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Article

Effects of Particulate Matter on the Risk of Gestational Hypertensive Disorders and Their Progression

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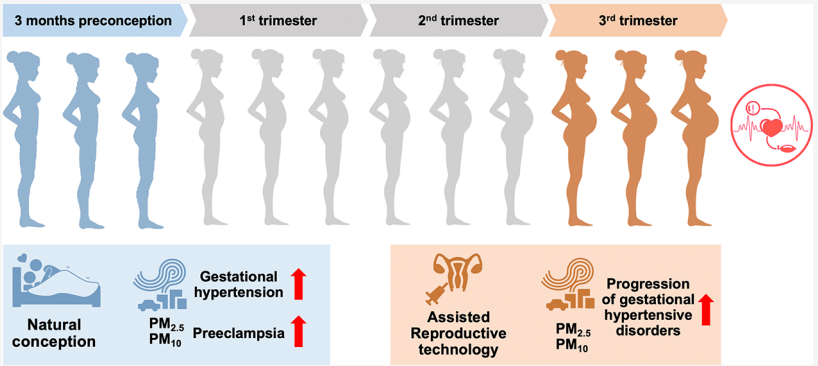

ABSTRACT: Associations between particulate matter (PM) and gestational hypertensive disorders (GHDs) are well documented, but there is no evidence on the associations between PM and GHD progression, especially among those with assisted reproductive technology (ART) conceptions. To explore the effects of PM on the risk of GHDs and their progression among pregnant women with natural or ART conception, we enrolled 185,140 pregnant women during 2014−2020 in Shanghai and estimated the associations during different periods using multivariate logistic regression. During the 3 months of preconception, 10 $\mu g/m^3$ increases in PM concentrations were associated with increased risks of gestational hypertension (GH) ($PM_{2.5}$: aOR = 1.076, 95% CI: 1.034−1.120; PM_{10}: aOR = 1.042, 95% CI: 1.006−1.079) and preeclampsia ($PM_{2.5}$: aOR = 1.064, 95% CI: 1.008−1.122; PM_{10}: aOR = 1.048, 95% CI: 1.006−1.092) among women with natural conception. Furthermore, for women with ART conceptions who suffered current GHD, 10 $\mu g/m^3$ increases in PM concentrations in the third trimester elevated the risk of progression ($PM_{2.5}$: aOR = 1.156, 95% CI: 1.022−1.306 ; PM_{10}: aOR = 1.134, 95% CI: 1.013−1.270). In summary, women with natural conception should avoid preconceptional PM exposure to protect themselves from GH and preeclampsia. For women with ART conceptions suffering from GHD, it is necessary to avoid PM exposure in late pregnancy to prevent the disease from progressing.

KEYWORDS: *particulate matter, gestational hypertensive disorder, preeclampsia, progression, assisted reproductive technology*

1. INTRODUCTION

Given the rapid economic growth and increasing population size of East Asia, suboptimal air quality is expected to continue in this region for the next few years.[1] Fine particulate matter (PM) is considered to be one of the most important components of ambient air pollution. Fine PM includes PM <2.5 μm ($PM_{2.5}$) and PM <10 μm (PM_{10}), and these forms have received a large amount of attention due to the reported adverse effects of ambient air pollutants on serious health problems.[2] Pregnancy is a unique time in which the pregnant woman is more vulnerable to various ambient air pollutants. Current epidemiologic evidence suggests that gestational exposure to ambient pollutants, especially PM, is correlated with several adverse perinatal outcomes, including spontaneous abortion,[3] preterm birth,[4] low birth weight,[5] fetal growth restriction,[6] and hypertensive disorders during pregnancy.[7]

Gestational hypertensive disorders (GHDs) are the most common complications of pregnancy, affecting almost 10% of pregnancies in the third trimester.[8,9] In addition to maternal mortality, GHD and preeclampsia (PE) are the leading causes of perinatal death as well as placental abruption, preterm birth, and small for gestational age among infants, which lead to higher rates of admission to neonatal intensive care units.[10,11] Recently, there have been concerns that ambient air pollution exposure may also increase the risk of GHD. Accumulative

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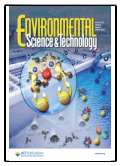

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evidence suggests associations between PM and GHD, although the associations appear inconsistent in each trimester.[12−17] The potential impact of PM with preconceptional exposures on GHD has also been reported.[16,17] Although most studies have explored the effect of PM on the occurrence of GHD (including gestational hypertension, PE, and PE with severe features), whether PM has an effect on the progression of GHD to the severe stage has not yet been reported.

Furthermore, in addition to the differences in PM concentrations and the ethnicity of the population,[12,18] we speculated that the inconsistent findings on the association between PM and GHD may also be attributed to the conception approach. With the increased use of assisted reproductive technology (ART), the composition of the conception approach has changed over the last decade.[19] According to the recent literature, pregnant women who conceived by ART were more likely to suffer from GHD and PE.[20] Thus, it is unclear whether pregnant women who conceive by ART are subject to the same effects of PM on GHD incidence and its progression as those who conceive naturally.

To address these research gaps, we performed this study covering a long study period of 6 years and including a large sample size of over 180,000 pregnant women from two major maternal and child health hospitals to explore the effects of PM on GHD incidence and its progression among pregnant women with natural conception and ART in Shanghai.

2. PATIENTS AND METHODS

2.1. Study Design and Population. This study was conducted in Shanghai, which has the highest population density in China, with a permanent population of almost 25 million. Shanghai is located in the area of the Yangtze River Delta, which has a subtropical, humid, monsoon climate with distinct seasons. This study was designed to assess the associations of PM with the risk of GHDs and their progression. The study population was recruited from two hospitals, namely, Obstetrics and Gynecology Hospital (OB/GYN Hospital) and International Peace Maternity and Child Health Hospital (IPMCH Hospital), which are the two largest maternal and child health hospitals in Shanghai, with three divisions located in the city center (Supplementary Figure S1). Pregnant women who received antenatal care and delivered in the two hospitals from July 1, 2014, and October 31, 2020, were included in this analysis. We excluded pregnant women who resided outside of Shanghai for more than 1 month during the study period (from 3 months of preconception to delivery) to avoid measurement bias on PM exposures. All procedures of this study were reviewed and approved by the Institutional Review Boards of both hospitals (OB/GYN Hospital: 2020-204; IPMCH Hospital: GKLW-2019-51). The requirement for written informed consent was waived by the ethics committee, given the retrospective design.

2.2. Environmental Data and Exposure Assessment. In this study, environmental data were collected from daily reports from the China National Environmental Monitoring Centre (CNEMC) during the study period. According to the protocol of the China National Air Quality Monitoring Network, the concentrations of $PM_{2.5}$ and PM_{10} in Shanghai were measured consecutively at 10 designated national monitoring sites before 2018. After 2018, the concentrations of $PM_{2.5}$ and PM_{10} were measured at 10 original national monitoring sites and 9 newly established national monitoring sites covering 16 districts of Shanghai (the locations of the 19 national monitoring sites are shown in Supplementary Figure S1). The exposure data of $PM_{2.5}$ and PM_{10} in China were estimated at high spatial (15 km × 15 km) and temporal (1 h) resolutions based on relatively high-resolution Chinese Air Quality Reanalysis (CAQRA) datasets, which were developed by assimilating over 1000 surface air quality monitoring sites from CNEMC in a postprocessing mode using their own developed chemical data assimilation system (ChemDAS).[21] Furthermore, meteorological data on the daily maximum and minimum temperature and relative humidity was also obtained from the China National Weather Data Sharing System. The assessment of the individual exposure to PM and meteorological parameters was based on the data from the nearest monitoring site to the residential address of each participant to represent the exposure level to some extent. Daily average concentrations of $PM_{2.5}$, PM_{10}, maximum and minimum temperature, and relative humidity were obtained from 3 months before pregnancy and over the entire pregnancy until the day of delivery. We estimated the average individual exposure concentration for four exposure windows in this study: 3 months before pregnancy (as a proxy of preconceptional exposure), first trimester, second trimester, and third trimester. The average concentrations of the exposure parameters during these four exposure windows were calculated.

2.3. Data Collection and Pregnancy Outcomes. Before creating perinatal care profiles, baseline information, including sociodemographic characteristics, reproductive history, and mode of current conception, was collected from all pregnant women by in-person interview. In our study, mode of current conception was classified into natural conception and ART. ART was defined as all procedures for initiating pregnancy, which include intra-uterine insemination, in vitro fertilization, intracytoplasmic sperm injection, gamete and embryo cryopreservation, and preimplantation genetic test.[22]

Data related to pregnancy complications, including diabetes mellitus during pregnancy, gestational diabetes mellitus (GDM), chronic hypertension in pregnancy, GHD, intrahepatic cholestasis of pregnancy (ICP), and gestational thyroid dysfunction, as well as the number of fetuses, were reverified by the participants' medical health records. The diagnosis of GHD (including gestational hypertension, PE, and PE with severe features) was based on the American College of Obstetricians and Gynecologists Practice Bulletin.[23] PE with severe features was defined as PE with following conditions, including systolic blood pressure of 160 mmHg or more, or diastolic blood pressure of 110 mmHg or more on two occasions at least 4 h apart, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, new-onset headache unresponsive to medication, and visual disturbances.[23] The progression of GHD can be defined as the progression to PE, PE with severe features, or adverse outcomes (including eclampsia, thrombocytopenia, and placental abruption) in patients with gestational hypertension.[23−25]

2.4. Statistical Analysis. The characteristics of the study population, distribution of weekly concentrations of PM, and meteorological data are presented using descriptive statistics. Categorical variables are displayed as frequencies with proportions, while continuous variables with a normal distribution are displayed as the means with standard deviations.

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Table 1. Maternal Characteristics of All Pregnant Women[a]

	All (N = 185,140) no. (%)	GH (N = 5357) no. (%)	PE (N = 4515) no. (%)	PE with severe features (N = 3032) no. (%)	GHD with progression (N = 2282) no. (%)
Maternal sociodemographic characteristics					
age, mean ± SD, years	30.74 ± 4.02	31.31 ± 4.33	31.27 ± 4.29	31.62 ± 4.51	31.67 ± 4.45
pregestational BMI, mean ± SD, kg/m^2	21.25 ± 2.84	23.27 ± 3.70	23.02 ± 3.66	22.73 ± 3.62	23.13 ± 3.66
marriage					
married	183,451 (99.09)	5299 (98.92)	4478 (99.18)	3001 (98.98)	2262 (99.12)
single	1689 (0.91)	58 (1.08)	37 (0.82)	31 (1.02)	20 (0.88)
race					
Han	176,179 (95.16)	5140 (95.95)	4351 (96.37)	2806 (92.55)	2143 (93.91)
minority	4998 (2.70)	114 (2.13)	91 (2.02)	122 (4.02)	65 (2.85)
foreign	3963 (2.14)	103 (1.92)	73 (1.62)	104 (3.43)	74 (3.24)
residence					
residents	128,779 (69.56)	4077 (76.11)	3377 (74.80)	2018 (66.56)	1633 (71.56)
immigrants	56,361 (30.44)	1280 (23.89)	1138 (25.20)	1014 (33.44)	649 (28.44)
occupation					
employed	176,279 (95.21)	5071 (94.66)	4145 (91.81)	2820 (93.01)	2095 (91.81)
self-employed	3795 (2.05)	112 (2.09)	157 (3.48)	89 (2.94)	67 (2.94)
unemployed	5066 (2.74)	174 (3.25)	213 (4.72)	123 (4.06)	120 (5.26)
medical insurance					
public	126,094 (68.11)	3730 (69.63)	3115 (68.99)	2035 (67.12)	1540 (67.48)
private	59,046 (31.89)	1627 (30.37)	1400 (31.01)	997 (32.88)	742 (32.52)
History of reproduction					
parity					
0	136,721 (73.85)	4272 (79.75)	3673 (81.35)	2303 (75.96)	1779 (77.96)
1	46,162 (24.93)	1032 (19.26)	787 (17.43)	681 (22.46)	463 (20.29)
≥2	2257 (1.22)	53 (0.99)	55 (1.22)	48 (1.58)	40 (1.75)
number of previous abortions					
0	118,017 (63.74)	3440 (64.22)	2878 (63.74)	1894 (62.47)	1448 (63.45)
1−2	60,300 (32.57)	1712 (31.96)	1437 (31.83)	977 (32.22)	720 (31.55)
≥3	6823 (3.69)	205 (3.83)	200 (4.43)	161 (5.31)	114 (5.00)

[a]GH, gestational hypertension; PE, preeclampsia; GHD, gestational hypertensive disorders; SD, standard deviation; BMI, body mass index.

The weekly incidence rates of GHD (including GH, PE, and PE with severe features) were calculated as the percentages among all pregnant women admitted to the hospital for delivery. The weekly incidence rates of GHD with progression were calculated as the percentages among all pregnant women with GHD admitted to the hospital for delivery. The temporal trends of $PM_{2.5}$ and PM_{10} were plotted to observe the overall relationships with GHD and GHD with progression. The trends of weekly incidence rates of GHD and GHD with progression were fitted and plotted using natural spline smoothing with 6 degrees of freedom (df) per year, as we previously described.[26,27]

The associations between exposures of $PM_{2.5}$ and PM_{10} and GHD (including GH, PE, and PE with severe features) were estimated for three periods, namely, 3 months of preconception, the first trimester, and the second trimester, as GHDs often occur and are diagnosed late at the second trimester or third trimester. When analyzing the associations between GHD with progression and exposures of $PM_{2.5}$ and PM_{10}, we further estimate the associations for the third trimester, as most GHD cases progress to the severe degree at the third trimester and before and during the delivery.[23−25] All these associations were estimated using logistic regression models with adjustment of potential confounding factors. Confounding factors were selected by Spearman correlation analysis. All the variables were initially sorted according to their absolute Spearman correlation coefficient values with respect to GHD and GHD with progression. Variables with absolute correlation coefficient values over 0.02 as well as those with P values less than 0.05 were treated as potential confounding factors, as indicated in Supplementary Figures S2−S5. The confounding factors with clinical considerations based on a directed acyclic graph (Supplementary Figure S6) were finally selected for inclusion in the adjusted models. Potential confounders were adjusted in the models including BMI, mode of conception, GDM, diabetes mellitus in pregnancy, residence, parity, age, and number of fetuses for GH; number of fetuses, BMI, mode of conception, parity, ICP, GDM, occupation, diabetes mellitus in pregnancy, and age for PE; number of fetuses, mode of conception, BMI, ICP, diabetes mellitus in pregnancy, and age for PE with severe features; and number of fetuses, mode of conception, race, GDM, age, occupation, and diabetes mellitus in pregnancy for GHD with progression. Temperature, relative humidity, the season of the pregnancy, and hospital were also treated as confounding effects in the models. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated to indicate the risk of GHD and GHD with progression for an increase in $PM_{2.5}$ and PM_{10}. All analyses were conducted using R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria). All of the statistical analyses were calculated using two-sided tests with a 5% level of significance.

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Table 2. Gestational Complications of All Pregnant Women[a]

	All (N = 185,140) no. (%)	GH (N = 5357) no. (%)	PE (N = 4515) no. (%)	PE with severe features (N = 3032) no. (%)	GHD with progression (N = 2282) no. (%)
SBP at early pregnancy, mean ± SD, mmHg	112.42 ± 12.97	124.54 ± 12.66	121.89 ± 13.51	121.91 ± 13.66	121.89 ± 12.69
DBP at early pregnancy, mean ± SD, mmHg	69.15 ± 10.22	78.52 ± 9.89	75.91 ± 10.77	76.88 ± 10.83	76.66 ± 10.12
diabetes mellitus in pregnancy					
no	177,030 (95.62)	4932 (92.07)	4205 (93.13)	2734 (90.17)	2070 (90.71)
yes	8110 (4.38)	425 (7.93)	310 (6.87)	298 (9.83)	212 (9.29)
gestational diabetes mellitus					
no	167,027 (90.22)	4593 (85.74)	3829 (84.81)	2694 (88.85)	2018 (88.43)
yes	18,113 (9.78)	764 (14.26)	686 (15.19)	338 (11.15)	264 (11.57)
intrahepatic cholestasis of pregnancy					
no	183,580 (99.16)	5323 (99.37)	4414 (97.76)	2912 (96.04)	2229 (97.68)
yes	1560 (0.84)	34 (0.63)	101 (2.24)	120 (3.96)	53 (2.32)
gestational thyroid dysfunction					
no	175,428 (94.75)	5055 (94.36)	4214 (93.33)	2859 (94.29)	2150 (94.22)
hyperthyroidism	4710 (2.54)	146 (2.73)	184 (4.08)	112 (3.69)	92 (4.03)
hypothyroidism	5002 (2.70)	156 (2.91)	117 (2.59)	61 (2.01)	40 (1.75)
number of fetuses					
singletons	179,908 (97.17)	5136 (95.87)	3973 (88.00)	2598 (85.69)	1928 (84.49)
multiples	5232 (2.83)	221 (4.13)	542 (12.00)	434 (14.31)	354 (15.51)
preterm birth					
term	171,967 (92.88)	4916 (91.77)	3838 (85.01)	1715 (56.56)	1646 (72.13)
very preterm	1445 (0.78)	41 (0.77)	51 (1.13)	227 (7.49)	76 (3.33)
preterm	11,728 (6.33)	400 (7.47)	626 (13.86)	1090 (35.95)	560 (24.54)
mode of delivery					
vaginal	97,735 (52.79)	2330 (43.49)	1510 (33.44)	497 (16.39)	557 (24.41)
cesarean section	79,522 (42.95)	2817 (52.59)	2832 (62.72)	2413 (79.58)	1603 (70.25)
instrumental	7883 (4.26)	210 (3.92)	173 (3.83)	122 (4.02)	122 (5.35)
mode of conception					
natural conception	171,763 (92.77)	4728 (88.26)	3728 (82.57)	2477 (81.70)	1787 (78.31)
assisted reproductive technology	13,377 (7.23)	629 (11.74)	787 (17.43)	555 (18.30)	495 (21.69)

[a]GH, gestational hypertension; PE, preeclampsia; GHD, gestational hypertensive disorders; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

3. RESULTS

This analysis finally included a total of 185,140 eligible pregnant women who delivered at the OB/GYN Hospital or IPMCH Hospital during the study period. The residence distribution of all participants is indicated in Supplementary Figure S1. Among all pregnant women, 5357 were diagnosed with GH, 4515 were diagnosed with PE, and 3032 were diagnosed with PE with severe features. The weekly incidence rates of GH, PE, and PE with severe features were 2.93, 2.53, and 1.89% on average, respectively. Among all 12,904 patients with GHD, 2282 exhibited GHD with progression, with a weekly incidence rate of 17.73% (Supplementary Table S1). Furthermore, the weekly concentrations of $PM_{2.5}$ and PM_{10}, as well as weather conditions during the study period, are also summarized in Supplementary Table S1.

The distribution of sociodemographic characteristics and reproductive history of all the pregnant women are shown in Table 1. The occurrence of pregnancy complications among all study participants is listed in Table 2. In addition, the distribution of maternal characteristics and pregnancy complications stratified to the pregnant women with natural and ART conception are listed in Supplementary Tables S2 and 3 and Tables S4 and 5, respectively. Among these characteristics, variables related to the occurrence of GH, PE, PE with severe features, and GHD with progression were selected by Spearman correlation analysis, as shown in Supplementary Figures S2−S5. Notably, GH, PE, PE with severe features, and GHD with progression shared the same positive-related variables, including maternal age, mode of conception, number of fetuses, diabetes mellitus in pregnancy, mode of delivery, and preterm birth. The mode of delivery and preterm birth were not treated as confounding factors to be included in the adjustment models for clinical consideration, as indicated in DAG in supplementary Figure S6.

The temporal trends of $PM_{2.5}$ and PM_{10} and the scatter plots with smoothed fitted lines of the weekly incidence of GH, PE, PE with severe features, and GHD with progression are displayed in Supplementary Figure S7. The fitted spline curves for GH, PE, and GHD with progression were similar to the temporal trends of $PM_{2.5}$ and PM_{10}. The fitted spline curves for PE with severe features were only partially matched to the temporal trends for $PM_{2.5}$ and PM_{10}. Before estimating the actual effects of $PM_{2.5}$ and PM_{10} on GHD and GHD with progression, we performed Spearman correlation analysis between $PM_{2.5}$ and PM_{10} exposure levels at different periods separately. As shown in Supplementary Figure S8, no positive correlation was found between any period. Thus, it is necessary to determine the sensitive exposure windows of $PM_{2.5}$ and PM_{10} for GHD and GHD with progression.

The actual effects of $PM_{2.5}$ and PM_{10} at different periods on the risk of GHD and GHD with progression after adjusting for

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Table 3. Risk of Gestational Hypertensive Disorders Associated with Increases in Concentrations of Particulate Matter (per Unit)[a]

	GH aOR (95% CI)[b]	PE aOR (95% CI)[c]	PE with severe features aOR (95% CI)[d]
All participants			
$PM_{2.5}$ (per 10 $\mu g/m^3$)			
3 months before conception	1.086 (1.046, 1.127)	1.059 (1.008, 1.112)	0.962 (0.869, 1.064)
first trimester	0.987 (0.947, 1.028)	1.000 (0.917, 1.090)	0.892 (0.794, 1.002)
second trimester	1.077 (0.998, 1.163)	1.042 (0.989, 1.098)	0.962 (0.850, 1.088)
PM_{10} (per 10 $\mu g/m^3$)			
3 months before conception	1.047 (1.013, 1.082)	1.044 (1.005, 1.084)	0.933 (0.858, 1.015)
first trimester	1.002 (0.940, 1.068)	0.938 (0.875, 1.006)	0.916 (0.836, 1.004)
second trimester	1.061 (0.998, 1.128)	0.965 (0.906, 1.027)	0.951 (0.865, 1.046)
Natural conception			
$PM_{2.5}$ (per 10 $\mu g/m^3$)			
3 months before conception	1.076 (1.034, 1.120)	1.064 (1.008, 1.122)	0.971 (0.867, 1.087)
first trimester	0.985 (0.943, 1.029)	1.000 (0.910, 1.100)	0.885 (0.779, 1.008)
second trimester	1.064 (0.980, 1.155)	1.050 (0.992, 1.111)	0.993 (0.863, 1.141)
PM_{10} (per 10 $\mu g/m^3$)			
3 months before conception	1.042 (1.006, 1.079)	1.048 (1.006, 1.092)	0.946 (0.861, 1.038)
first trimester	1.010 (0.943, 1.082)	0.937 (0.867, 1.011)	0.923 (0.834, 1.021)
second trimester	1.065 (0.998, 1.136)	0.985 (0.919, 1.055)	0.987 (0.886, 1.099)
Assisted reproductive technology			
$PM_{2.5}$ (per 10 $\mu g/m^3$)			
3 months before conception	1.100 (0.977, 1.239)	1.062 (0.943, 1.196)	0.941 (0.745, 1.188)
first trimester	0.992 (0.883, 1.114)	1.047 (0.842, 1.301)	0.989 (0.770, 1.271)
second trimester	1.177 (0.948, 1.460)	1.121 (0.994, 1.264)	0.856 (0.657, 1.116)
PM_{10} (per 10 $\mu g/m^3$)			
3 months before conception	1.085 (0.984, 1.195)	1.047 (0.955, 1.149)	0.886 (0.733, 1.071)
first trimester	0.914 (0.743, 1.125)	1.009 (0.839, 1.215)	0.971 (0.794, 1.188)
second trimester	1.092 (0.920, 1.296)	0.882 (0.763, 1.021)	0.834 (0.684, 1.017)

[a]GH, gestational hypertension; PE, preeclampsia; aOR, adjusted odds ratio; CI, confidence interval; $PM_{2.5}$, particulate matter no greater than 2.5 microns; PM_{10}, particulate matter no greater than 10 microns. [b]Odds ratio was adjusted for BMI, residence, age, temperature, relative humidity, season, and hospital. [c]Odds ratio was adjusted for BMI, occupation, age, temperature, relative humidity, season, and hospital. [d]Odds ratio was adjusted for BMI, age, temperature, relative humidity, season, and hospital.

potential confounding factors are presented in Table 3. Consistent with the crude trends shown in Supplementary Figure S7, increases in the concentrations of $PM_{2.5}$ and PM_{10} during the 3 months before conception were associated with an increased risk of GH ($PM_{2.5}$: aOR = 1.086, 95% CI: 1.046−1.127; PM_{10}: aOR = 1.047, 95% CI: 1.013−1.082) and PE ($PM_{2.5}$: aOR = 1.059, 95% CI: 1.008−1.112; PM_{10}: aOR = 1.044, 95% CI: 1.005−1.084). Despite that a decreased risk of PE was found after exposure to the increased concentrations of PM_{10} during the first trimester with approaching significance (aOR = 0.938, 95% CI: 0.875−1.006), exposure to $PM_{2.5}$ and PM_{10} during other periods did not show any risk of GH and PE. As for PE with severe features, the overall risk was associated with a descending tendency as the exposure concentrations of $PM_{2.5}$ and PM_{10} increase during any periods, especially during the first trimester with approaching significance ($PM_{2.5}$: aOR = 0.892, 95% CI: 0.794−1.002; PM_{10}: aOR = 0.916, 95% CI: 0.836−1.004). However, these associations did not indicate statistical significances. Additionally, we further estimated the effects of $PM_{2.5}$ and PM_{10} on the risk of GHD stratified according to the mode of conception. Among women with natural conception, the effects of exposure to increased concentrations of $PM_{2.5}$ and PM_{10} during the 3 months before conception on the incidences of GH ($PM_{2.5}$: aOR = 1.076, 95% CI: 1.034−1.120; PM_{10}: aOR = 1.042, 95% CI: 1.006−1.079) and PE ($PM_{2.5}$: aOR = 1.064, 95% CI: 1.008−1.122; PM_{10}: aOR = 1.048, 95% CI: 1.006−1.092) were the same as those in the overall population. However, $PM_{2.5}$ and PM_{10} were found to have no significant associations with GH, PE, and PE with severe features among women that conceived with ART.

Furthermore, we estimated the effects of $PM_{2.5}$ and PM_{10} on the risk of GHD with progression (Table 4). Increased concentrations of $PM_{2.5}$ and PM_{10} in the third trimester increased the risk of progression among those who already suffered GHD ($PM_{2.5}$: aOR = 1.086, 95% CI: 1.027−1.149; PM_{10}: aOR = 1.081, 95% CI: 1.025−1.139). Notably, the impacts of exposure to $PM_{2.5}$ and PM_{10} in the third trimester on the progression of GHD were especially obvious among women conceived by ART ($PM_{2.5}$: aOR = 1.156, 95% CI: 1.022−1.306; PM_{10}: aOR = 1.134, 95% CI: 1.013−1.270), while $PM_{2.5}$ and PM_{10} showed no effects on the progression of GHD among women with natural conception.

4. DISCUSSION

In this analysis of over 180,000 pregnant women, we found that pregnant women who conceived naturally were at a higher risk of GH and PE after exposure to $PM_{2.5}$ and PM_{10} during the 3 months before conception, while pregnant women who conceived with ART had a high risk of progression to severe GHD after exposure to $PM_{2.5}$ and PM_{10} during late pregnancy. Our findings therefore add a new perspective to the hitherto

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Table 4. Risk of Gestational Hypertensive Disorder with Progression Associated with Increases in Concentrations of Particulate Matter (per Unit)[a]

	GHD with progression aOR (95% CI)[b]
All participants	
$PM_{2.5}$ (per 10 $\mu g/m^3$)	
3 months before conception	1.108 (0.990, 1.240)
first trimester	1.057 (0.936, 1.194)
second trimester	0.989 (0.924, 1.058)
third trimester	1.086 (1.027, 1.149)
PM_{10} (per 10 $\mu g/m^3$)	
3 months before conception	1.008 (0.949, 1.071)
first trimester	1.092 (0.998, 1.194)
second trimester	0.952 (0.865, 1.047)
third trimester	1.081 (1.025, 1.139)
Natural conception	
$PM_{2.5}$ (per 10 $\mu g/m^3$)	
3 months before conception	1.098 (0.968, 1.244)
first trimester	1.025 (0.895, 1.174)
second trimester	0.989 (0.917, 1.067)
third trimester	1.060 (0.994, 1.130)
PM_{10} (per 10 $\mu g/m^3$)	
3 months before conception	1.010 (0.944, 1.080)
first trimester	1.101 (0.995, 1.218)
second trimester	0.955 (0.859, 1.061)
third trimester	1.050 (0.989, 1.115)
Assisted reproductive technology	
$PM_{2.5}$ (per 10 $\mu g/m^3$)	
3 months before conception	1.180 (0.907, 1.537)
first trimester	1.196 (0.892, 1.605)
second trimester	0.997 (0.856, 1.160)
third trimester	1.156 (1.022, 1.306)
PM_{10} (per 10 $\mu g/m^3$)	
3 months before conception	0.996 (0.867, 1.145)
first trimester	1.047 (0.833, 1.316)
second trimester	0.958 (0.768, 1.195)
third trimester	1.134 (1.013, 1.270)

[a]GHD, gestational hypertensive disorders; aOR, adjusted odds ratio; CI, confidence interval; $PM_{2.5}$, particulate matter no greater than 2.5 microns; PM_{10}, particulate matter no greater than 10 microns. [b]Odds ratio was adjusted for mode of conception, race, age, occupation, temperature, relative humidity, season, and hospital.

published literature on the association between PM and GHD for women with different conception approaches.

Most previous studies focused the exposure windows on the pregnancy periods, and few studies revealed the relationship before conception. In 2019, Nobles et al. reported null effects of $PM_{2.5}$ and PM_{10} 3 months of preconception on the incidences of GH and PE.[16] However, in our study, exposure to $PM_{2.5}$ and PM_{10} during the 3 months before conception was found to be positively associated with GH and PE, which was consistent with the results from Zhu et al.[17] According to Pedersen et al., these inconsistent findings might be attributed to population heterogeneity.[28] In addition to the period before conception, inconsistent relationships between PM and GHD also existed during the pregnancy periods. The results from Europe and North America all revealed that the elevated risk of GHD was much more sensitive to the higher levels of $PM_{2.5}$ and PM_{10} in late pregnancy than in early pregnancy.[13,16,29,30] Findings from Shanghai revealed an association between GH and $PM_{2.5}$ exposure during the first trimester but not during the second trimester.[31] Recently, a meta-analysis of cohort studies confirmed that maternal exposure to PM in the first trimester was associated with GH and PE.[32] Furthermore, the composition of ambient pollutants is another factor that leads to discrepancies in the relationships between PM and GHD; even in China, the composition of ambient pollutants varies from area to area.[2] That is why our study indicated a positive association between GH and $PM_{2.5}$ exposure in the first trimester, which is consistent with the study by Su et al. in the same city[31] but different from the observations in other areas, such as Shenzhen and Heibei.[33,34] Notably, the preconception exposure window also encompasses potential impacts on spermatogenesis for the male partner. Thus, in this case, attention might be paid to the association between male exposure to $PM_{2.5}$ and PM_{10} and risk of GHD for their partner.

Although the overall levels of $PM_{2.5}$ and PM_{10} decreased as the year progressed, the incidence rates of GHD did not have the same tendency to decrease and there were even elevations in GH and PE. This might be related to the increased number of pregnant women who resorted to ART over the years, as indicated in Supplementary Figure S9. Recent studies revealed that both fresh and frozen-thawed embryo transfer leads to an increased risk of GHD in late pregnancy.[20,35] We speculated that ART might be an important confounding factor that influences the effect of PM on the risk of GHD. Thus, we conducted a stratified analysis on the effect of PM on GHD and its progression according to the mode of conception. The findings from our study revealed different risk profiles for GHD and its progression with different sensitive exposure windows for $PM_{2.5}$ and PM_{10}. For pregnant women who conceived by ART and had already suffered from GHD, it is necessary to avoid PM exposure in the third trimester to prevent the disease from progressing. From our previous findings, ART procedures like ovarian stimulation and hormone replacement therapy have been found to increase the risk of GH and PE.[20] For women who conceived with ART, exposure to the $PM_{2.5}$ and PM_{10} during the third trimester might act as a two-hit factor to aggravate the GHD and lead to its progression. This can help to interpret that the association among the ART population might be attributed to the additive effect of ART and PM exposure on GHD and its progression. Additionally, there are concerns that the associations might be attributable to the population features such as maternal age or reproductive history, rather than ART. Thus, we conducted a stratification analysis among the ART population according to age (Supplementary Table S6 and 7) and primary or secondary infertility (Supplementary Tables S8 and 9) and found that the ART population with advanced age or secondary infertility showed higher adjusted ORs for GHD with progression after exposure to $PM_{2.5}$ and PM_{10} during the third trimester than those aged below 35 years or with primary infertility. Notably, the risk of GHD with progression still increased significantly after exposure to $PM_{2.5}$ and PM_{10} during the third trimester, regardless of the maternal age or reproductive history. Furthermore, there are also concerns that truncated exposures at the third trimester related to preterm delivery might lead to bias when analyzing associations between PM and the progression of GHD; we provided stratified analysis according to the preterm birth (Supplementary Table S10) and found that preterm delivery showed no influences on the original findings. In our study, the adjusted ORs for GH and PE after preconceptional PM

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exposures seemed higher in women that conceived with ART than those with natural conceptions, despite of the statistical insignificance. This might be attributed to the reduced number of cases in the ART population after stratified analysis, which led to relative wider confidence intervals than in women with natural conception. Thus, further cohort studies with a larger sample size in the ART population are urged to confirm the associations between preconceptional PM exposures and GHDs. As far as our findings are concerned, we can only find the impacts of PM exposures during the third trimester on the progression of GHD, which was not revealed by other studies previously.

From the current findings of our study, there were also some of the ORs that showed a broadline effect in confidence intervals without statistical significance. This does not mean that PM exposures at other periods will not increase the risk of GHDs and their progression. Actually, according to the previous studies,[14,16,33] exposure to $PM_{2.5}$ and PM_{10} across the entire pregnancy was related to the increase risk of GH and PE. The positive findings in our study were more likely to indicate sensitive exposure windows for the risk of GHDs and their progression.

The underlying mechanism by which $PM_{2.5}$ and PM_{10} affect hypertensive disorders of pregnancy is still unclear. In this study, we noticed a susceptibility exposure window of PM for GHD and PE among women who conceived naturally. Unlike most studies, this study showed the effect of preconception PM exposure on GHD and PE among women who conceived naturally, rather than a short-term effect such as in the second or third trimester. Three months before conception is a critical time window for a pregnant woman, as the fertilized ovulatory follicle normally originates from a cohort of pre-antral follicles, which would experience approximately 65 days of growth, 10 days of selection, and 10 days of maturation.[36] During these 3 months, it would be affected by many internal and external factors. According to Nachman et al., exposure to air pollutants, especially $PM_{2.5}$, during the preconception period induces both intrauterine and systemic inflammatory reactions,[37,38] which provide a poorer systemic and local environment for placental vascular remodeling in healthy women. Enhanced systemic oxidative stress, increased proinflammatory cytokine production, and vascular resistance in pregnant women may result in placental and endothelial dysfunction and subsequently elevate blood pressure in late pregnancy.[39] Furthermore, studies also revealed that placental vascularization might be suppressed through multiple other routes by PM, such as via activation of pathological pathways in the placenta and changes in placental DNA methylation, which can contribute to the pathophysiology of GHDs.[40−42]

Our study has several strengths. Although reports on the association between PM and GHD are widespread, this study is the first to report on the associations of GHD with its progression and with the ART population. This study has a large sample size and data from two of the three largest maternal and child health hospitals in Shanghai, which indicate better representation of the population. Furthermore, the large sample size enabled us to observe differences in the risk of GHD, PE, and its progression. There are also some limitations in this study. This study used monitoring site-based concentrations as individual exposures, and the daily PM concentration data from monitoring sites do not represent the spatial variability of air pollution among individuals. As the study population is mobile, it is difficult for us to take the spatial differences in individual exposure into consideration. Secondly, there was a time interval between the occurrence of GHD and its diagnosis. Therefore, estimating the association at the exact time was not possible. Thirdly, in this study, we only estimated the associations between PM and GHDs and their progression. However, the risk of GHDs can also be increased by exposure to other air pollutants including sulfur dioxide and nitrogen dioxide,[33,43] which might have a combined effect with PM on the risk of GHDs and their progression and lead to confounding bias. Furthermore, as a retrospective study, selection bias was inevitable; we failed to include part of women who experienced early pregnancy loss or stillbirth, which might have affected the potential impacts of PM. We believed that prospective cohorts with high quality are needed in the future to finish the follow-up of adverse outcomes comprehensively.

In summary, PM showed different effects on the risk of GHD among pregnant women with natural conception and ART. Exposure to $PM_{2.5}$ and PM_{10} during the 3 months before conception was associated with an increased risk of GH and PE only among pregnant women with natural conception. Differently, in pregnant women who conceived with ART, exposure to $PM_{2.5}$ and PM_{10} during late pregnancy would increase the risk of GHD progression. Our research suggested that taking protective measures against PM at a certain stage was especially needed for women with different conception approaches. Air quality improvement is also urgent for women's health.

■ ASSOCIATED CONTENT

Data Availability Statement

Data from all participants included in this study were anonymized and were available only to authorized members of the study team; sharing of anonymized data is permitted only with research groups who are investigating other specific pregnancy-related conditions.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.2c06573.

Basic description of the weekly incidences of GHDs, weather conditions, and concentrations of air pollutants; maternal characteristics and gestational complications of pregnant women with natural conception and ART conception; stratified analysis of risk of GHDs and their progression associated with increases in concentrations of PM (per unit); geographical distribution of the residences of the pregnant women of each district, research hospitals, and monitoring sites; Spearman correlation between each feature and GHDs and their progression; directed acyclic graph; temporal trends of PM levels and weekly incidence rates of gestational hypertensive disorders with fitted spline curves from July 2014 to October 2020; correlation coefficients of PM between different periods; weekly trends for $PM_{2.5}$ and PM_{10} and weekly rates of deliveries for pregnancies conceived by assisted reproductive technology with fitted spline curves from July 2014 to October 2020 (PDF)

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C.L.: conceptualization, formal analysis, software, writing—original draft. J.-J.X.: investigation, writing—original draft. F.-Y.Z.: data curation, formal analysis. Y.-Z.G.: data curation. K.-Z.Q.: data curation, resources. H.-F.H.: conceptualization, project administration, supervision. Y.-T.W.: supervision, funding acquisition, project administration, supervision.

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Notes

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ABBREVIATIONS

aOR	adjusted odds ratio
ART	assisted reproductive technology
CI	confidence interval
GDM	gestational diabetes mellitus
GH	gestational hypertension
GHDs	gestational hypertensive disorders
ICP	intrahepatic cholestasis of pregnancy
PE	preeclampsia
PM	particulate matter
$PM_{2.5}$	particulate matter <2.5 μm
PM_{10}	particulate matter <10 μm.

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