/day among smokers	8.2 ± 5.9	2–20		7.4 ± 5.1	1–30	
Trimester 2*			47 (24.7)			275 (15.7)
Cigarettes/day among smokers	7.3 ± 5.2	2–20		6.0 ± 4.4	1–20	
Trimester 3*			42 (22.1)			253 (14.4)
Cigarettes/day among smokers	7.0 ± 5.6	2–20		5.7 ± 4.8	1–30	
Passive smokers*			125 (65.8)			950 (54.2)
No. cigarettes/day smoked by others at home	13.4 ± 12.1	1–60		11.3 ± 10.7	1–70	
Alcohol						
≥ 1/week before pregnancy			24 (12.6)			265 (15.1)
≥ 1/week during pregnancy			12 (6.3)			104 (5.9)
Gestational age at delivery (from LMP)	39.8 ± 1.1	37–42		39.8 ± 1.1	37–43	
Winter at conception			103 (54.2)			846 (48.3)
Winter at delivery			80 (42.1)			867 (49.5)
First year of study			99 (9.6)			932 (90.4)
Second year of study			91 (10)			821 (90.0)
Birth weight (g)*	2,656 ± 223	1,800–3,050		3,430 ± 389	2,400–5,450	
Father's characteristics <sup>b</sup>						
Age at delivery	28.2 ± 7.1	17–57		27.3 ± 6.1	16–55	
Years of education*	11.4 ± 1.8	8–18		11.7 ± 2.0	6–23	
Completed high school <sup>a</sup>			153 (86.8)			1,482 (84.5)
Smokers*			119 (62.0)			944 (53.8)
Total cigarettes per day	15.3 ± 7.9	1–40		14.3 ± 7.9	1–80	
Alcohol: ≥ 1/week			77 (40.5)			804 (45.9)
Employed during pregnancy			165 (86.8)			1,589 (90.6)
Ambient levels of PM <sub>10</sub> , Teplice, month 1*,**	48.2 ± 12.6	28.9–81.0		45.7 ± 12.1	28.9–81.1	
Ambient levels of PM <sub>2.5</sub> , Teplice, month 1*,**	35.6 ± 11.7	17.1–64.6		33.4 ± 11.2	17.1–64.6	

Abbreviations: PM<sub>2.5</sub>, particulate matter ≤ 2.5 μm in size; PM<sub>10</sub>, particulate matter ≤ 10 μm in size; SD, standard deviation.

<sup>a</sup>Education systems have changed several times in the Czech Republic; at certain times the completion of the equivalent of high school was 11 years, at other times it was 12 years. This cut-off used < 11 years versus ≥ 11 years. <sup>b</sup>Data on fathers obtained from mothers; some of these data are incomplete. \*Significant difference at  $p < 0.05$ , by  $t$ -test or chi square. \*\*Only the mean PM<sub>10</sub> and PM<sub>2.5</sub> levels in the first month of pregnancy were significantly different,  $p < 0.05$ .



the U.S. Environmental Protection Agency (8). The VAPS is a modified dichotomous sampler that collects ambient aerosol in two fine particle samples and a coarse particle sample; 24-hr values were obtained directly from the analysis of filters. Each mother's PM<sub>10</sub> and PM<sub>2.5</sub> levels were estimated using averages for each of nine consecutive 30-day periods after the EDC; these periods correspond roughly to the 9 months of gestation. For each month, the PM data were divided into three categories for analysis: low (L), medium (M), and high (H). For PM<sub>10</sub>, these cutoffs were L, < 40 µg/m<sup>3</sup>; M, 40 to < 50 µg/m<sup>3</sup>; and H, ≥ 50 µg/m<sup>3</sup>. PM<sub>2.5</sub> cutoffs were L, < 27 µg/m<sup>3</sup>; M, 27–37 µg/m<sup>3</sup>; and H, ≥ 37 µg/m<sup>3</sup>. These cutoffs are roughly equal to tertiles for both pollutants. In the analyses, these categories were examined as dummy variables (medium vs. low, high vs. low) so that a dose–response relationship was not imposed on the initial analyses. An additional analysis using continuous data was done to evaluate the possibility of a dose–response relationship.

The univariate relationships between IUGR and characteristics of the parents were initially examined using *t*-test and chi-square analyses (19). Important parental characteristics identified in the literature included maternal age, education, marital status, number of live births, height, prepregnancy weight, alcohol consumption, maternal active and passive smoking, and paternal smoking (20–24). Parental employment and occupational exposures were also evaluated.

Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using PROC LOGISTIC (25). Each month of pregnancy was analyzed separately, allowing some factors to vary over time (e.g., particulate matter, maternal smoking and alcohol consumption, and season). Although particulate matter levels were associated with season, season alone might also be a surrogate for other changes such as weather patterns (e.g., temperature levels) and consumption of fruits and vegetables. Summer was defined as the months from April through September and winter as October through March. Because air pollution levels have changed in Teplice District over time, the potential for secular changes over the time frame of this study were evaluated by comparing results from the 2 years. Characteristics of the parents summarized in Table 1 were evaluated for inclusion in the model. Some factors considered for analysis were highly correlated (e.g., mother's smoking history, her passive smoking, and paternal smoking), and thus development of the final model used a

stepwise approach to select the most important factors. After this initial stage, other factors were examined for potential confounding by comparing the ORs for exposure with and without that factor (25).

## Results

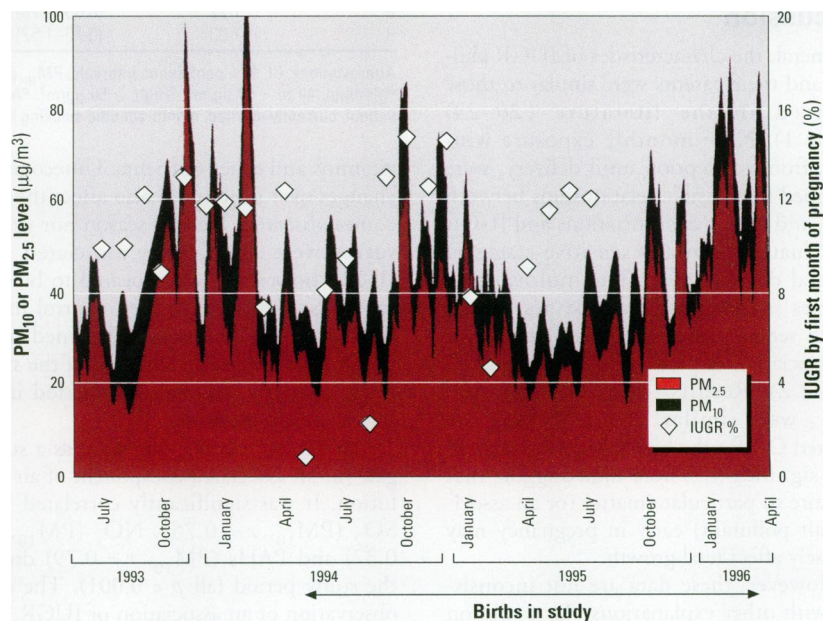
Daily concentrations of PM<sub>10</sub> varied from 4 to 333 µg/m<sup>3</sup>, with a mean of 47.6 µg/m<sup>3</sup> [standard deviation (SD) = 31.6 µg/m<sup>3</sup>] from May 1993 through March 1996; 30-day averages, calculated for nine time periods for each pregnancy, varied from 29 to 86 µg/m<sup>3</sup>, with a mean of 47.7 µg/m<sup>3</sup> (SD = 12.6 µg/m<sup>3</sup>) during the period studied (Figure 1). For PM<sub>2.5</sub> the daily levels varied from 1 to 332 µg/m<sup>3</sup>, with a mean of 35.6 µg/m<sup>3</sup> (SD = 26.3 µg/m<sup>3</sup>); 30-day averages varied from 17 to 70 µg/m<sup>3</sup>, with a mean of 35.7 µg/m<sup>3</sup> (SD = 11.8 µg/m<sup>3</sup>). The values were highest in winter months because of inversions and greater use of coal for heating, and were lowest in summer months (Figure 1). The correlation between season and particulate matter levels was significant, ranging from 0.49 to 0.60 (*p* < 0.01) for monthly average PM<sub>10</sub> and from 0.50 to 0.62 (*p* < 0.01) for monthly average PM<sub>2.5</sub>.

A total of 2,478 women had live births during the 2-year study period. Of these, a total of 535 were excluded: 308 births of non-European ethnic origins, 16 twin births, 109 second pregnancies to a mother with a birth already in the study, and 92 preterm births (< 37 weeks gestation). Only 10 mothers refused to participate. Thus, the

study included 1,943 women who gave birth to infants between 37 and 43 gestational weeks (as determined by the physician using the ultrasound and the maternal report of LMP). A total of 190 (9.8%) infants in the study were below the 10th percentile of birth weight for GA (Table 1). Parents of IUGR infants differed from the remainder of the parents in both parents' education, marital status, and smoking, and on maternal height, weight, and number of cigarettes smoked per day before and throughout the pregnancy (Table 1).

Elevated crude ORs were observed for IUGR at medium and high PM<sub>10</sub> levels in the first month of pregnancy (Table 2). As compared to the lowest level, the medium level OR was 1.47 (CI, 0.99–2.16) and the high level OR was 1.85 (CI, 1.29–2.66). PM<sub>2.5</sub> levels were highly correlated with PM<sub>10</sub> (*r* = 0.98, *p* < 0.01); therefore, the analyses for PM<sub>2.5</sub> followed similar patterns: IUGR was not significantly elevated with the medium exposure (OR, 1.16; CI, 0.80–0.69), but was for the high exposure (OR, 1.68; CI, 1.18–2.40).

The factors described in Table 1 were evaluated for use in multivariable logistic regression. Because of significant correlation among a number of these variables, the final models included prepregnancy weight, height, marital status (currently married vs. not currently married), maternal smoking (none, 1–9 cigarettes/day, or ≥ 10 cigarettes/day), education (completed high school vs. less schooling), season of conception, and the year within the study period



**Figure 1.** Fifteen-day running averages of PM<sub>10</sub> and PM<sub>2.5</sub> levels (µg/m<sup>3</sup>) as compared to percent IUGR by first month of pregnancy. Abbreviations: IUGR, intrauterine growth retardation; PM<sub>2.5</sub>, particulate matter ≤ 2.5 µm in size; PM<sub>10</sub>, particulate matter ≤ 10 µm in size.

(year 1 vs. year 2). Although season and year of study were not significantly related to IUGR, these were confounders in the analysis for the first month of gestation, and as such were present in all final analyses. Because of the time lag between conception, recognition of pregnancy, and the subsequent behavior changes resulting from personal choice or prenatal symptoms, the prepregnancy smoking history was also used for the first 2 months of pregnancy.

Season and year were tested for confounding because of their association with exposure and their potential association with IUGR. When added to the final model, the year alone did not appreciably affect the results; however, season did. When both season and year were added, confounding was noted, especially in the high exposure groups (Table 3). Subsequent analyses all include season and year.

Both the medium and high exposures were statistically significant for PM<sub>10</sub>: the medium level OR was 1.62 (CI, 1.07–2.46) and the OR for the high level was 2.64 (CI, 1.48–4.71) (Table 4). Similar patterns were also observed for PM<sub>2.5</sub>: medium level ORs were 1.26 (0.81–1.95) and high level ORs were 2.11 (1.20–3.70). Once the analysis with dummy variables suggested an exposure–response relationship, an analysis of continuous data was examined. Increases in ORs were found for the first month of pregnancy: for each 20- $\mu\text{g}$  interval, the OR for PM<sub>10</sub> was 1.50 (CI, 1.15–1.96); for PM<sub>2.5</sub> it was 1.34 (CI, 0.98–1.82;  $p = 0.06$ ). These findings suggest an increasing dose–response relationship.

## Discussion

In general, the characteristics of IUGR children and their parents were similar to those observed in the literature (20–24) (Table 1). Nine monthly exposure windows, from conception until delivery, were examined for possible relationships between PM<sub>10</sub> and PM<sub>2.5</sub> concentrations and IUGR to evaluate potentially sensitive stages of prenatal development. The multivariable analyses suggest that the first gestational month seems to be the critical period for the association of particles with fetal growth (Table 2). Results for both PM<sub>10</sub> and PM<sub>2.5</sub> were similar, although only the adjusted OR for the high PM<sub>2.5</sub> was statistically significant. These data suggest that exposure to particulate matter (or an associated air pollutant) early in pregnancy may adversely affect fetal growth.

However, these data are not inconsistent with other explanations. Air pollution in this region varies seasonally, as do other factors in the environment. For example, seasonal variations in fruit and vegetable consumption could affect the intake of

**Table 2.** Crude odds ratios (OR) of intrauterine growth retardation for particulate matter  $\leq 10 \mu\text{m}$  in size, by month of gestation.

Month	Medium <sup>a</sup>			High <sup>b</sup>		
	OR	CI	p-Value	OR	CI	p-Value
1	1.47	(0.99–2.16)	0.055	<b>1.85</b>	<b>(1.29–2.66)</b>	<b>0.001</b>
2	1.14	(0.78–1.67)	0.50	1.30	(0.90–1.86)	0.16
3	1.10	(0.76–1.60)	0.62	1.16	(0.81–1.66)	0.41
4	1.34	(0.92–1.95)	0.13	1.16	(0.80–1.67)	0.44
5	0.92	(0.64–1.31)	0.63	0.86	(0.59–1.24)	0.42
6	0.90	(0.64–1.27)	0.54	0.69	(0.47–1.02)	0.06
7	0.82	(0.58–1.16)	0.26	0.77	(0.53–1.12)	0.17
8	1.08	(0.77–1.51)	0.66	0.78	(0.52–1.17)	0.23
9	0.90	(0.64–1.28)	0.56	0.89	(0.61–1.30)	0.53

CI, 95% confidence intervals. Significant results in bold.  
<sup>a</sup>Medium, 40 to < 50  $\mu\text{g}/\text{m}^3$ . <sup>b</sup>High,  $\geq 50 \mu\text{g}/\text{m}^3$ .

**Table 3.** Evaluation of confounding for the first month of pregnancy.

	PM <sub>10</sub> odds ratio (CI)		PM <sub>2.5</sub> odds ratio (CI)	
	Medium <sup>a</sup>	High <sup>b</sup>	Medium <sup>c</sup>	High <sup>d</sup>
Basic model <sup>e</sup>	1.46 (0.98–2.17)	1.85 (1.28–2.69)	1.12 (0.77–1.64)	1.68 (1.17–2.42)
With year	1.48 (1.00–2.21)	1.93 (1.32–2.82)	1.14 (0.78–1.67)	1.74 (1.20–2.53)
With season	1.57 (1.04–2.36)	2.39 (1.37–4.17)	1.21 (0.79–1.85)	1.95 (1.14–3.33)
With season + year	1.62 (1.07–2.46)	2.64 (1.48–4.71)	1.26 (0.81–1.95)	2.11 (1.20–3.70)

Abbreviations: CI, 95% confidence intervals; PM<sub>2.5</sub>, particulate matter  $\leq 2.5 \mu\text{m}$  in size; PM<sub>10</sub>, particulate matter  $\leq 10 \mu\text{m}$  in size.

<sup>a</sup>Medium, 40 to < 50  $\mu\text{g}/\text{m}^3$ . <sup>b</sup>High,  $\geq 50 \mu\text{g}/\text{m}^3$ . <sup>c</sup>Medium, 27 to < 37  $\mu\text{g}/\text{m}^3$ . <sup>d</sup>High,  $\geq 37 \mu\text{g}/\text{m}^3$ . <sup>e</sup>Adjusted for maternal height, prepregnancy weight, completed high school, currently married, and month-specific smoking habits.

**Table 4.** Adjusted odds ratios of intrauterine growth retardation for PM<sub>10</sub> by month of gestation.

Month	Medium <sup>a</sup>			High <sup>b</sup>		
	Adjusted odds ratio <sup>c</sup>	CI	p-Value	Adjusted odds ratio <sup>c</sup>	CI	p-Value
1	<b>1.62</b>	<b>(1.07–2.50)</b>	<b>0.02</b>	<b>2.64</b>	<b>(1.48–4.71)</b>	<b>0.001</b>
2	1.09	(0.72–1.63)	0.69	1.01	(0.60–1.69)	0.98
3	1.02	(0.68–1.54)	0.93	0.87	(0.51–1.47)	0.59
4	1.27	(0.85–1.90)	0.25	0.93	(0.55–1.58)	0.78
5	0.92	(0.62–1.36)	0.66	0.82	(0.48–1.39)	0.46
6	0.95	(0.65–1.39)	0.77	0.74	(0.42–1.30)	0.29
7	0.83	(0.57–1.21)	0.33	0.83	(0.49–1.42)	0.50
8	1.22	(0.83–1.79)	0.31	1.16	(0.66–2.03)	0.61
9	1.03	(0.70–1.52)	0.88	1.25	(0.73–2.12)	0.42

Abbreviations: CI, 95% confidence intervals; PM<sub>10</sub>, particulate matter  $\leq 10 \mu\text{m}$  in size. Significant results in bold.

<sup>a</sup>Medium, 40 to < 50  $\mu\text{g}/\text{m}^3$ . <sup>b</sup>High,  $\geq 50 \mu\text{g}/\text{m}^3$ . <sup>c</sup>Adjusted for maternal height, prepregnancy weight, completed high school, currently married, month-specific smoking habits, year, and season.

vitamins and other nutrients. Unrecognized changes over time could also affect the outcomes observed. Neither season nor year of survey were significantly associated with IUGR; however, both appeared to be confounders, and thus required control in the final analyses. The results obtained using adjustment for season and year of the study make a strictly seasonal/time period interpretation less probable.

Particulate matter may serve as a surrogate for an associated component of air pollution. It was significantly correlated with SO<sub>2</sub> (PM<sub>10</sub>,  $r = 0.75$ ), NO<sub>x</sub> (PM<sub>10</sub>,  $r = 0.37$ ) and PAHs (PM<sub>10</sub>,  $r = 0.79$ ) during the study period (all  $p < 0.001$ ). The early observation of an association of IUGR with SO<sub>2</sub> levels in early pregnancy (11) may have been due to the transiently high correlation between SO<sub>2</sub> and particulate matter in the initial stage of the study: the correlation

between PM<sub>10</sub> (PM<sub>2.5</sub>) and SO<sub>2</sub> decreased from 0.94 (0.94) in the first year of the study to 0.72 (0.73) in the subsequent year, as the levels of SO<sub>2</sub> declined.

Two overlapping classes of particles (PM<sub>10</sub> and PM<sub>2.5</sub>) were examined to determine the possible differences in their effect. Monthly averages were highly correlated (0.97;  $p < 0.001$ ) during the study period. The general patterns of results for both were consistent, although the association was stronger between IUGR and PM<sub>10</sub>. Because respiratory tract deposition of particles generally increases with size from 2.5  $\mu\text{m}$  to 10  $\mu\text{m}$  (26), PM<sub>10</sub> may better represent an individual's total exposure.

Particulate matter is difficult to study. It is not an exactly defined toxicant; its dispersion and composition depends on the particular source. For this study, detailed data are available on the origin and composition

of pollutants in the Teplice region from an air quality monitoring and receptor modeling study (8). Emissions from residential space heating and power plants were identified as major sources of fine particle mass including a spectrum of PAHs and their nitro-derivatives. No matter which particular toxicant associated with particulate matter could affect fetal growth, the biologic mechanisms remain to be explained. The effective components would need to be inhaled and absorbed into the maternal bloodstream. Highly biologically active compounds (e.g., PAHs or their nitro-derivatives) might interfere with some process or processes, affecting development or nutrition of the fetus. Alternatively, some related toxicant could cross the placenta with direct effects on fetal development. In a recent biomarker study, Perera and co-workers (27) found a significant association of fetal development [low birth weight (LBW) and head circumference of newborns] with PAH-DNA adduct levels; these results suggest that transplacental exposure to PAHs in ambient air may compromise fetal development. Topinka et al. (28) investigated DNA adducts in placentas of mothers from a subset of the women in this study, comparing them to mothers living in a less polluted area; DNA adduct levels were significantly higher in the placentas from Teplice District.

The timing of the associations observed in this study (during early gestation) is consistent with observations in studies of laboratory animals: acute radiation administered during early gestation induced IUGR in rats; the most sensitive stage was early organogenesis, corresponding to days 15–28 of human gestation (29). In addition, exposure to cyclophosphamide around the time of implantation induced growth retardation in mice fetuses (30). Others have found that IUGR is one of the most common outcomes of mutagenic treatment, even in prezygotic stages (31).

Effects during early pregnancy are consistent with current information on the etiology of IUGR. Nutrient and oxygen supply to the fetus during various gestational stages is a key factor in the regulation of fetal growth (32,33). Several new findings on this topic suggest that the pathogenesis resulting in IUGR is triggered by an abnormal reaction between trophoblast and uterine tissues in the first weeks of pregnancy (9,10). The altered growth may arise from defective trophoblast invasion, resulting in suboptimal placentation and maternal hemodynamic maladaptation (10,34). These changes could result in reduced growth and fetal adaptation to undernutrition with subsequent permanent changes in

the structure and function of a range of organs and tissues (5,32). This hypothesis locates the start of IUGR pathogenesis to the time around implantation. The timing of IUGR-PM<sub>10</sub> associations in this study is compatible with this hypothesis.

At this time, few papers have examined potential associations of pregnancy outcomes and air pollution. In 1992, Bobák and Leon (35) reported an association of TSP (total suspended particles) and SO<sub>2</sub> with neonatal and postneonatal mortality. In a study based on the same data, these investigators reported a significant association of LBW with SO<sub>2</sub> and TSP level in 45 districts in the Czech Republic (36). Woodruff et al. (37) found an association of early postneonatal mortality with PM<sub>10</sub> level after birth for selected causes of death in the United States.

Two recent reports from China (38,39) examined reproductive effects of SO<sub>2</sub> and TSP in a large, well designed study in Beijing. The first report (38) is of a significant association of both pollutants with increased preterm births. The second study (39) reports an increasing exposure-response relationship of LBW, controlled for GA, with SO<sub>2</sub> and TSP level. In their examination of timing of air pollution effects, the investigators first examined third trimester exposures. These were associated with LBW: for each 100 µg/m<sup>3</sup> increase in TSP exposure, the OR was 1.10 (CI, 1.01–1.20). The association was significant in 2 of 4 years of the study. Examination of potential additional effects of exposures earlier in gestation, controlling for third trimester exposures, did not significantly add to the model. The earlier exposures were not examined independently of the third trimester exposures. The two studies (in Beijing and in Teplice) both examined full-term births (GA of 37 weeks or more). Similar proportions of the two study groups were LBW: 2.9% in Beijing and 2.4% in Teplice. However, the outcome measures were not strictly comparable: in Beijing, LBW was used, with an adjustment for length of gestation; in Teplice, lower birth weight by GA or IUGR was used. The difference between the two definitions is illustrated in a comparison of LBW and IUGR in Teplice: 22.6% of IUGR births were also LBW, but 93.5% of LBW were IUGR. Thus, using LBW as an outcome tends to focus on births with shorter gestations, whereas IUGR tends to focus on smaller births at all gestations. Other differences occur in the exposure sources and measurements: outdoor TSP in Beijing mostly comes from coal combustion for cooking and heating whereas Teplice's pollution comes mostly from traffic and power plants (most of the local home heating has been converted from

coal to gas in recent years). Thus, the actual composition of air pollution may be substantially different. TSP levels were higher in the Chinese study: mean concentration in the third trimester ranged from 211 to 618 µg TSP/m<sup>3</sup>, as compared to 43 to 182 µg TSP/m<sup>3</sup> in Teplice District during the study period. However, the important component of TSP is the respirable fraction; the proportion of finer respirable particles in TSP in Beijing was not reported. Etiologies of both IUGR and LBW are complex and only partly understood. More data are needed to make a meaningful comparison of the Teplice and Beijing studies.

The results presented here are based on data of unequal reliability. Some questionnaire data (maternal age, other personal data, birth weight, or infant sex) were cross-checked using several information sources. Pollution data were measured using U.S. Environmental Protection Agency developed and regularly calibrated equipment and standardized methods; these data should be reliable. However, an important assumption is made in the assignment of exposure to the different time periods: that the measured level at the central air pollution station is representative of an individual woman's exposure. Different areas within the community, varying wind conditions in this mountainous area, varying personal habits, and differences in daily routine may result in wide variations in an individual's actual exposure. In addition, an effective centralized information and warning system for the Teplice region notifies inhabitants to minimize outdoor activities during inversion episodes. If these warnings are heeded, the true exposures may be lower during the more extreme weather conditions. Thus, the estimation of associations for higher PM<sub>10</sub> levels could be at lower levels because of changes in behavior during those episodes.

Data on indoor/outdoor exposures from the Teplice region (40) suggest that PM<sub>10</sub> levels in nonsmoker's homes are approximately 50–60% of outdoor PM<sub>10</sub> exposure. Concentrations in smoker's homes are substantially higher and therefore are less affected by outdoor levels. This emphasizes the importance of controlling for active/passive smoking in the analysis. In this study group, active smoking of the mothers and their exposure to environmental tobacco smoke were correlated; therefore, just their active smoking was controlled in the analysis.

Another factor affecting the correct estimation of exposure is the determination of the EDC. Errors in EDC could blur or wholly dissolve the exposure-period relationship; systematic error may shift to another time period. To prevent this shift, the EDC determination was estimated using maternal

prenatal records completed in early pregnancy. Thus, systematic errors in the EDC, as well as in the determination of the length of gestation, are less likely.

On the other hand, some other information could be less reliable. Information about drinking or smoking in pregnancy might be underestimated because of the woman's concern about reporting the continuation of these behaviors during pregnancy. Because the key associations were identified for the first month of pregnancy, where prepregnancy data were used, pregnancy related underreporting of alcohol and cigarette use should not affect these results.

Effects during the first month of gestation were observed for monthly averages  $> 40 \mu\text{g}/\text{m}^3$ . These levels are also observed in other industrialized parts of Czech Republic (41) and in other countries (37). Therefore, potential adverse effects of pollutants may be relevant for a broader population.

## Conclusions

This paper examined the relationship between IUGR and ambient levels of particulate matter finer than  $10 \mu\text{m}$  in Teplice District, a highly polluted region in the Czech Republic. Increases in IUGR were associated with  $\text{PM}_{10}$  levels over  $40 \mu\text{g}/\text{m}^3$  and  $\text{PM}_{2.5}$  levels over  $37 \mu\text{g}/\text{m}^3$  during early pregnancy in the highly polluted district of Teplice. This relationship remains after controlling for season. The timing of this effect is compatible with a current hypothesis that IUGR may be induced during the early stages of development. Present data suggest the need for further work on the relationship of IUGR and varying components of air pollution. Future investigations could include an examination of the physical and chemical properties of particles, PAH fractions, and examination of biomarkers (DNA adducts, cotinine). Such data should increase our understanding of the potential role of the environment on IUGR risk.

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