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The introduction to air pollution on pregnancy outcome (APPO) study: a multicenter cohort study

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Objective
The air pollution on pregnancy outcome (APPO) study is a prospective hospital-based cohort study designed to investigate the maternal and fetal effects of a particulate matter with an aerodynamic below 10 μm (PM10) and PM2.5 (below 2.5 μm) exposure. This study aims to analyze a relationship between particulate matter and adverse pregnancy outcomes and to find related biomarkers and develop management guidelines.

Methods
About 1,200 pregnant women are recruited for 3 years (from January 2021 to December 2023) from seven university hospitals to investigate the effects of particulate matter on pregnancy complications and adverse pregnancy outcomes. We collect biological samples by 5 mL of maternal venous blood and 15 mL of urine in each trimester of pregnancy, and 5 mL of umbilical cord blood and 2×2×2 cm of placental tissue are collected after delivery. In addition, by applying PM10 and PM2.5 concentration values and time-activity patterns from the time weighted average model, the individual predicted exposure of air pollution for the pregnant women are obtained.

Results
The average exposure of PM10 and PM2.5 of the participants in the entire period of pregnancy, was exceeded the World Health Organization air quality guidelines (an annual level, PM10 >15 μg/m³, PM2.5 >5 μg/m³). Moreover, it was revealed that the PM concentration was increasing toward the 3rd trimester of pregnancy.

Conclusion
The APPO study will be able to identify the degree of exposure to air pollution in pregnant women and use it as basic data for estimating individual exposure to particulate matter. And the results of the APPO study will facilitate in the development of health management for pregnant women against air pollution.

Keywords: Particulate matter; Air pollution; Environmental exposure; Pregnant women; Pregnancy complications

Introduction

Air pollution, a mixture of pollutants found in the air, is a major environmental problem in public health. In particular, the effect of perinatal exposure to air pollution is a significant concern because pregnant women are more vulnerable to environmental toxicants [1-4]. Many studies have shown an association between maternal exposure to air pollution and adverse pregnancy outcomes [2,5-13]. These studies suggest that maternal exposure to air pollution may increase the risk of adverse birth outcomes, including abortion, stillbirth, preterm birth (PTB), low birth weight (LBW), intrauterine growth retardation, and neonatal mortality [13-15]. Although particulate matter with an aerodynamic diameter <10 μm (PM10) has been on the decline since 2002 in Korea, the average annual PM10 and PM2.5 (particulate matter with an aerodynamic below 2.5 μm) concentrations in Seoul are still higher than those in major cities in developed countries [16]. Particularly, PM2.5, which has been measured in Korea since 2015, is very small and not filtered through skin pores and bronchial tubes; therefore, it penetrates blood vessels and placenta, causing an inflammatory reaction [16-18]. In addition, the airborne spread of severe acute respiratory syndrome coronavirus 2 virus (coronavirus disease 2019, [COVID-19]), which was outbroken from the end of 2019, has more adverse effects on human respiratory health, and a positive correlation has been observed between its viral spread and air pollution [19,20]. Atmospheric PM could create a suitable environment for transporting the virus to greater distances and induce inflammation in lung cells, thereby increasing the susceptibility of patients and severity of the disease course in COVID-19 [19,20]. These processes can be more lethal because pregnant women are vulnerable to respiratory system [21,22].

Previous studies have reported that adverse pregnancy outcomes such as LBW and PTB are related to air pollution using regional ambient PM10 data from the residence of pregnant women and national birth data [12,15,23]. However, these studies are limited in that they do not reflect the exposure level of modern people in the real world who mainly live indoors and, therefore, have to deal with indoor air quality, rather than outdoor air quality. In addition, the studies could not analyze in detail exposure status according to each individual's lifestyle.

The air pollution on pregnancy outcome (APPO) study aims to analyze adverse pregnancy outcomes, related to particulate matter, identify related biomarkers, and develop management guidelines. We will establish individual air pollution exposure methods and collect and analyze integrated information on the effects of each exposure level on pregnancy outcomes. In addition, we will aim to discover predictive factors for pregnancy complications caused by PM10 and PM2.5 and develop management indicators for pregnant women. Thus, this article introduces the planning processes, study design, protocols, current status, and future directions of the APPO study.

Materials and methods

1. APPO study design

1) Basic concept and process

The APPO study is a prospective hospital-based cohort study designed to investigate the effects of PM10 and PM2.5 exposure on mothers and fetuses. Pregnant women were included in this study. To develop the specific hypotheses relevant to PM exposure and the maternal and fetal effects, our team reviewed a list of hypotheses from previous studies, including published articles, reports, and textbooks. Based on

Table 1. Hypotheses for pregnancy outcomes by environmental exposures in APPO study

Categorie	Outcome
Adverse pregnancy outcomes	Abortion, spontaneous preterm labor, PPROM, gestational hypertension, preeclampsia, gestational diabetes mellitus
Diseases other than pregnancy complications	Respiratory tract infection, asthma, depression, autoimmune disease, skin problem (e.g., PUPPP), etc
Neonatal complications	Low Apgar score, LBW, admission in NICU, congenital anomaly

APPO, air pollution on pregnancy outcome; PPROM, preterm premature rupture of membrane; PUPPP, pruritic urticarial papules and plaques of pregnancy; LBW, low birth weight; NICU, neonatal intensive care unit.

this review, key research hypotheses were established, and medical, social, and other factors that can affect pregnant women and fetuses were considered. Thus, we generated key hypotheses regarding pregnancy, childbirth, and neonatal prognosis associated with environmental exposure (Table 1).

2) Cohort composition

The APPO study plans to investigate the effects of particulate matter on mothers and fetuses by recruiting more than 1,200 participants from January 2021 to December 2023. Six university hospitals (Kangwon National University Hospital, Keimyung University Dongsan Medical Center, Korea University Guro Hospital, Severance Hospital, Ewha Womans University Mokdong Hospital, and Ewha Womans University Seoul Hospital) participated in 2021, and Ulsan University Hospital was included in 2022. The hospitals were located in a metropolitan area (Seoul), an industrial complex (Guro-gu in Seoul, Ulsan), and a mountainous area (Gangwon-do) to fully reflect the characteristics of different regions. Seoul was selected as an important area for this study because of its large population, high traffic volume, severe air pollution, and several apartments [24]. Moreover, Ulsan was selected as another research area as the largest industrial city in South Korea [24].

2. Study protocol

1) Recruitment of participants

To investigate the effects of particulate matter on pregnancy complications and adverse pregnancy outcomes, early pregnant women without underlying diseases were selected for the study. The inclusion and exclusion criteria are presented in Table 2. Participants were excluded if they withdrew their consent or could not provide information on delivery because of follow-up loss. When the participants visited the hospital for regular evaluation in the 1st, 2nd, and 3rd trimester of pregnancy, we collected information related to pregnancy complications through questionnaires, ultrasound sonography, and blood and urine tests. After delivery, umbilical cord blood and placental tissue were collected, and information regarding pregnancy outcomes was obtained from medical records. A flowchart of the APPO study is shown in Fig. 1.

2) Collection of biological samples

Biological samples collected include 5 mL of maternal venous blood and 15 mL of urine in each trimester of pregnancy; in addition, 5 mL of umbilical cord blood and 2×2×2 cm placental tissue were collected after delivery. Placental tissue was mainly collected at the Ewha Womans University Mokdong Hospital, a representative institute. Biological samples were collected when participants visited for regular evaluation to avoid discomfort, and all biological samples were collected after obtaining informed consent from the participants. Whole blood samples collected in ethylene-diamine-tetraacetic acid tubes were dispensed into cryo-tubes (1.0 mL), and urine was stored in a cryo-tube (10 mL). Samples for long-term storage were transferred to the institution (Seegene Medical Foundation, Seoul, Korea) on the same day by refrigeration to prevent deterioration. The storage samples were labeled with a unique number, collection date, and sample name; afterward, they were systematically stored and managed in a laboratory freezer (-80°C) after being delivered by the Department of Obstetrics and Gynecology at Ewha Womans University Mokdong Hospital. Specific laboratory test results for each biological specimen

Table 2. Inclusion and exclusion criteria for the APPO study

Inclusion criteria	Exclusion criteria
Women who are in the first trimester of pregnancy (<GA 14 weeks) at the time of the initial contact with the study	Women who are in multiple pregnancies
Women who are >18 years of age and are singleton pregnant women without underlying disease	Women who has medical complications that may affect adverse pregnancy outcome (cardiovascular disease, pulmonary disease, kidney disease, endocrine disorder, thrombotic disease, connective tissue disease, hepatobiliary disease, cancer, etc.)
Written consent	Women who has severe depression or epilepsy
	Women who has hereditary congenital disorder

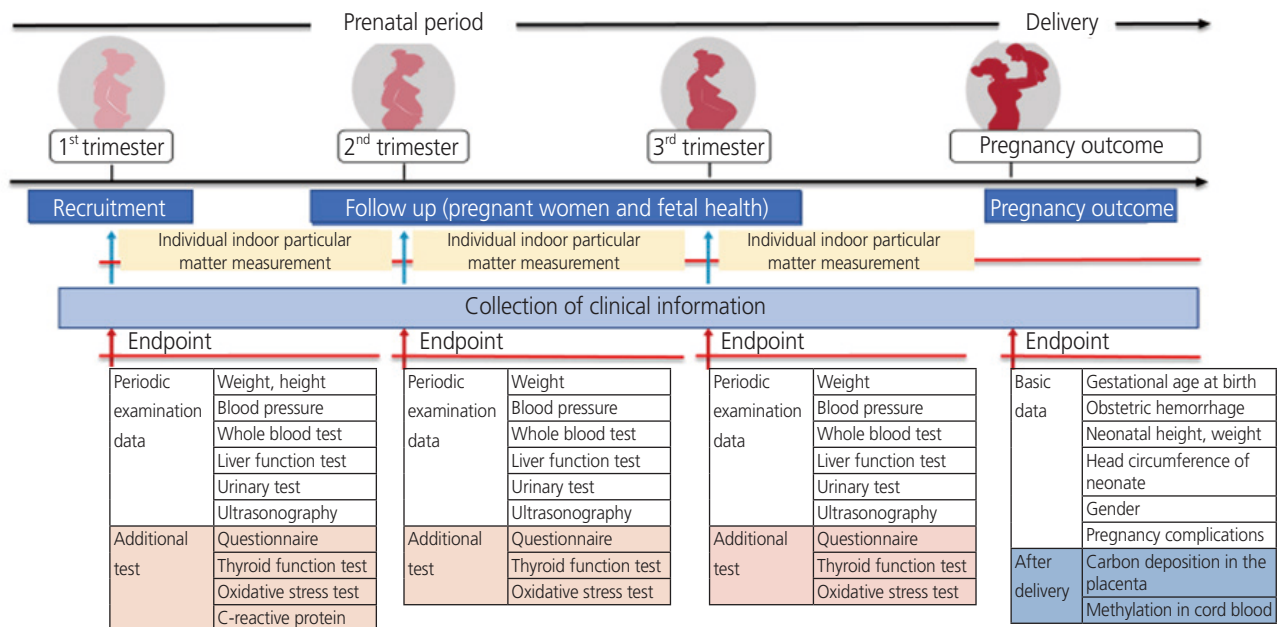APPO, air pollution on pregnancy outcome; GA, gestational age.

Fig. 1. The process of APPO study. APPO, air pollution on pregnancy outcome.

are presented in Table 3. Tests for systemic diseases, such as inflammation, thyroid disease, and metabolic syndrome, were mainly analyzed from blood samples, and additional tests, such as oxidative stress, were analyzed from urine samples. 8-hydroxy-2'-deoxyguanosine (8-OHdG) is an oxidized nucleoside of DNA frequently detected in damaged nuclear and mitochondrial DNA; and 8-OHdG is excreted in the urine following DNA repair [25]. There is much evidence that malondialdehyde (MDA) is not only a biomarker of generalized cellular oxidative stress, but may also be a risk factor for specific diseases [25]. MDA is the most studied product of polyunsaturated fatty acid peroxidation and is related to lipid oxidation among oxidative stress markers [26]. Moreover, the placenta and umbilical cord blood are mainly used to test the effects in neonates. Black carbon is a major component of the fine dust produced during the combustion of fossil fuels and biomass. It is small enough to be inhaled and deposited directly in the lungs [27]. Therefore, we hypothesized that it can eventually be deposited in the placenta through a blood vessel and observable in the placental tissue. Furthermore, DNA methylation is an epigenetic mechanism related to the fetal programming theory, which states that the environment in utero affects fetal gene expression. Therefore, this study plans to analyze the DNA methylation status in umbilical cord blood to predict its effect on the fetus (Table 3).

3) Assessment of outcomes: clinical information

We collected the following clinical information from each mother's medical record: prenatal clinical information (cervical length, blood pressure), labor and delivery (delivery date, gestational age, mode of delivery, weight of placenta), pregnancy complications (preterm premature rupture of membrane, dystocia, cephalopelvic disproportion, breech or other abnormal presentation, placenta previa, placental abruption, obstetrical hemorrhage, precipitating labor, PTB, umbilical cord prolapse, eclampsia), neonatal data (sex, height, weight, 1' and 5' Apgar score), neonatal complications (meconium aspiration syndrome, fetal asphyxia), and other information (fever, anesthetic use). In addition, oxidative stress index, smoking exposure, carbon particle analysis, and analysis of cord blood DNA methylation are required for risk analysis of particulate matter; therefore, they would be analyzed in high PM10 and PM2.5 concentrations.

4) Data control and management

We used clinical research and trial management system (iCReaT ver. 2, National Institute of Health, Cheongju, Korea) a web-based system, to input, store, and integrate the aforementioned data. iCReaT was developed to provide evidence-based health care services in an efficient and integrated manner by the National Institute of Health in Korea;

Table 3. List of laboratory tests for biospecimen during the study period

Purpose of test	Specimen	Laboratory test	1st trimester	2nd trimester	3rd trimester	Delivery
Collection of regular checkup data						
Inflammation/coagulation status	Blood	CBC (Hb, WBC, platelet)	O		O	
Liver function status	Blood	AST, ALT, γ-GTP	O		O	
Metabolic syndrome	Blood	Total cholesterol, triglyceride, LDL, HDL	O		O	
Gestational diabetes mellitus	Blood	Glucose challenge test, HbA1c		O		
Kidney function status	Blood	BUN, creatinine	O		O	
Additional close examination						
Thyroid function status	Blood	TSH, free T4	O		O	
Systemic inflammatory status	Blood	hs-CRP	O	O	O	
Oxidative stress index	Urine	8-OHdG, MDA	O	O	O	
Smoking exposure assessment	Urine	Cotinine	O			
Maternal-neonatal effects	Placenta	Black carbon particle				O
Neonatal effects	Cord blood	DNA methylation analysis				O

CBC, complete blood count; Hb, hemoglobin; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine transaminase; γ-GTP, gamma glutamyl transferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; BUN, blood urea nitrogen; TSH, thyroid stimulating hormone; free T4, free thyroxine; hs-CRP, high sensitivity C-reactive protein; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; MDA, malondialdehyde.

it oversees clinical research, including clinical trials, research plan review, project management, data input and extraction, and report provision [28]. Data quality was monitored periodically, the program automatically screened, and additional investigations conducted to obtain information about the questionnaire items left blank or insufficient answers were supplemented. The iCReaT system was suitably configured to handle the special requirements of the APPO study, and a training program for its use was provided for all administrators and researchers. Access to all data was limited to the certified researchers in the study protocol.

3. Calculation of estimated individual exposure to PM

1) Questionnaires
In this study, we investigated the current status of PM that pregnant women in Korea are exposed to indoors through a web-based questionnaire (kopen.or.kr), and we collected information on the participants' sociodemographic characteristics, lifestyle, living environment, and risk perception level of fine dust. This questionnaire was developed by a cohort of housewives, and it was possible to indirectly evaluate exposure to air pollution by examining house occupancy, cooking, and cleaning times, which are factors that generate indoor fine dust, and indoor/outdoor ventilation (number of windows opened). These data were input and stored in the iCReaT system of each institution, and a representative research director integrated and managed the data.

In addition, it was recommended that all participants fill out a time-activity log on the web-based questionnaire. They recorded the information using a time-activity diary, and activity information was collected at 1-hour intervals. The activities were organized according to the following classifications: main activity, extra activity, transportation, indoors, and outdoors. Participants' time activities were analyzed to identify the indoor and outdoor residence time patterns. The identified pattern was used to calculate individual exposure to indoor and outdoor PM10 and PM2.5.

2) Measurement of outdoor air pollution concentration
The outdoor PM concentrations (PM10 and PM2.5) were collected from a nearby urban atmospheric measurement network based on the addresses of the pregnant women who participated in the study. The urban air monitoring station data used in this study were obtained from air Korea (https://www.airkorea.or.kr/web), which is operated by the Korean Ministry of Environment. Air Korea has been disclosing its national real-time air pollution level information via a website since December 2005 [29]. As at 2021, there were 614 stations in 162 cities and counties in Korea for air quality monitoring of sulfur dioxide, nitrogen dioxide, ozone, carbon monoxide, PM10, and PM2.5 [29].

3) Measurement of indoor air pollution concentration
The indoor concentrations of PM10 and PM2.5 were measured by placing a fine dust meter in the living room of each participant's home. AirGuardK (Kweather Co, Seoul, Korea) was used to measure fine particles (PM10, PM2.5), carbon dioxide (CO_2), volatile organic compounds (VOCs), temperature, humidity, and noise. These measurements were taken online at 1-minute intervals. The measured indoor air quality data are stored in the indoor air quality monitoring platform through the long-term evolution communication network to prevent loss. In addition, the data are collected and stored every minute. Measurements were carried out for a week during each trimester of pregnancy, and the measured concentration value was determined in real time using the internet of things and information and communication technology.

4) Personal exposure prediction using a time-weighted average model
We used a time-weighted average model to estimate the individual PM exposure in pregnant women. The time-weighted average model is a concept in which an individual's exposure over a 24-hour period can be expressed as the sum of exposure to each microenvironment weighted to a time-activity pattern. Although it was not possible to measure the concentration of air pollutants in all local environments, individual exposure to PM10 and PM2.5, using a time log and time-weighted model, can be predicted [25-28]. The time-weighted model can be expressed by the following equations: $C_{per}=\sum(T_{indoor}\times C_{indoor}+T_{outdoor}\times C_{outdoor})$ where, C_{per}: predicted personal exposure, T_{indoor}: indoor activity time rate (indoor activity time/24hr), C_{indoor}: indoor PM2.5 concentration, $T_{outdoor}$: outdoor activity time rate (outdoor activity time/24hr). $C_{outdoor}$: outdoor PM2.5 concentration.

In this study, by applying PM10 and PM2.5 concentration values and temporal activity patterns from the time-weighted

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Table 4. General characteristics of participants who has completed delivery (by the time of June 2022)

	Value
Demographic factors	
Age (yr)	333 (33.6±4.1)
Maternal height (cm)	333 (162.2±5.1)
Pre-pregnancy weight (kg)	333 (58.5±9.6)
Pre-pregnancy BMI (kg/m^2)	333 (22.2±3.4)
Marital status	
Married	326 (97.9)
Single, divorced	6 (1.8)
Education	
≤High school	29 (8.7)
College	237 (71.2)
≥Graduate school	66 (19.8)
Occupation	
Yes	223 (67.0)
No	109 (32.7)
Income (KRW/month)[a]	
<4,000,000	77 (23.1)
4,000,000-5,990,000	57 (17.1)
≤6,000,000	77 (23.1)
Environmental factors	
Place of residence	
Urban areas	309 (92.8)
Rural and mountain areas	12 (3.6)
Industrial complex	2 (0.6)
Floors of residence	
<10 floors	194 (58.3)
≥10 floors	110 (33.0)
Distance to the road	
<50 m	119 (35.7)
50-100 m	143 (42.9)
>100 m	70 (21.0)
Adjacent road lane	
<Four lanes	128 (38.4)
≥Four lanes	204 (61.3)
Traffic volume	
High	161 (48.3)
Usual	130 (39.0)
Low	41 (12.3)
Lifestyle factors	
Smoking during pregnancy	

Table 4. General characteristics of participants who has completed delivery (by the time of June 2022) (Continued)

	Value
Yes	29 (8.7)
No	303 (91.0)
Exposure to secondhand smoke during pregnancy	
Yes (in home)	16 (4.8)
Yes (in the workplace)	29 (8.7)
Drinking alcohol during pregnancy	
Yes	19 (5.7)
No	313 (94.0)
Drinking coffee during pregnancy	
Yes	157 (47.1)
No	174 (52.3)
Physical activity	
Yes	79 (23.7)
No	253 (76.0)
Main cooking style	
Roasting	139 (41.7)
Boiling or poaching	65 (19.5)
Frying in oil	119 (35.7)
Clinical characteristics	
Parity	
Nulliparity	156 (46.8)
≥1 parity	177 (53.2)
Pregnancy method	
Natural pregnancy	287 (86.2)
By ART	46 (13.8)
History of preterm birth	
Yes	12 (3.6)
No	321 (96.4)
Gestational age at birth	332 (38.4±1.8)
Methods of delivery	
Vaginal delivery	118 (35.4)
Cesarean section	214 (64.3)
Characteristics of neonate	
Gender	
Male	179 (53.8)
Female	152 (45.6)
Weight (g)	330 (3,138±456.1)
Height (cm)	330 (49.2±2.5)
Apgar score	

Table 4. General characteristics of participants who has completed delivery (by the time of June 2022) (Continued)

	Value
1 min	331 (8.4±1.3)
5 min	331 (9.3±1.1)
Neonatal complications	
Preterm birth	26 (7.8)
Low birth weight	9 (2.7)
Admission in NICU (yes)	45 (13.5)

Values are presented as mean±standard deviation of continuous variables or number (%) of categorical variables.
BMI, body mass index; ART, assisted reproductive technology; NICU, neonatal intensive care unit.
[a]KRW, Korean won; 1 US dollar ≒ 1,300 KRW.

Table 5. Individual exposure concentrations of particulate matter (μg/m^3)

	1st trimester	2nd trimester	3rd trimester	Total
PM 2.5				
Number	127	285	281	302
Median (IQR)	5.93 (3.57-8.41)	6.11 (3.67-9.71)	8.15 (4.45-15.94)	7.33 (4.48-11.04)
Mean	6.52 (±4.14)	8.36 (±7.80)	12.02 (±11.46)	9.34 (±7.55)
Min	0.19	0.26	0.00	0.40
Max	26.24	47.45	81.58	56.24
PM 10				
Number	126	281	281	302
Median (IQR)	10.79 (7.08-15.30)	11.49 (7.27-18.23)	12.75 (8.01-22.33)	12.83 (8.27-18.87)
Mean	12.06 (±7.24)	15.67 (±14.33)	20.90 (±24.40)	17.02 (±15.05)
Min	0.31	0.63	1.33	1.18
Max	45.83	84.84	201.48	100.56

Values are presented as mean±standard deviation number (%).
PM, particulate matter; IQR, interquartile range.

average model, predicted individual exposure values for pregnant women was obtained. For pregnant women who worked in the office, PM10 and PM2.5 concentrations at the workplace were excluded because of the lack of measurement data. As a result, a time-weighted average model of indoor and outdoor PM10 and PM2.5 concentration values and temporal activity patterns was applied to represent the predicted values for individual exposure.

Results

1. General characteristics of participants
Table 4 shows the distribution of sociodemographic char-acteristics, living environment, lifestyle, and clinical details for 333 participants of the APPO study by June 2022 who had completed childbirth. The mean age of the pregnant women was 33.6 years, and their pre-pregnancy body mass index was 22.2, which was within the normal range. Most participants were married college graduates. They were un-likely to smoke or drink alcohol during pregnancy; however, 47.1% consumed coffee during pregnancy. Additionally, most participants lived in urban areas (92.8%), 3.6% in rural and mountainous areas, and 0.6% in industrial complexes. They were naturally pregnant and delivered at an average of 38 weeks and 4 days of gestation. The proportions of male (n=179, 53.8%) and female (n=152, 45.6%) neonates were similar, and the mean birth weight was 3,138 g. The

incidence of PTB was 7.8% and 2.7% of the newborns had LBW (Table 4).

2. Individual exposure to PM10 and PM2.5 concentrations

The estimated individual exposure amounts of PM10 and PM2.5 for participants are shown in Table 5. PM10 and PM2.5 exposures were presented as values for each trimester of pregnancy and the entire period of pregnancy. The average exposure of PM10 and PM2.5 among the participants in the entire period of pregnancy exceeded the World Health Organization air quality guidelines (an annual level, PM10 >15 $\mu g/m^3$, PM2.5 >5 $\mu g/m^3$) [30]. Moreover, it was revealed that the PM concentration was increasing toward the 3rd trimester of pregnancy. Based on these results, it is possible to analyze the relationship between PM and pregnancy outcomes.

Discussion

The APPO study aims to analyze adverse pregnancy outcomes resulting from PM exposure, identify related biomarkers, and develop management guidelines. In detail, about 1,200 pregnant women will be recruited over 3 years to collect data on fine dust exposure; in addition, methods for measuring exposure to fine particles for each pregnant woman and estimating output will be established. Standardization of the protocol used in this APPO study will play an important role in establishing the study design and its future applications. Moreover, it could provide a basis for estimating individual exposure to PM and identifying air pollution sources. Furthermore, it could influence the development of action points and policy support directions for disease control in pregnant women.

The first strength of this study is the direct collection of measured data on indoor fine dust considering the lifestyle of pregnant women. Periodic and repeated measures of environmental exposure during pregnancy could provide a unique and powerful opportunity for etiological investigation of various environmental exposures at different time points and their effects on maternal health. In addition, the concentration of outdoor PM and individual exposure estimates were calculated using a time-activity log to reflect the actual exposure level as accurately as possible. Second, this study had a sufficiently large sample size to investigate maternal and fetal health outcomes. Participants were recruited from various areas in Korea to ensure that the study results are representative of all parts of the country. Furthermore, the variability in environmental exposure data for each area provides a good opportunity to detect the environmental impacts on health outcomes. Finally, the influence of multiple environmental exposures on various health outcomes was assessed. Air pollutants such as PM10, PM2.5, CO_2, VOCs, temperature, humidity, and noise were directly measured indoors. Thus, the results could be analyzed for synergistic effects, beyond the effect on a single substance, when multiple environmental pollutants were exposed simultaneously. This APPO study will elucidate the mechanisms involved and expand relevant research on the potential interactions among several risk factors.

However, the study had some limitations that need to be addressed. It was impossible to measure all possible environmental exposures, despite the development of extensive measurement techniques and individual activity analyses. In addition, all specific organs or bodily fluids could not be collected for genomic studies, despite urine, blood, and umbilical cord blood samples being collected to analyze exposure detection and identification of predictive biomarkers.

Recently, air pollution and abnormal climate change have become serious and considerable issues worldwide. In addition, securing the health of pregnant women and fetuses is necessary because of the low fertility rate and increase in the proportion of high-risk pregnancies in Korea. Notably, continuous attention to maternal environment and health is needed for a sustainable society. Therefore, we conducted a prospective cohort study on pregnant women. We expect that this APPO study will identify the degree of exposure to air pollution among pregnant women and use the results as basic data for estimating individual exposure to fine dust. The results of this APPO study will facilitate the development of health management strategies for pregnant women against air pollution.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Ethical approval

Patient consent

Funding information

References

1. Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, Gilliland FD. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the children's health study. Environ Health Perspect 2005;113:1638-44.
2. Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. Using new satellite based exposure methods to study the association between pregnancy $PM_{2.5}$ exposure, premature birth and birth weight in Massachusetts. Environ Health 2012;11:40.
3. Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D, et al. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect 2006;114:1287-92.
4. van den Hooven EH, Pierik FH, de Kluizenaar Y, Willemsen SP, Hofman A, van Ratingen SW, et al. Air pollution exposure during pregnancy, ultrasound measures of fetal growth, and adverse birth outcomes: a prospective cohort study. Environ Health Perspect 2012;120:150-6.
5. Williams L, Spence A, Tideman SC. Implications of the observed effects of air pollution on birth weight. Soc Biol 1977;24:1-9.
6. Parker JD, Woodruff TJ, Basu R, Schoendorf KC. Air pollution and birth weight among term infants in California. Pediatrics 2005;115:121-8.
7. Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect 2003;111:1773-8.
8. Bobak M. Outdoor air pollution, low birth weight, and prematurity. Environ Health Perspect 2000;108:173-6.
9. Wang X, Ding H, Ryan L, Xu X. Association between air pollution and low birth weight: a community-based study. Environ Health Perspect 1997;105:514-20.
10. Ha EH, Hong YC, Lee BE, Woo BH, Schwartz J, Christiani DC. Is air pollution a risk factor for low birth weight in Seoul? Epidemiology 2001;12:643-8.
11. Lee BE, Ha EH, Park HS, Kim YJ, Hong YC, Kim H, et al. Exposure to air pollution during different gestational phases contributes to risks of low birth weight. Hum Reprod 2003;18:638-43.
12. Seo JH, Leem JH, Ha EH, Kim OJ, Kim BM, Lee JY, et al. Population-attributable risk of low birthweight related to PM10 pollution in seven Korean cities. Paediatr Perinat Epidemiol 2010;24:140-8.
13. Ha EH, Lee BE, Park HS, Kim YS, Kim H, Kim YJ, et al. Prenatal exposure to PM10 and preterm birth between 1998 and 2000 in Seoul, Korea. J Prev Med Public Health 2004;37:300-5.
14. Kang J, Lee JY, Song H, Shin SJ, Kim J. Association between in vitro fertilization success rate and ambient air pollution: a possible explanation of within-year variation of in vitro fertilization success rate. Obstet Gynecol Sci 2020;63:72-9.
15. Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect 2013;121:267-373.
16. Statistics KOREA Government Official Work Conference. Air pollution in major cities [Internet]. Daejeon: Statistics KOREA Government Official Work Conference; c2022 [cited 2022 Oct 17]. Available from: https://www.index.go.kr/unity/potal/main/EachDtlPageDetail.do?idx_cd=2789.
17. Bell ML, Belanger K, Ebisu K, Gent JF, Lee HJ, Koutrakis P,

et al. Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources. Epidemiology 2010;21:884-91.

18. Basu R, Harris M, Sie L, Malig B, Broadwin R, Green R. Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California. Environ Res 2014;128:42-51.

19. Fattorini D, Regoli F. Role of the chronic air pollution levels in the Covid-19 outbreak risk in Italy. Environ Pollut 2020;264:114732.

20. Comunian S, Dongo D, Milani C, Palestini P. Air pollution and COVID-19: the role of particulate matter in the spread and increase of COVID-19's morbidity and mortality. Int J Environ Res Public Health 2020;17:4487.

21. Ahn KH, Kim HI, Lee KS, Heo JS, Kim HY, Cho GJ, et al. COVID-19 and vaccination during pregnancy: a systematic analysis using Korea National Health Insurance claims data. Obstet Gynecol Sci 2022;65:487-501.

22. Akbar MIA, Gumilar KE, Andriya R, Wardhana MP, Mulawardhana P, Anas JY, et al. Clinical manifestations and pregnancy outcomes of COVID-19 in indonesian referral hospital in central pandemic area. Obstet Gynecol Sci 2022;65:29-36.

23. Peters A, Döring A, Wichmann HE, Koenig W. Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 1997;349:1582-7.

24. Kim BM, Ha M, Park HS, Lee BE, Kim YJ, Hong YC, et al. The mothers and children's environmental health (MOCEH) study. Eur J Epidemiol 2009;24:573-83.

25. Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta 2004;339:1-9.

26. Del Rio D, Stewart AJ, Pellegrini N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovasc Dis 2005;15:316-28.

27. Kirchstetter TW, Novakov T. Controlled generation of black carbon particles from a diffusion flame and applications in evaluating black carbon measurement methods. Atmospheric Environ 2007;41:1874-88.

28. Korea National Institute of Health. iCReaT web-based clnical research management system [Internet]. Cheongju: Korea National Institute of Health; c2022 [cited 2022 Oct 17]. Available from: http://icreat.nih.go.kr/icreat/webapps/com/hismainweb/jsp/guide_n2.jsp?sel=03 Updated 2017.

29. Korea Environment Corporation. AirKorea website by the Korean Ministry of Environment [Internet]. Incheon: Korea Environment Corporation; c2022 [cited 2022 Oct 17]. Available from: airkorea.or.kr/web/.

30. World Health Organization. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide [Internet]. Geneva: WHO; c2021 [cited 2022 Dec 19]. Available from: https://apps.who.int/iris/handle/10665/345329.