




## Article

# Effect of Particulate Matter 2.5 on Fetal Growth in Male and Preterm Infants through Oxidative Stress

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**Citation:** Park, S.; Kwon, E.; Lee, G.; You, Y.-A.; Kim, S.M.; Hur, Y.M.; Jung, S.; Jee, Y.; Park, M.H.; Na, S.H.; et al.

Effect of Particulate Matter 2.5 on Fetal Growth in Male and Preterm Infants through Oxidative Stress.

*Antioxidants* **2023**, *12*, 1916.

<https://doi.org/10.3390/antiox12111916>

Academic Editors: Reto Asmis and Yasuhiro Yoshida

Received: 19 September 2023

Revised: 17 October 2023

Accepted: 24 October 2023

Published: 26 October 2023



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**Abstract:** Particulate matter 2.5 (PM<sub>2.5</sub>) levels are associated with adverse pregnancy outcomes. In this retrospective cohort study, we examined whether the concentration of indoor PM<sub>2.5</sub> affected pregnancy outcomes. Additionally, we evaluated biomarkers of pregnancy-related complications caused by fine dust. We collected clinical information and data based on residential addresses from the Air Korea database to assess PM<sub>2.5</sub> exposure levels. As a multicenter prospective cohort study, we measured the indoor PM<sub>2.5</sub> concentration and inflammatory and oxidative stress markers. The PM<sub>2.5</sub> concentration of the low-birth-weight (LBW) delivery group was 27.21 µg/m<sup>3</sup>, which was significantly higher than that of the normal-birth-weight (NBW) group (26.23 µg/m<sup>3</sup>) ( $p = 0.02$ ). When the newborns were divided by sex, the PM<sub>2.5</sub> concentration of the LBW group was 27.89 µg/m<sup>3</sup> in male infants, which was significantly higher than that of the NBW group (26.26 µg/m<sup>3</sup>) ( $p = 0.01$ ). In the prospective study, 8-hydroxy-2-deoxyguanosine significantly increased in the high-concentration group (113.55 ng/mL, compared with 92.20 ng/mL in the low-concentration group); in the high-concentration group, the rates of preterm birth (PTB) and small size for gestational age significantly increased ( $p < 0.01$ ,  $p = 0.01$ ). This study showed an association between PM<sub>2.5</sub>, oxidative stress, and fetal growth, with the PTB group being more vulnerable.

**Keywords:** 8-hydroxy-2-deoxyguanosine; biomarker; indoor air; low birth weight; particulate matter; preterm birth; sex difference; small for gestational age

## 1. Introduction

Low birth weight (LBW; birth weight < 2500 g, regardless of gestational age), small for gestational age (SGA; birth weight below the 10th percentile for gestational age), and preterm birth (PTB; delivery at <37 weeks of gestation) are complications of pregnancy that directly affect the prognosis of newborns [1–7]. The incidence of LBW varies by country (range, 6–25%); however, LBW births are associated with short- and long-term complications [8,9]. The prevalence of SGA births is approximately twice that of LBW [10]. Previous studies have investigated sociodemographic and medical risk factors as well as environmental risks (i.e., exposure to toxic substances) for LBW [10].

Particulate matter (PM) 2.5 (PM<sub>2.5</sub>, particles with an aerodynamic diameter of  $\leq 2.5$   $\mu\text{m}$ ), one of the major air pollutants, has been reported to be associated with various adverse pregnancy outcomes [11,12]. In particular, associations between PM<sub>2.5</sub> and LBW, PTB, and SGA infants have been reported [5–7,11]. Most studies have conducted exposure assessments using outdoor air quality measurements [5,7,11,13]. Recently, it was found that 80–90% of individuals live indoors, and the importance of indoor air quality has been gradually emphasized [14,15]. Therefore, the importance of measuring indoor PM concentrations is increasing, and individual indoor fine dust exposure may reveal better causal relationships between PM<sub>2.5</sub> and pregnancy outcomes [14,16,17].

There is a lack of understanding of the pathogenesis of PM<sub>2.5</sub> affecting fetal growth. Various studies have been conducted to understand the cause of fetal growth restriction [18,19]. The analysis of sex differences is useful in understanding biological mechanisms. Although biological mechanisms are influenced by PM regardless of sex, sex-specific effects remain controversial [11,16,20]. It is also controversial whether exposure to PM at any stage of pregnancy has a greater effect on fetal growth [21,22].

Recently, various biomarkers have been developed to evaluate exposure to fine dust [23], and attempts have been made to explain fetal growth based on DNA methylation or telomere length in cord blood [16,24–26]. However, cord blood is not suitable for biomonitoring, because it is difficult to sample during pregnancy. Although there are many studies on oxidative stress, inflammation, DNA damage, and epigenetic modulation as biomarkers of exposure to PM, there are few biomarker studies on pregnant women [23].

Therefore, this study aimed to examine whether the concentration of PM<sub>2.5</sub> affects fetal growth through indoor PM measurement. We also evaluated biomarkers of pregnancy-related complications caused by fine dust as well as indicators for the biomonitoring of PM<sub>2.5</sub> exposure.

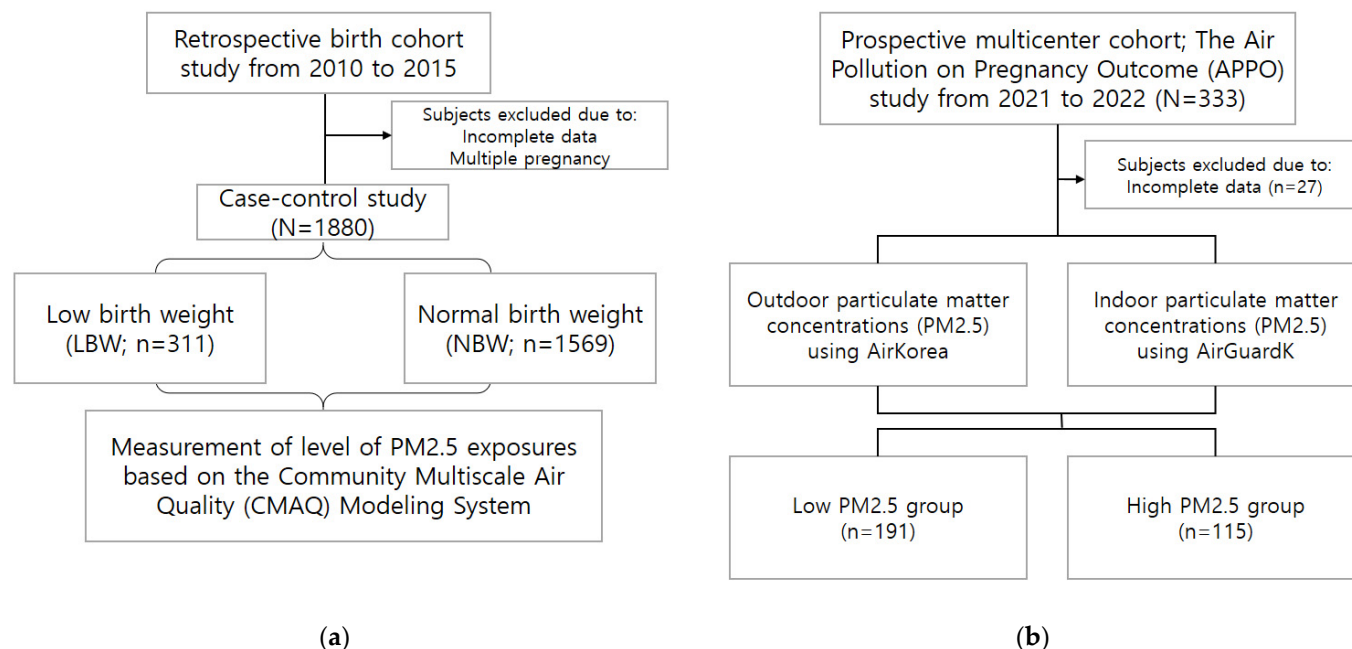
## 2. Materials and Methods

### 2.1. Study Design of Cohort I

The first study was a hospital-based retrospective cohort study of 1880 pregnant women who delivered live babies between 2010 and 2015 at the Ewha Womans University Mokdong Hospital (EUMC 2020-07-043). We collected information on maternal age; body mass index (BMI); gestational age at birth (GAB); neonatal sex; weight and height at birth; appearance, pulse, grimace, activity, and respiration (APGAR) score; and place of residence at the time of delivery. The Air Korea database was used for PM<sub>2.5</sub> exposure assessment, which includes hourly accumulated air pollution monitoring data for components such as sulfur dioxide, PM<sub>10</sub>, carbon monoxide, nitrogen dioxide, and ozone from the Ministry of Environment of Korea. The level of PM<sub>2.5</sub> exposure was measured using the Community Multiscale Air Quality (CMAQ) modeling system. PM<sub>2.5</sub>, from CMAQ modeling data, was estimated using meteorological research and forecasting models comprising three overlapping weather data sources at 3, 9, and 27 km for a specific time period. PM<sub>2.5</sub> exposure levels during pregnancy were determined based on residential address (city, county, and district, or si, gun, and gu in the Korean language). For each address, daily PM<sub>2.5</sub> concentrations were matched to each individual according to their delivery date. Each individual's outdoor air quality data were collected for each pregnancy trimester,

extending to data from the week of delivery. PM<sub>2.5</sub> data were collected from 2009 to 2015, depending on the pregnancy period of the study participants.

We stratified the groups by birth weight and height and performed Student's *t*-test (Figure 1a). LBW was defined as a weight at birth of <2500 g, and low birth height (LBH) was defined as a height at birth of <46.3 cm for male and <45.6 cm for female infants.



**Figure 1.** Study flow chart of Cohorts I (a) and II (b).

## 2.2. Study Design of Cohort II

A multicenter prospective cohort study of air pollution in pregnant women (APPO) was conducted to investigate the effects of PM on mothers and fetuses by recruiting > 1200 participants between January 2021 and December 2023 in seven university hospitals across Korea. Each hospital was located in a metropolitan area, an industrial complex, or a mountainous area. The participants were singleton pregnant women with no underlying diseases before 28 weeks of gestation.

In the second study, 333 women who had delivered were selected as participants (Figure 1b). We collected data on basic demographic and health-related characteristics including age, BMI, socioeconomic status, and obstetric history. Routine blood tests were conducted to measure the white blood cell (WBC) counts and high-sensitivity C-reactive protein (hs-CRP) levels as inflammatory markers, and urine samples were collected during the second trimester. The pregnancy outcomes were evaluated after delivery.

This study was approved by the Ethical Research Committee of Ewha Womans University Mokdong Hospital (EUMC 2021-04-032), Yonsei University Severance Hospital (4-2021-0414), Kangwon National University Hospital (KNUH-B-2021-04-012-008), Keimyung University Dongsan Medical Center (2021-04-073), Korea University Guro Hospital (2021GR0233), Ewha Womans University Seoul Hospital (2021-04-022), and Ulsan University Hospital (2022-04-020). All participants provided written informed consent.

## 2.3. PM Exposure Assessment

The indoor PM<sub>2.5</sub> concentration was measured by placing a fine dust meter at breathing height in the living room of a pregnant woman's house. An AirGuard K (Kweather Co., Seoul, Republic of Korea) instrument was used for measurements using the sensor-based method. The indoor PM<sub>2.5</sub> was measured online at 1-min intervals. The measured indoor PM<sub>2.5</sub> data were stored in an indoor air quality monitoring platform (IAQ Station) using Long-Term Evolution. Measurements were performed for at least 1 week, and the

measured concentration values were recorded in real time using the Internet of Things and Information and Communication Technology. For indoor PM<sub>2.5</sub>, after removing outliers, the average value of measurements for each trimester of pregnancy was derived, and the average of the two or three trimesters was defined as PM<sub>2.5</sub>. The participants were divided according to the PM<sub>2.5</sub> exposure level as follows: <10 µg/m<sup>3</sup> (low PM<sub>2.5</sub> group) and ≥10 µg/m<sup>3</sup> (high PM<sub>2.5</sub> group) concentration groups, which are the World Health Organization's annual limit standard concentrations (2005 air quality guidelines).

Outdoor PM<sub>2.5</sub> concentrations were collected from a nearby urban atmospheric measurement network based on the residential addresses of the study participants. The Urban Air Monitoring Station data used in this study were obtained from the Air Korea database (<https://www.airkorea.or.kr/web> (accessed on 1 May 2021)) of the Korean Ministry of the Environment.

#### 2.4. Collection of Blood and Urine Samples

We collected 5 mL maternal venous blood and 15 mL urine. Blood and urine samples were collected at regular follow-up visits. Whole blood samples collected in ethylenediaminetetraacetic acid tubes were transferred to cryotubes, and urine was stored in one cryotube. Samples were transferred to the institution (the Seegene Medical Foundation, Seoul, Republic of Korea) on the same day as collection under refrigeration to prevent deterioration (−80 °C).

#### 2.5. Measurement of Oxidative Stress and Inflammatory Markers

The oxidative stress markers 8-hydroxy-2-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) were measured in urine samples collected during the second trimester of pregnancy. The collected urine samples were transported directly to the laboratory and stored at −80 °C before processing. The urine samples were filtered with a 0.2-µm filter (Sartorius, S6534-FMOSK, Göttingen, Germany) for the assay and diluted at 1:20 to measure the concentration of 8-OHdG using enzyme-linked immunosorbent assay (ELISA) kits (Abcam, Ab201734, Waltham, Boston, MA, USA). The concentration of MDA in urine was measured using an MDA ELISA kit (ab118970; Abcam). Among the inflammatory markers, the WBC count was measured using an XN-9000 (Symex, Kobe, Japan) according to the manufacturer's protocol, from the participant's whole blood sample, through an automated complete blood cell count. The hs-CRP level was measured using a particle-enhanced immunoturbidimetric assay according to the manufacturer's protocol using a Cobas 8000 C702 analyzer (Roche, Basel, Switzerland).

#### 2.6. Statistical Analysis

Clinical characteristics were analyzed according to continuous variables (age and BMI) and categorical variables (marital status, education level, occupation, monthly income, gravidity, and pregnancy methods). Pregnancy outcomes were analyzed according to continuous (GAB, birth weight, height, and APGAR score) and categorical variables (delivery mode, neonate sex, and pregnancy complications). Pregnancy complications were defined using the following criteria (LBW: birth weight of <2500 g; LBH: birth height <46.3 cm for male and <45.6 cm for female infants; SGA: birth weight < 10th percentile for gestational age; PTB: delivery at <37 weeks of gestation) and analyzed as categorical variables. Oxidative stress (8-OHdG and MDA) and inflammatory markers (hs-CRP and WBC count) were analyzed as continuous variables. Categorical variables were expressed as frequencies (percentages) and analyzed using chi-square and Fisher's exact tests. Continuous variables were expressed as means ± standard deviations (SDs) and were compared using the *t*-test or Mann–Whitney U test. Logistic regression model was used to estimate the associations between LBW and PM<sub>2.5</sub> exposure (1 µg/m<sup>3</sup>) in each trimester with adjustment for covariates (maternal age, parity, maternal pre-pregnancy BMI, preeclampsia, and gestational age). Statistical significance was defined as *p* < 0.05. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 20.0; IBM Corp., Armonk, NY, USA).

### 3. Results

#### 3.1. Association between PM<sub>2.5</sub> Exposure and Birth Weight and Height According to Neonatal Sex Using a Retrospective Cohort Study

Among the 1880 neonates, 1569 had a normal birth weight (NBW) and 311 had LBW. The two groups showed significant differences in GAB, birth weight, height, and APGAR scores ( $p < 0.01$ ); however, there were no significant differences in maternal age, pre-pregnancy BMI, and neonatal sex (Table 1). The average outdoor PM<sub>2.5</sub> concentration was 27.35  $\mu\text{g}/\text{m}^3$  (Table 2 and Supplementary Table S1). The PM<sub>2.5</sub> concentration in the second trimester for pregnant women who delivered LBW babies was 27.21  $\mu\text{g}/\text{m}^3$ , which was significantly higher than the value of 26.23  $\mu\text{g}/\text{m}^3$  in the NBW group ( $p = 0.02$ , Table 3). When the delivered newborns were divided by sex, the PM<sub>2.5</sub> concentration in the second trimester for male LBW babies was 27.89  $\mu\text{g}/\text{m}^3$ , which was significantly higher than the value of 26.26  $\mu\text{g}/\text{m}^3$  in male infants with NBW ( $p = 0.01$ ), but there was no significant difference in female infants ( $p = 0.74$ , Table 3).

**Table 1.** Characteristics of study population of Cohort I.

Characteristics	NBW ( <i>n</i> = 1569)		LBW ( <i>n</i> = 311)		<i>p</i> -Value
Age (years)	33.20	4.16	32.79	4.47	0.12
Pre-BMI (kg/m <sup>2</sup> )	21.46	3.59	21.52	3.65	0.92
GAB (wks)	39.02	1.35	33.30	3.49	<0.01 *
Neonate Sex					
Male	791	82.14%	172	17.86%	0.12
Female	780	84.78%	140	15.22%	
Birth weight (g)	3266.44	394.83	1824.04	497.55	<0.01 *
Birth height (cm)	49.76	1.88	42.08	4.06	<0.01 *
APGAR 1 min	9.30	1.12	6.76	2.54	<0.01 *
APGAR 5 min	9.88	0.55	8.27	2.24	<0.01 *
Pregnancy complications					
PTB	81	24.40%	251	75.60%	<0.01 *

Categorical variables are expressed as frequencies (percentages) and were analyzed using the chi-square test. Continuous variables are expressed as means  $\pm$  SDs and were compared using *t*-tests. APGAR, appearance, pulse, grimace, activity, respiration; BMI, body mass index; GAB, gestational age at birth; SD, standard deviation. \*  $p < 0.05$  considered statistically significant.

**Table 2.** Summary of PM<sub>2.5</sub> concentration ( $\mu\text{g}/\text{m}^3$ ) by second trimester of pregnancy.

	Mean	SD	Min	25th	50th	75th	Max	<i>p</i> -Value
[Cohort I]	27.35	4.48	17.73	23.33	27.89	30.72	41.68	<0.01 <sup>*,1</sup>
[Cohort II]								<0.01 <sup>*,2</sup>
Indoor	10.57	10.47	0.53	4.35	7.8	12.02	69.25	
Outdoor	17.27	7.48	1.69	12.00	16.71	20.14	43.50	

<sup>1</sup> Statistical significance of concentration of PM<sub>2.5</sub> between Cohorts I and II. <sup>2</sup> Statistical significance between indoor and outdoor PM<sub>2.5</sub> of Cohort II. PM<sub>2.5</sub>, particulate matter 2.5. \*  $p < 0.05$  considered statistically significant.

**Table 3.** Comparison of PM<sub>2.5</sub> exposure ( $\mu\text{g}/\text{m}^3$ ) by each trimester in NBW, LBW, NBH, and LBH, according to sex.

Exposure Period	All Newborns			Males			Females		
	NBW ( <i>n</i> = 1567)	LBW ( <i>n</i> = 313)	<i>p</i> -Value	NBW ( <i>n</i> = 791)	LBW ( <i>n</i> = 169)	<i>p</i> -Value	NBW ( <i>n</i> = 774)	LBW ( <i>n</i> = 141)	<i>p</i> -Value
Entire	27.17 $\pm$ 4.30	27.40 $\pm$ 4.67	0.43	27.24 $\pm$ 4.37	27.79 $\pm$ 4.82	0.17	27.11 $\pm$ 4.24	26.93 $\pm$ 4.48	0.65
First trimester	28.75 $\pm$ 7.63	28.04 $\pm$ 7.70	0.15	28.91 $\pm$ 7.87	28.38 $\pm$ 7.94	0.45	28.59 $\pm$ 7.38	27.71 $\pm$ 7.42	0.21
Second trimester	26.23 $\pm$ 6.78	27.21 $\pm$ 6.53	0.02 *	26.26 $\pm$ 6.70	27.89 $\pm$ 6.79	0.01 *	26.22 $\pm$ 6.86	26.38 $\pm$ 6.15	0.78
Third trimester	26.40 $\pm$ 6.43	27.04 $\pm$ 8.56	0.23	26.39 $\pm$ 6.28	26.94 $\pm$ 8.63	0.46	26.38 $\pm$ 6.57	27.03 $\pm$ 8.40	0.40

Continuous variables are expressed as means  $\pm$  SDs and compared using *t*-tests. LBH, low birth height; LBW, low birth weight; NBH, normal birth height; NBW, normal birth weight. \*  $p < 0.05$  considered statistically significant.



When the neonates were divided into term and PTB groups, the concentration of PM<sub>2.5</sub> for the LBW infants in the PTB group was 27.29 µg/m<sup>3</sup>, which was significantly higher than the concentration of 25.89 µg/m<sup>3</sup> for NBW babies, respectively ( $p = 0.02$ , Table 4). In the PTB group, the PM<sub>2.5</sub> concentration of the preterm normal birth weight (PNBW) and preterm low birth weight (PLBW) groups showed significant differences between the first and second trimesters, respectively ( $p = 0.05$ ,  $p = 0.04$ ), with more significant differences in the male group ( $p < 0.01$ ,  $p = 0.01$ , Table 4). In contrast, in female infants in the PTB group, there were no statistically significant differences between the PNBW and PLBW groups in any trimester ( $p = 0.88$ , Table 4). In the term birth group, there was no significant difference between the NBW and LBW groups at term in any trimester ( $p = 0.30$ ; Supplementary Table S2).

**Table 4.** Subgroup analysis for comparison of PM<sub>2.5</sub> exposure (µg/m<sup>3</sup>) by each trimester in the NBW and LBW at preterm in Cohort I.

Exposure Period	All Newborns			Male Infants			Female Infants		
	PNBW ( <i>n</i> = 84)	PLBW ( <i>n</i> = 260)	<i>p</i> -Value	PNBW ( <i>n</i> = 48)	PLBW ( <i>n</i> = 149)	<i>p</i> -Value	PNBW ( <i>n</i> = 36)	PLBW ( <i>n</i> = 111)	<i>p</i> -Value
Entire	25.89 ± 4.15	27.29 ± 4.78	0.02 *	25.06 ± 4.03	27.61 ± 4.90	<0.01 *	27.00 ± 4.10	26.87 ± 4.64	0.88
First trimester	25.81 ± 6.63	27.58 ± 7.57	0.05	24.35 ± 6.21	27.73 ± 7.65	<0.01 *	27.77 ± 6.76	27.48 ± 7.50	0.84
Second trimester	25.57 ± 6.26	27.25 ± 6.58	0.04 *	24.82 ± 5.87	27.81 ± 6.82	0.01 *	26.58 ± 6.69	26.51 ± 6.22	0.95
Third trimester	26.69 ± 6.15	27.23 ± 8.98	0.55	26.92 ± 5.61	27.27 ± 9.09	0.80	26.39 ± 6.86	27.02 ± 8.77	0.66

Continuous variables were expressed as means ± SDs and compared using *t*-test. PNBW, preterm normal birth weight; PLBW, preterm low birth weight. \*  $p < 0.05$  considered statistically significant.

Pregnant women who were exposed to PM<sub>2.5</sub> had a significantly higher risk of LBW than those who were not exposed, with an adjusted odds ratio (OR) of 1.06 (95% confidence interval [CI]: 1.01–1.10, Table 5). In male infants, the risk of LBW was higher, with an OR of 1.12. The susceptibility period was in the first and second trimester, with ORs of 1.05 and 1.07, respectively (95% CI: 1.01–1.10 and 1.03–1.12, Table 5).

**Table 5.** Association between PM<sub>2.5</sub> exposure (per 1 µg/m<sup>3</sup>) in each trimester and logistic regression analysis.

Risk of LBW by PM <sub>2.5</sub> Exposure (per 1 µg/m <sup>3</sup> )									
Stage	All Newborns			Male Infants			Female Infants		
	OR	95% CI	<i>p</i> -Value	OR	95% CI	<i>p</i> -Value	OR	95% CI	<i>p</i> -Value
Entire	1.06	1.01–1.10	0.02 *	1.12	1.04–1.20	<0.01 *	1.00	0.93–1.07	0.94
First trimester	1.02	1.00–1.05	0.08	1.05	1.01–1.10	0.02 *	1.00	0.96–1.04	0.86
Second trimester	1.03	1.00–1.06	0.04 *	1.07	1.03–1.12	<0.01 *	1.00	0.96–1.04	0.90
Third trimester	1.00	0.98–1.03	0.80	1.00	0.96–1.04	0.85	1.01	0.97–1.05	0.73

Models adjusted for maternal age, parity, maternal pre-pregnancy body mass index, preeclampsia, and gestational age. CI, confidence interval; OR, odds ratio. \*  $p < 0.05$  considered statistically significant.

### 3.2. Study Population of APPO and Measurement and Correlation of Indoor/Outdoor PM<sub>2.5</sub>

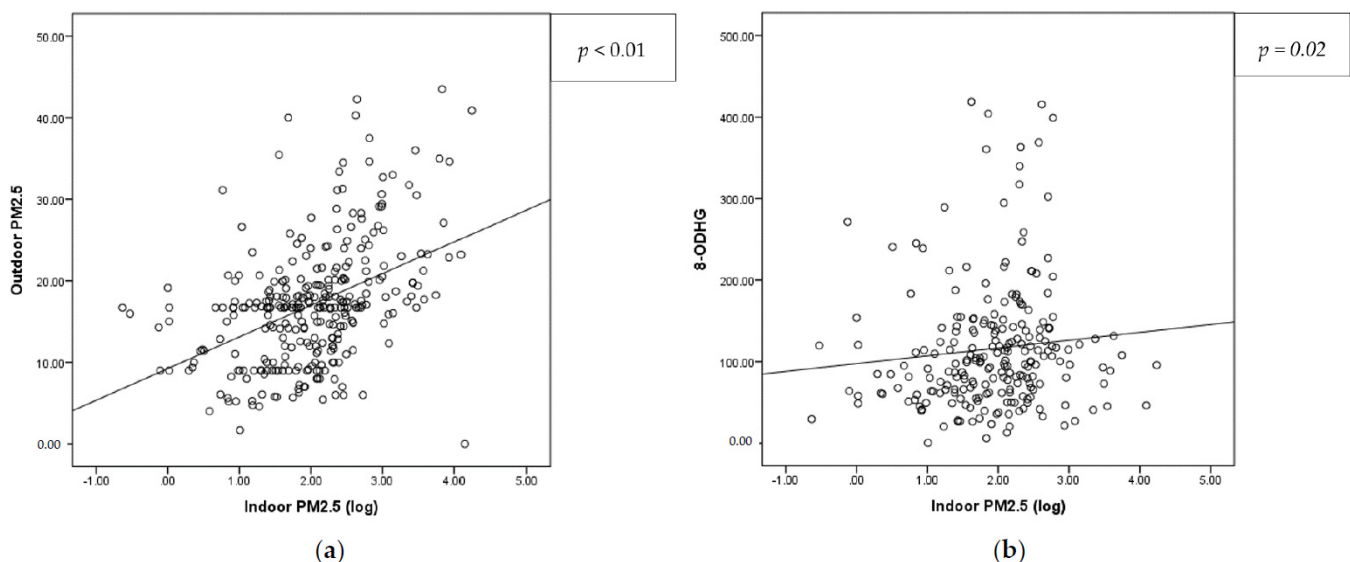
An analysis was performed on 306 of 333 delivery participants, excluding those with incomplete data. According to the PM<sub>2.5</sub> exposure levels of the participants, the numbers in the low and high PM<sub>2.5</sub> groups were 191 and 115, respectively (Table 6). There were no significant differences in the characteristics of the study population between the high and low PM<sub>2.5</sub> concentration groups (Table 6).

The average of the indoor PM<sub>2.5</sub> concentration in the second trimester of pregnancy among the APPO study participants was 10.57 µg/m<sup>3</sup>, and that of the outdoor PM<sub>2.5</sub> was 17.27 µg/m<sup>3</sup>. The two measurements showed a statistically significant positive correlation ( $p < 0.01$ ,  $r^2 = 0.187$ ) (Table 2, Figure 2a). The concentration of outdoor PM<sub>2.5</sub> in Cohort I was significantly lower than that in Cohort II ( $p < 0.01$ , Table 2).

**Table 6.** Characteristics of study population in Cohort II.

Characteristics	Low PM <sub>2.5</sub> ( <i>n</i> = 191)		High PM <sub>2.5</sub> ( <i>n</i> = 115)		<i>p</i> -Value
Age (years)	33.74	±3.62	33.12	±4.50	0.19
Pre-BMI (kg/m <sup>2</sup> )	21.86	±3.31	21.56	±3.17	0.43
Married state					
Married	167	100.0%	133	97.8%	0.16
Unmarried	0	0.0%	3	2.2%	
Education level					0.14
High school graduation or below	13	6.8%	13	9.5%	
University graduates	154	92.3%	123	90.4%	
Occupation					
Yes	112	67.1%	94	69.1%	0.70
No	55	32.9%	42	30.9%	
Monthly income					
<4 million won	35	36.1%	35	37.6%	0.95
4–6 million won	27	27.8%	24	25.8%	
>6 million won	35	36.1%	34	36.6%	
Gravidity					
1	80	47.9%	68	50.0%	0.65
2	61	36.5%	50	36.8%	
≥3	26	15.6%	18	13.2%	
Pregnancy methods					
Natural	143	85.6%	116	85.3%	0.91
IUI	2	1.2%	1	0.7%	
IVF-ET	22	13.2%	19	14.0%	

Categorical variables are expressed as frequencies (percentages) and were analyzed using chi-square and Fisher's exact tests. Continuous variables are expressed as means ± SDs and were compared using the *t*-test or Mann–Whitney U test. IUI, intrauterine insemination; IVF-ET, in vitro fertilization–embryo transfer.

**Figure 2.** Correlation analysis between (a) indoor and outdoor PM<sub>2.5</sub>, and (b) indoor PM<sub>2.5</sub> and 8-OHdG. 8-OHdG, 8-hydroxy-2-deoxyguanosine; PM<sub>2.5</sub>, particulate matter 2.5.

### 3.3. Association between PM<sub>2.5</sub> Exposure and Pregnancy Complications

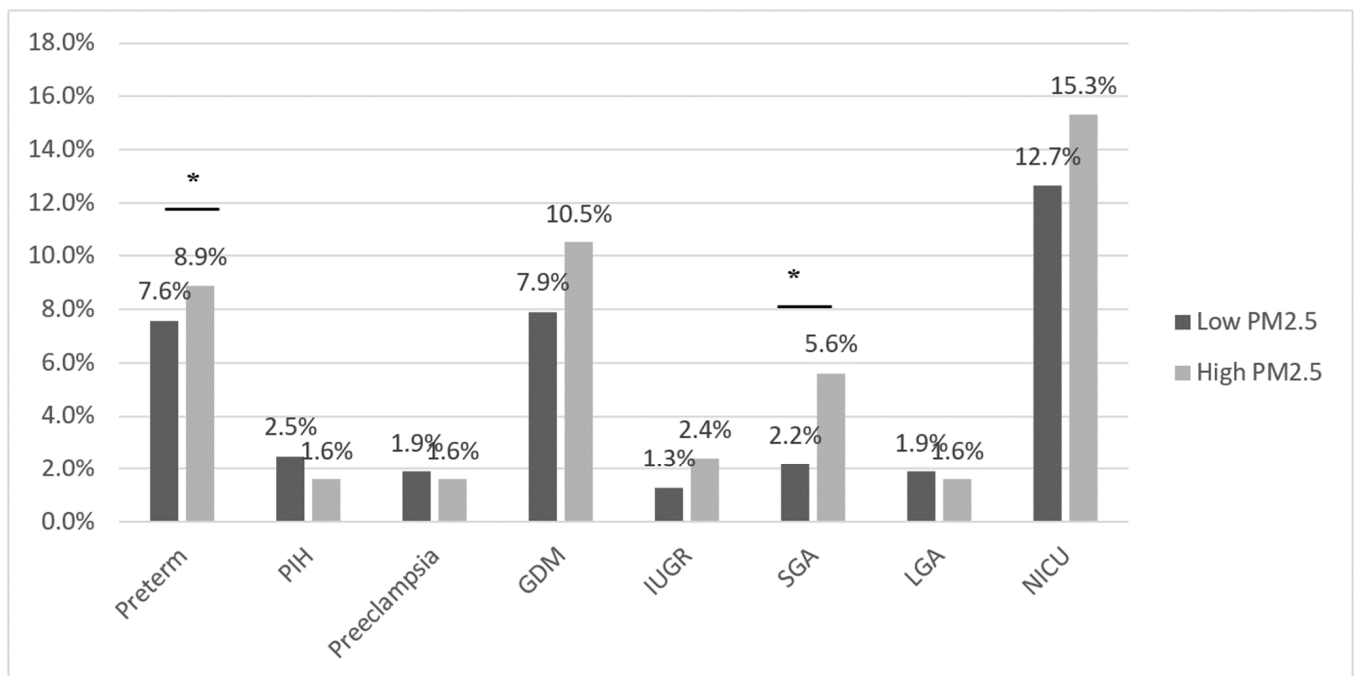
The oxidative stress marker 8-OHdG was significantly increased in the high-concentration group to 113.55 ng/mL, compared to 92.20 ng/mL in the low-concentration group, and there was a positive correlation ( $p = 0.02$ ,  $r^2 = 0.010$ ) (Table 7, Figure 2b). There were no differences in the MDA or inflammatory marker levels between the two groups (Table 7). There were no differences in GAB, delivery mode, neonatal sex, birth weight, or APGAR

score (Table 8). The mean birth height was 48.9 cm in the high-concentration group, which was significantly lower than that in the low-concentration group (49.5 cm;  $p = 0.04$ ; Table 8). In the high-concentration group, PTB significantly increased from 4.2% to 13.2%, and SGA significantly increased from 0.6% to 5.1% ( $p < 0.01$ ,  $p = 0.01$ ) (Table 8, Figure 3).

**Table 7.** Oxidative stress and inflammatory markers between the low and high PM<sub>2.5</sub> groups.

	Low PM <sub>2.5</sub> ( <i>n</i> = 191)		High PM <sub>2.5</sub> ( <i>n</i> = 115)		<i>p</i> -Value
Oxidative stress marker					
8-OHdG (ng/mL)	92.20	61.16–138.19	113.55	79.69–153.27	0.02 *
MDA (μM)	18.49	8.66–37.18	16.02	9.99–30.34	0.54
Inflammatory marker					
Hs-CRP (mg/L)	2.00	1.00–3.00	1.79	1.00–2.99	0.74
WBC ( $1 \times 10^3/\mu\text{L}$ )	8.80	7.00–9.72	8.00	7.00–10.00	0.98

Continuous variables are expressed as medians (interquartile ranges) and were compared using the Mann–Whitney U test. 8-OHdG, 8-hydroxy-2-deoxyguanosine; Hs-CRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; WBC, white blood cells. \*  $p < 0.05$  considered statistically significant.



**Figure 3.** Pregnancy complications in the PM<sub>2.5</sub> concentration group. GDM, gestational diabetes mellitus; IUGR, intrauterine growth restriction; LGA, large for gestational age; NICU, neonatal intensive care unit; PIH, pregnancy-induced hypertension; PM<sub>2.5</sub>, particulate matter 2.5; SGA, small for gestational age. \*  $p < 0.05$  considered statistically significant.

**Table 8.** Association between PM<sub>2.5</sub> exposure and pregnancy complications.

	Low PM <sub>2.5</sub> ( <i>n</i> = 191)		High PM <sub>2.5</sub> ( <i>n</i> = 115)		<i>p</i> -Value
Pregnancy outcome					
GAB (wks)	38.22	±1.59	37.96	±1.95	0.22
Delivery mode					0.86
ND	61	36.5%	51	37.5%	
CS	106	63.5%	85	62.5%	



Table 8. Cont.

	Low PM <sub>2.5</sub> ( <i>n</i> = 191)		High PM <sub>2.5</sub> ( <i>n</i> = 115)		<i>p</i> -Value
Neonate Sex					
Male	112	58.9%	56	49.1%	0.10
Female	78	41.1%	58	50.9%	
Birth weight (g)	3150.7	±391.6	3112.0	±522.5	0.50
Birth height (cm)	49.5	±2.2	48.9	±2.8	0.04 *
APGAR 1 min	8.45	±1.22	8.36	±	0.61
APGAR 5 min	9.43	±0.84	9.21	±1.37	0.13
Pregnancy complications					
LBW	4	5.1%	4	6.9%	0.47
LBH	5	2.6%	8	7.0%	0.07
PTB	8	4.2%	15	13.2%	<0.01 *
SGA	1	0.6%	7	5.1%	0.01 *
NICU admission	20	12.0%	23	16.9%	0.32

Categorical variables are expressed as frequencies (percentages) and were analyzed using chi-square and Fisher's exact tests. Continuous variables are expressed as means ± SDs or medians (interquartile range) and were compared using the *t*-test or Mann–Whitney U test. CS, cesarean section; ND, normal delivery; NICU, neonatal intensive care unit; SGA, small for gestational age. \* *p* < 0.05 considered statistically significant.

#### 4. Discussion

In this study, the association between PM<sub>2.5</sub> and LBW was confirmed through a retrospective cohort study, and its effect was found to be more pronounced in the male and PTB groups. Furthermore, a multicenter prospective cohort study revealed the relationship between PM<sub>2.5</sub> and birth height, SGA, and PTB by measuring the actual indoor PM<sub>2.5</sub>. The oxidative stress marker 8-OHdG, which was used to explore the pathogenesis of these pregnancy complications and identify biomarkers, showed a positive correlation with PM<sub>2.5</sub>.

Our results are similar to those of previous studies that showed an association between PM<sub>2.5</sub> and fetal growth and PTB [11,27–30]. Regarding the biological mechanism by which PM<sub>2.5</sub> affects fetal growth, the effects of oxidative stress, placental inflammation or dysfunction, endothelial dysfunction, and blood coagulation have been reported [18,19]. The pathogenesis of PM-induced PTB involves systemic inflammation caused by the inhalation of toxic particles [31,32]. Many large-scale studies have confirmed these results; however, most have been retrospective [4,11,13], which is a limitation. Although the number of participants was small, pregnancy complications were confirmed in a prospective study using actual indoor PM<sub>2.5</sub> measurement.

Several studies have shown that male fetuses are vulnerable to intrauterine growth restriction [27,33] and PTB [34]. Although the sex difference in fetuses affected by PM<sub>2.5</sub> remains controversial [11,16,33], this study showed an association between LBW and PM<sub>2.5</sub>, especially in male infants. To understand the sex differences, it is necessary to understand the biological mechanisms underlying PM<sub>2.5</sub> [35]. Male fetuses grow faster than female fetuses and require more oxygen; therefore, the possibility that toxic substances inhibit this process has been suggested [33,35]. Another mechanism is that an increase in inflammatory mediators in the blood caused by air pollution increases the blood viscosity [36], which affects placental function. In general, placental dysfunction is more prevalent in male fetuses [37,38]. The cohort of the APPO study could not confirm the sex differences owing to the small number of participants, but it is necessary to confirm whether PM<sub>2.5</sub> actually affects fetal growth to continuously recruit participants in the future.

Similar to previous studies showing the relationships between PM<sub>2.5</sub> and environmental pollutants and oxidative stress, this study showed a relationship between PM<sub>2.5</sub> and 8-OHdG levels [39]. In brief, 8-OHdG is a reactive oxygen species that has been used as a marker of DNA damage because of its mutagenic potential [40]. The results of this study show the possibility of using 8-OHdG as a biomarker of PM<sub>2.5</sub> exposure. In particular, urine samples have the advantage that they can be collected from patients non-invasively, and

since 8-OHdG shows high stability in urine, it can be used as a biomarker [41]. By verifying the effectiveness of 8-OHdG in the future, it can be used as a biomarker for biomonitoring, suggesting the possibility that the use of antioxidants affects the prognosis of newborns [24]. PM not only affects the outcomes of newborns and pregnancy but also long-term diseases in offspring, according to the concept of fetal programming [42,43].

Most existing studies have estimated fine dust exposure concentrations based on differences in air quality by region and location [4,11,28,44]. However, as 80–90% of individuals live indoors, owing to COVID-19, the outdoor activity of pregnant women further decreased, and the importance of indoor air quality has been emphasized [45,46]. In this APPO study, indoor PM<sub>2.5</sub> measurements were performed in the residences of pregnant women for at least 1 week, and it is thought that this can give causality to the biological mechanism of any relationship between PM<sub>2.5</sub> and a disease. The results of this study, using correlation analysis between indoor and outdoor PM<sub>2.5</sub>, explain that outdoor conditions significantly affect indoor air quality; however, the correlation can be explained by only 18.7% influence. This indicates that the indoor air quality can be affected by various human activities, including smoking and cooking [14,17], thereby suggesting that education regarding lifestyle changes may also be important for better pregnancy outcomes. Through this survey, we will conduct additional research on the group in which indoor PM<sub>2.5</sub> increases in preparation for actual outdoor PM<sub>2.5</sub>. We plan to conduct further research on active intervention measures to prevent pregnancy complications.

In this study, there was a difference in PM<sub>2.5</sub> concentrations between Cohorts I and II, either because of the air pollution reduction effect owing to the COVID-19 lockdown [47] or because the participants in Cohort I were recruited from a metropolitan area, whereas the participants in Cohort II were recruited from the countryside.

To our knowledge, this was the first study to examine the relationship between fine dust and fetal growth in pregnant Korean women with continuously measured indoor PM<sub>2.5</sub> concentrations. It was also the first study to measure oxidative stress and develop fine dust exposure evaluation indicators in pregnant women with actual indoor PM<sub>2.5</sub> measurement.

The strength of this study was that it was a prospective multicenter cohort study that investigated the maternal and fetal health effects of PM on pregnancy in patients from various regions of South Korea. Compared with a previous study that measured only outdoor data, it was more reasonable to confirm the causal relationship between fine dust and pregnancy complications through fine dust concentrations measured using individual indoor air quality values.

However, this study had several limitations. Although we measured the indoor fine dust concentrations of the participants for at least 1 week, there was a limitation in that the cumulative concentration during the entire pregnancy could not be calculated. Moreover, other stressful conditions that may affect pregnancy complications, including alcohol abuse and infection, were not considered. Recent, various studies have reported on air pollutants, including PM<sub>1.0</sub>, and their health effects; however, this study focused on PM<sub>2.5</sub> and did not analyze other air pollutants.

A correlation between PM<sub>2.5</sub> and 8-OHdG was observed, but no correlation with actual complications was found. Therefore, in the future, we will recruit more participants and make efforts to calculate the cumulative concentrations of fine dust in pregnant women and evaluate the biological mechanisms of 8-OHdG as a biomarker. Moreover, various stressful conditions that can be confounding variables in pregnancy outcomes should be included, and the impact of other air pollutants should be considered during the analysis.

## 5. Conclusions

This study confirmed the association between PM<sub>2.5</sub> and LBW through a retrospective cohort study, and its effect was found to be more pronounced in the male and PTB groups. Furthermore, through a multicenter prospective cohort study, we determined the relationships between PM<sub>2.5</sub> and birth height, SGA, and PTB by measuring the actual indoor

PM<sub>2.5</sub>. The oxidative stress marker showed a positive correlation with PM<sub>2.5</sub>, suggesting its potential as a biomarker for PM<sub>2.5</sub> exposure. However, further research on the actual mechanisms of action, efficacy, and relevance to pregnancy outcomes is needed. Furthermore, we will continue to identify interventions to lower indoor PM levels.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/antiox12111916/s1>, Table S1: Summary of PM<sub>2.5</sub> concentration (µg/m<sup>3</sup>) by each trimester of pregnancy of Cohort I; Table S2: Subgroup analysis of comparison of PM<sub>2.5</sub> exposure (µg/m<sup>3</sup>) by each trimester in the NBW and LBW at full term of Cohort I.

**Author Contributions:** S.P. enrolled the participants, interpreted the data, and wrote and edited the manuscript. E.K. analyzed the data and wrote the manuscript. G.L. curated the data and performed the experiments. Y.-A.Y. designed the study and edited the manuscript. S.M.K. performed the experiments. Y.M.H. developed the protocol and enrolled the subjects. S.J. performed the data curation and visualization. Y.J. curated and analyzed data. M.H.P., S.H.N., Y.-H.K., G.J.C., J.-G.B. and S.-J.L. enrolled the participants. S.H.L. developed the protocols and performed the experiments. Y.J.K. edited the manuscript, obtained funding, and supervised the study. All authors have read and agreed to the published version of the manuscript.

**Funding:** This study was supported by a research program funded by the Korea National Institute of Health (grant code# 2021-ER1208-01). This work was partly supported by the Institute of Information Communications Technology Planning Evaluation (grant funded by the Korea Government [MSIT]) (No. RS 2022 00155966 Artificial Intelligence Convergence Innovation Human Resources Development Ewha Womans University) and a Korea Evaluation Institute of Industrial Technology (KEIT) grant funded by the Korea Government (MOTIE). This research was also supported by BK21 FOUR (Fostering Outstanding Universities for Research) funded by the Ministry of Education (MOE, Korea) and National Research Foundation of Korea (NRF-5199990614253).

**Institutional Review Board Statement:** The first retrospective cohort study was approved by the Ethical Research Committee of Ewha Womans University Mokdong Hospital (EUMC 2020-07-043). As this was a retrospective cohort study, the consent of the subjects was not required. The second prospective cohort study was approved by the Ethical Research Committee of Ewha Womans University Mokdong Hospital (EUMC 2021-04-032), Yonsei University Severance Hospital (4-2021-0414), Kangwon National University Hospital (KNUH-B-2021-04-012-008), Keimyung University Dongsan Medical Center (2021-04-073), Korea University Guro Hospital (2021GR0233), Ewha Womans University Seoul Hospital (2021-04-022), and Ulsan University Hospital (2022-04-020). All the participants provided written informed consent.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data supporting the findings of this study are available in the article. Raw data supporting the findings of this study cannot be shared openly to protect personally identifiable information.

**Conflicts of Interest:** The authors declare no conflict of interest.

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