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Article

Observed Effects on Very Early Pregnancy Linked to Ambient $PM_{2.5}$ Exposure in China among Women Undergoing *In Vitro* Fertilization-Embryo Transfer

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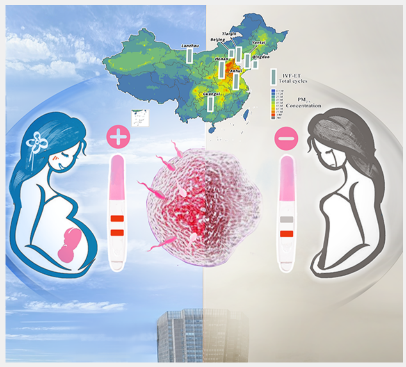
ABSTRACT: The adverse effect of ambient $PM_{2.5}$ exposure on very early pregnancy (VEP) remains controversial among epidemiological studies but is supported by toxicological evidence. We adopted a multicenter retrospective cohort of 141,040 cycles to evaluate the effect of $PM_{2.5}$ exposure on the VEP using the *in vitro* fertilization and embryo transfer platform and high-resolution $PM_{2.5}$ data in China. We first investigated the association between $PM_{2.5}$ exposure 1 week before and 1 week after the embryo transfer date and VEP. The average $PM_{2.5}$ concentrations of the 2 weeks were approximately 47 $\mu g/m^3$. The pooled results revealed a negative association between women's accumulated $PM_{2.5}$ exposure during the 2 weeks near the day of embryo transfer and success odds of VEP with the relative risk of 0.999 (95% CI: 0.997−0.999) at each increase of 10 $\mu g/m^3$. The women with the fresh cycle or one transplanted embryo were considered as a vulnerable population. Furthermore, seven periods for the fresh cycle and five periods for the frozen cycle from 85 days before oocyte retrieval to the day of gestational sac detection by ultrasound detection were defined. For these exposure periods, no association between the average $PM_{2.5}$ exposure and VEP risk was identified. Our study provided large-scale population evidence for the association between $PM_{2.5}$ exposure near embryo transfer day and VEP and identified vulnerable populations among women undergoing *in vitro* fertilization-embryo transfer.



KEYWORDS: *Fine particulate matter, Very early pregnancy, IVF-ET, Biochemical pregnancy, Clinical pregnancy*

INTRODUCTION

A severe decline in child births has occurred over the past half century, particularly in industrialized regions with various environmental pollution; thus, widespread infertility and the increasing need for assisted reproduction are now major health issues.[1] It is estimated that 8−12% of couples of reproductive-age were affected by infertility.[2] Epidemiological studies have suggested that $PM_{2.5}$ exposure is associated with reduced fertility.[3−5] Meanwhile, the toxic effect of $PM_{2.5}$ has been intensively explored with *in vitro* and *in vivo* animal studies,[6,7] e.g., oxidative stress damage, inflammatory effect, and immune abnormality. Such toxic alteration in turn affects reproductive disfunction, such as ovarian injury.[8] $PM_{2.5}$ can even induce apoptosis of ovarian granulosa cells and oocytes, resulting in disrupted embryo development and female fertility.[9] However, the evidence of the toxic effect of $PM_{2.5}$ on very early pregnancy (VEP) is relatively less due to the difficulty in monitoring this outcome during such an early pregnancy period.

Assisted reproductive technology (ART) is widely recognized as one of the most effective treatments for infertility, of which *in vitro* fertilization and embryo transfer (IVF-ET) stand out as the prominent approach. IVF-ET treatment can provide very detailed clinical records during the VEP period and allowed us to investigate the relationship between $PM_{2.5}$ exposure and the loss risk of VEP. Until 2018, approximately nine million ART babies have been born in the world.[10] In the Chinese mainland, there were 517 assisted reproductive centers by the end of 2019, and their ART cycles had reached 1.15 million in 2017, ranking as the highest in the world.[11] The adverse effect of $PM_{2.5}$ on the pregnancy loss using IVF-ET has

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been widely reported from epidemiological studies in USA,[12] France,[13] Spain,[14] Brazil,[15] Korea,[16] and China.[17,18] The couples with IVF-ET usually have high mental pressure and potential economic burden to make such a choice; hence, any measures that can improve the success likelihood should be taken, especially for covering a huge population size of $PM_{2.5}$ pollution. To date, more studies conducted in China (>50%) reported the adverse effect of $PM_{2.5}$ exposure on VEP using IVF-ET than those in other counties (see Table S1 in the Supporting Information (SI)). Such an effect has been attracting extreme public attention worldwide.

The current epidemiological studies have three obvious insufficiencies. First, the conclusions between $PM_{2.5}$ exposure and the likelihood of success of IVF-ET are inconsistent. Such a phenomenon can be caused by various influencing factors, e.g., $PM_{2.5}$ concentration, exposure period, population size, and medical conditions. For example, the population size ranged from 292 in France[13] to 230,243 cycles in USA,[19] while in China it ranged from 1,139[20] to 38,513 cycles.[21] Second, the vulnerable exposure time window and sensitive population were not ascertained, which is important for making specific prevention policies. In consideration of the short period of IVF-ET treatment, the acute effect of $PM_{2.5}$ exposure near the embryo transfer day is crucial. The days near the embryo implantation are critical to affect the success likelihood of IVF-ET.[22] Third, the high-resolution spatiotemporal $PM_{2.5}$ distribution was seldom adopted to conduct the risk assessment previously, resulting in potential bias of population exposure misclassification. Hence, the related evidence from a large cohort with a high-resolution $PM_{2.5}$ distribution was needed. We conducted a multicenter retrospective cohort study to ascertain the effect of $PM_{2.5}$ exposure on VEP.

METHODS

Study Population

This multicenter retrospective cohort study was conducted in eight typical IVF centers in China, including the First Affiliated Hospital of Anhui Medical University (AH), Peking University People's Hospital (BJ), the First Affiliated Hospital of Guangxi Medical University (GX), the Third Affiliated Hospital of Zhengzhou University in Henan Province (HN), the First Hospital of Lanzhou University (LZ), Women and Children's Hospital of Qingdao University (QD), Tianjin Central Hospital of Gynecology Obstetrics (TJ), and Yantai Yuhuangding Hospital (YT). The clinical records of IVF-ET with address information between January 2012 and December 2021 were extracted. Inclusion criteria were (1) between 18 and 50 years, (2) body mass index (BMI) between 15−40 kg/m^2 and (3) number of transferred embryos ≤2; the exclusion criteria were (1) use donor egg or sperm and (2) underwent preimplantation genetic testing, *in vitro* maturation (IVM), or later intracytoplasmic sperm injection. For BMI with values of <15 or >40 kg/m^2, we empirically consider that their data were recorded with error, which were confirmed with the health care workers in the eight centers. We consider that $PM_{2.5}$ can also cause adverse effects on sperm quality, which may subsequently affect the success of IVF-ET. Unfortunately, our current data cannot distinguish the partner's $PM_{2.5}$ exposure level by assuming that their $PM_{2.5}$ exposure is overall similar owing to their shared living conditions. For the couple using donor sperm, the $PM_{2.5}$ exposure profiles of the donors are unclear. This could introduce some uncertainties that might affect the study results. Therefore, we excluded individuals using donor sperm from our study. The flowchart of cohort creation is show in Figure S1. This study was approved by the Ethical Review Committee of Peking University People's Hospital (No.: 2021PHB358-001).

Outcomes and Covariates

We extracted transplantation records from the electronic medical record systems of eight centers. All data were anonymous, and only the admission number was used to match clinical records during the analysis. The information extracted from the medical records system includes general demographic characteristics, infertility diagnosis factors, treatment protocols, and treatment outcomes. The potential covariates we processed include female age, height, weight, educational level, employment status, infertility type, duration of infertility, causes of infertility, stimulation protocol, fertilization method, type of embryo transfer, number of transferred embryos, embryo transfer date, and residential address. The variable descriptions are provided in Table S2.

Two reproductive outcomes linked to the VEP were included: (1) biochemical pregnancy (BP), defined as women with positive human chorionic gonadotropin (hCG) test at 14 days after embryo transfer, and (2) clinical pregnancy (CP), defined as women with the presence of a gestational sac in the uterine cavity at 35 days after embryo transfer, as detected by ultrasonography.

$PM_{2.5}$ Exposure

We obtained the national $PM_{2.5}$ data of 1-km and 10-km resolution during 2011−2021 from the open database of Tracking Air Pollution in China (TAP, Web site: http://tapdata.org.cn/), the detailed methods of which were described previously.[23−25] We got the longitude and latitude of the study object's residential address and hospital's address using Baidu Map (http://api.map.baidu.com). $PM_{2.5}$ concentrations at the grid points closest to the residential address were used to characterize the exposure level. Average $PM_{2.5}$ concentrations at the grid points within the 5, 10, and 20 km buffer of residential address were used for sensitivity analysis. We focused on the effect of the $PM_{2.5}$ exposure in 1 week before and after the day of embryo transfer, with a time-period of 2 weeks in total. The time points and periods for assigning $PM_{2.5}$ exposure are depicted in Figure 2A. The $PM_{2.5}$ concentration in the embryo transplant day denoted as D0, while the average $PM_{2.5}$ concentrations in the sixth to the first days before the embryo transplant day were denoted as $D6_B$ to $D1_B$, and from the first to the sixth day after this day for each participant were denoted as $D1_A$ to $D6_A$, of which the total period was 13 days (P13). To investigate the accumulative effect, the average $PM_{2.5}$ concentrations during the periods from the sixth, fifth, ..., first days to the embryo transplant day and from this day to the first, second, ..., sixth days are denoted as $P6_B$, $P5_B$, ..., $P1_B$ and $P1_A$, $P2_A$, ..., $P6_A$, respectively.

To screen the sensitive exposure time window, a total of seven periods of the fresh cycle and five periods of the frozen cycle were defined according to the ovum development and IVF-ET treatment processes (Figure 4A,B). 85 days before oocyte retrieval to day of oocyte retrieval, day of oocyte retrieval to embryo transfer, day of embryo transfer to hCG-test, day of hCG-test to transvaginal ultrasound test, 85 days before oocyte retrieval to hCG-test, and 85 days before oocyte retrieval to transvaginal ultrasound test are denoted as P1 to P7 for fresh cycles. Thirty days before embryo transfer to embryo transfer, day of embryo transfer to hCG-test, day of hCG-test to transvaginal ultrasound test, 30 days before embryo transfer to hCG-test, and 30 days before embryo transfer to transvaginal ultrasound test are denoted as P1* to P5* for frozen cycles.

Statistical Analysis

The number of lost-to-follow-up subjects in this study was 349, accounting for approximately 0.2% of the total population. The missing data for covariates accounts for a very small percentage, of which the highest proportion is <0.5% for the variable of employment status. Therefore, we did not impute missing variables and conducted the analyses throughout our study using observations with complete clinical records. First, a log-binomial regression model was used to assess the association between $PM_{2.5}$ and IVF-ET outcomes in each center. The covariates were included in the model due to their clinical relevance to the outcomes as the following: female age, body mass

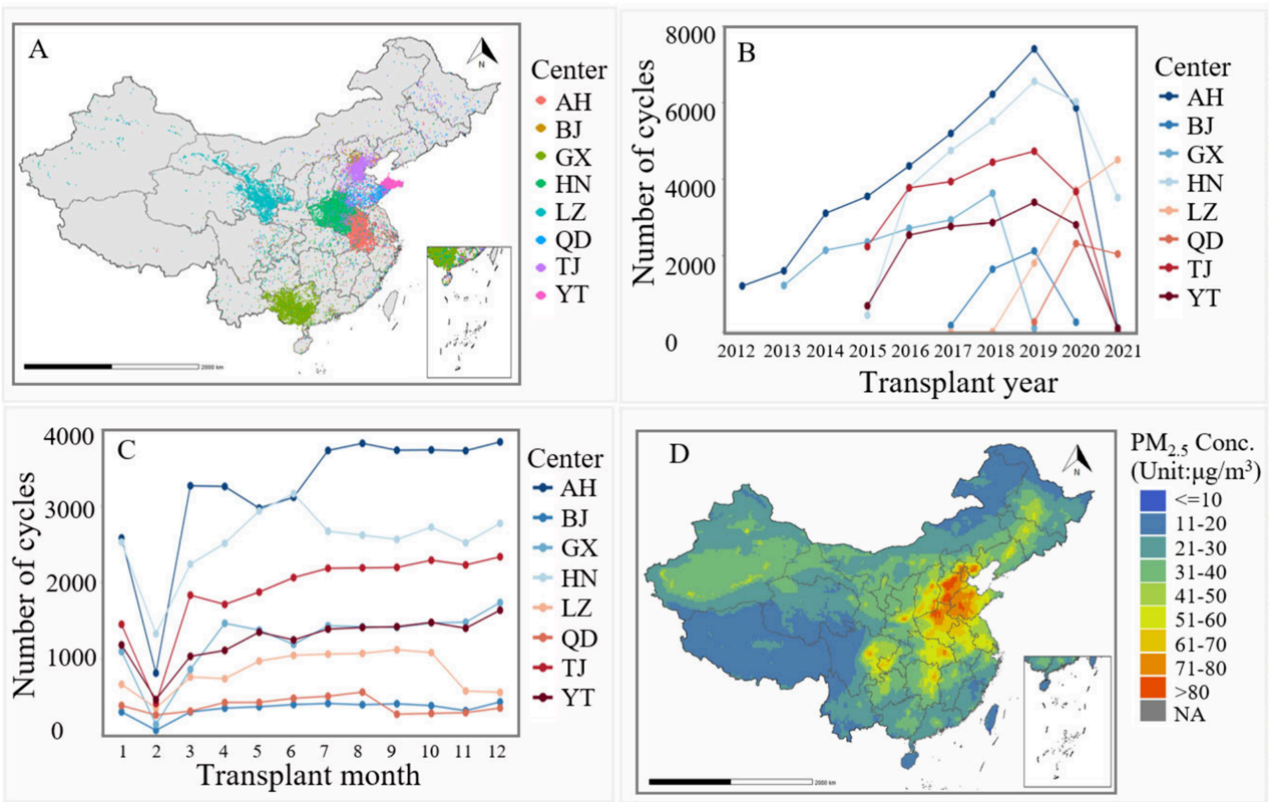

Figure 1. Basic survey information. (A) Geographical distribution of the included patients; (B and C) number of cycles over year and month, respectively; (D) average $PM_{2.5}$ concentration during the survey period (2012−2021). The national $PM_{2.5}$ data of 1-km resolution during 2012−2021 from the open database of Tracking Air Pollution in China (http://tapdata.org.cn/).

index (BMI), educational level, employment status, infertility type, duration of infertility, causes of infertility, stimulation protocol, fertilization method, type of embryo transfer, number of transferred embryos, and the nonlinear effect of temperature as modeled by a 3 degree-of-freedom (df) natural spline, seasonality as a 4 df natural spline of embryo transfer month, and longtime tendency as a 2 df natural spline of embryo transfer year. Second, the center-specific associations of $PM_{2.5}$ exposure with IVF-ET outcomes for the eight centers were combined by meta-analysis using the random-effect model, resulting in an overall estimation. Generalized estimating equation (GEE) model with the binomial link function of "logit" were used to assess the association between $PM_{2.5}$ and IVF-ET outcomes in each center, which can reduce the effect of the nonindependent observation of different transplant cycles for a woman on the association analysis.[26] However, due to the high prevalence of the concerned outcomes, the odds ratio (OR) obtained using the GEE method can overestimate the effect, which can be seen in most of the IVF centers (Figure S3). Here, we compared the OR from the GEE and general liner regression (GLR) with the binomial link function of "logit". They overall have minor differences; thus, we adopted GLR with binomial link function of "log" to estimate the RR. Overall, the RR was overall lower than OR obtained by using the logit link function of GLR and GEE.

Stratified analyses by endometriosis (yes, no), tubal factor (yes, no), ovulatory (yes, no), diminished ovarian reserve (yes and no), age (18−35 and >35 years), type of embryo transfer (fresh, frozen), and number of transferred embryos (1 and 2) were performed in each center. The center-specific subgroup associations of $PM_{2.5}$ exposure with IVF-ET outcomes for the eight centers were combined by a random-effect model of meta-analysis to obtain the overall effect estimates. *Z*-test were used to test the statistical difference between subgroups in the association between $PM_{2.5}$ exposure and IVF-ET outcomes.[27] For the sensitivity analysis, we compared the reliability of the associations by using $PM_{2.5}$ data from two different resolutions (1-km and 10-km). All statistical analyses were performed using R software, version 4.2.1; R packages "gee" and "glm" were used to fit model; package "meta" was used to pool estimates. A two-sided test *P* value <0.05 was considered statistically significant.

■ RESULTS

Subject Characteristics and Ambient $PM_{2.5}$ Exposure

A total of 86,817 patients who underwent IVF-ET with 141,040 cycles were finally included in this study (Figure S1), and the geographical distribution of their living addresses is depicted in Figure 1A, as well as the number of cycles during the survey period by year (Figure 1B) and month (Figure 1C). The characteristics of the included 141,040 transfer cycles are summarized in Table 1, and Table S3 provides information for the individual centers. Overall, the missing values took a very small part (<0.5%). Among them, AH contributed the highest number of cycles (27%), followed by HN (22%), TJ (16%), GX (11%), YT (11%), LZ (7.1%), BJ (3.0%), and QD (3.3%). The average female age was 31.7 ± 4.9 years. The majority (61%) of patients had normal BMI of 18.5−24 kg/m^2 and almost half of them had a college degree or above. The proportions of primary and secondary infertility were nearly equal. The average duration of infertility was 3.85 ± 3.03 years. As for causes of infertility, the proportions of individuals with tubal factors, ovulation disorders, diminished ovarian reserve, and endometriosis were 68%, 15%, 12%, and 6.2%, respectively. For treatment protocols, 60% of cycles underwent a long stimulation protocol, and 68% underwent IVF fertilization. More patients chose fresh cycles (64%) and

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Table 1. Demographic and Clinical Characteristics of 141040 *In Vitro* Fertilization and Embryo Transfer Cycles

Characteristics	Total cycles
Centers	
AH	38,588 (27%)[a]
BJ	4,195 (3.0%)
GX	15,098 (11%)
HN	30,581 (22%)
LZ	10,030 (7.1%)
QD	4,616 (3.3%)
TJ	22,793 (16%)
YT	15,139 (11%)
Age (years)	31.7 (4.9)[b]
BMI (kg/m^2)	
< 18.5	9,128 (6.5%)
18.5−24	85,935 (61%)
>24	45,977 (33%)
Educational level	
College degree and higher	37,638 (27%)
Junior College degree	27,807 (20%)
High school	26,555 (19%)
Junior high school and lower	48,341 (34%)
Missing[c]	699
Employment status	
Employed	98,759 (70%)
Unemployed	41,635 (30%)
Missing	646
Infertility type	
Primary infertility	69,434 (49%)
Secondary infertility	71,313 (51%)
Missing	293
Duration of infertility (years)	3.85 (3.03)
Infertility pathogenesis	
Male factor	
No	90,141 (64%)
Yes	50,899 (36%)
Endometriosis	
No	132,278 (94%)
Yes	8,762 (6.2%)
Tubal factor	
No	45,387 (32%)
Yes	95,653 (68%)
Ovulation disorder	
No	120,453 (85%)
Yes	20,587 (15%)
Diminished ovarian reserve	
No	123,541 (88%)
Yes	17,499 (12%)
Type of embryo transfer	
Fresh	90,302 (64%)
Frozen	50,738 (36%)
Fertilization method	
IVF	95,513 (68%)
ICSI	38,144 (27%)
IVF+ICSI	7,383 (5.2%)
Stimulation protocol	
GnRH antagonist	35,337 (25%)
Long agonist	84,077 (60%)
Other protocols	21,473 (15%)
Missing	153
Number of transferred embryos	
1	46,790 (33%)
2	94,250 (67%)

[a]Number, or number (percent). [b]Mean value (standard deviation, SD). [c]Missing information. There were eight centers, including the First Affiliated Hospital of Anhui Medical University (AH), Peking University People's Hospital (BJ), the First Affiliated Hospital of Guangxi Medical University (GX), the Third Affiliated Hospital of Zhengzhou University in Henan Province (HN), the First Hospital of Lanzhou University (LZ), Women and Children's Hospital of Qingdao University (QD), Tianjin Central Hospital of Gynecology Obstetrics (TJ), and Yantai Yuhuangding Hospital (YT).

transferred two embryos (67%). The incidences of BP and CP of all eight centers were 55% and 50%, respectively (Table S4).

The average $PM_{2.5}$ distributions during the survey period in China are provided in Figure 1D, and its seasonal variations are in Figure S2. The average ambient $PM_{2.5}$ concentrations of the patients were approximately 47 $\mu g/m^3$, of which TJ has the highest $PM_{2.5}$ concentration (58 $\mu g/m^3$), followed by HN (57 $\mu g/m^3$), AH (51 $\mu g/m^3$), BJ (41 $\mu g/m^3$), YT (36 $\mu g/m^3$), QD (35 $\mu g/m^3$), GX (31 $\mu g/m^3$), and LZ (27 $\mu g/m^3$) (Table S5).

Exposure to Ambient $PM_{2.5}$ and VEP

The pooled associations of the eight IVF centers between $PM_{2.5}$ and VEP are shown in Figure 2B−E. There was negative association between the accumulated $PM_{2.5}$ exposure during P13 (i.e., 2 weeks near the day of embryo transfer, Figure 2A) and successful odds of BP with the RR (95% confidence level, 95% CI) of 0.999 (0.997−0.999) (Figure 2B), of which the most sensitive exposure day was in $D6_B$ (i.e., the sixth before the embryo transplant day, Figure 2A) (Figure 2C). But for CP, no statistically significant association with the $PM_{2.5}$ exposure during these periods was found, while the RR was overall <1, indicating the hazardous effect of $PM_{2.5}$ (Figure 2D,E). The detailed effects in the eight locations are provided in Figures S4 and S5. To compare the effect of $PM_{2.5}$ spatial distribution resolution, the pooled association of $PM_{2.5}$ concentration with the resolutions between 1 and 10 km with VEP were comparable (Figure S6). Their overall results were consistent, except for BP during P13 with the RR (95% CI) of 0.998 (0.995−1.000), which has larger variation. This suggested that high-resolution $PM_{2.5}$ distribution may be more appropriate for the exposure assessment. We suspected that patients may stay around the hospital for the transport convenience during the period of controlled ovarian hyperstimulation. We thus used hospital-address-based $PM_{2.5}$ exposure to assess their associations. This revealed that the results were overall consistent with those using patients' self-reported addresses (Figure S7). In addition, the RRs in the association of $PM_{2.5}$ exposure with the failure odds of BP and CP both increased with large variation when using the hospital address to assign the $PM_{2.5}$ concentration.

We further conducted stratification analysis to investigate the vulnerable women during the concerned exposure period (Figure 3). The results for BP and CP were overall consistent. There were significant interaction effects between $PM_{2.5}$ exposure and the type of embryo on CP and BP, as well as for those between $PM_{2.5}$ exposure and endometriosis-induced infertility. This suggested that the women in fresh cycles tended to be more sensitive to the hazardous effects of $PM_{2.5}$

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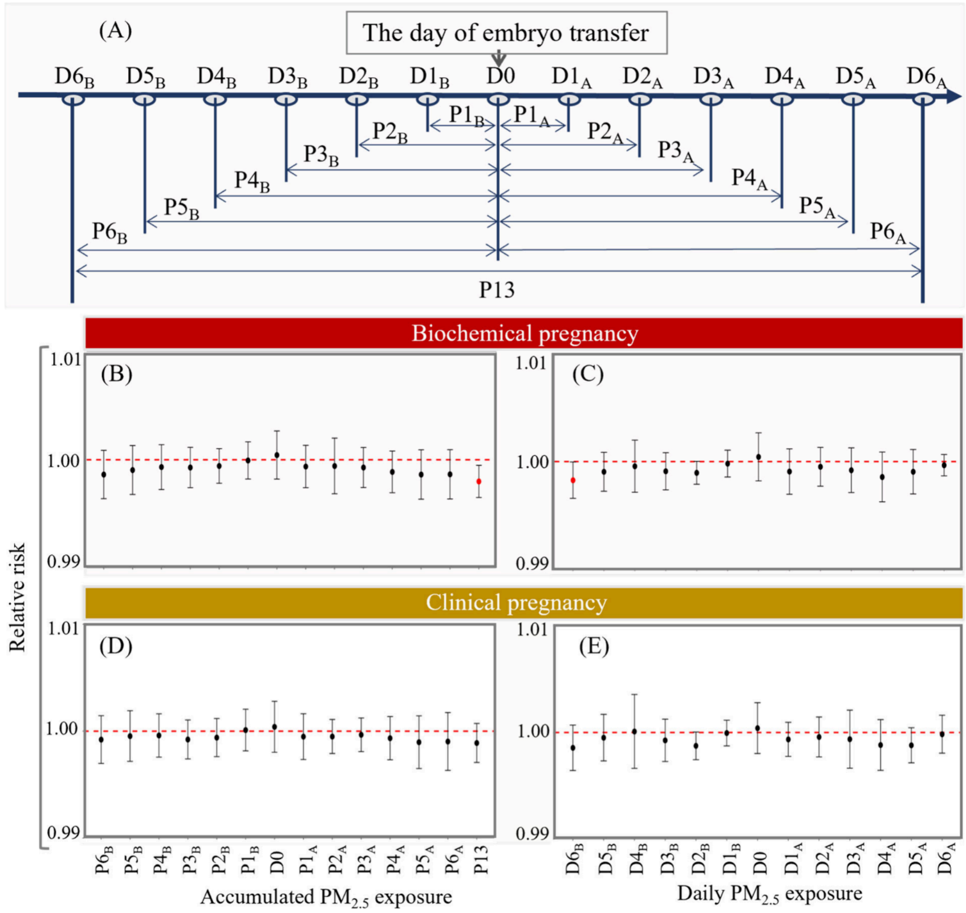

Figure 2. Pooled associations of $PM_{2.5}$ exposure in various exposure period or day with the success odds of biochemical pregnancy and clinical pregnancy. The results are presented as relative risk for every 10 $\mu g/m^3$ of $PM_{2.5}$ increase. (A) The time points and periods for assigning $PM_{2.5}$ exposure of patients. The embryo transplant day is denoted as D0, while the average $PM_{2.5}$ concentrations in the 6th to the 1st days before the embryo transplant day to the transplant day are denoted as $D6_B$ to $D1_B$, and from the 1st to the 6th day after the embryo transplant day for each patient are denoted as $D1_A$ to $D6_A$, of which the total period was 13 days. The average $PM_{2.5}$ concentrations during the periods from the 6th, 5th, ..., and 1st days to the embryo transplant day and from the embryo transplant day to the 1st, 2nd, ..., and 6th days are denoted as $P6_B$, $P5_B$, ..., $P1_B$, and $P1_A$, $P2_A$, ..., and $P6_A$, respectively. The period from $D6_B$ to $D6_A$ is denoted as P13. Two very early pregnancy includes (B and C) biochemical pregnancy and (D and E) clinical pregnancy. The related associations based on the exposure assessments of the average period and daily time are depicted in left and right panels, respectively. Red point indicates statistical significance with P value <0.05.

exposure. $PM_{2.5}$ exposure has a stronger association with the failure odds of BP and CP among the women without endometriosis diseases. No significant interaction effects were found between $PM_{2.5}$ exposure and the other confounders of women's age, number of embryos, the infertility pathogenesis of ovulation disorder, tube factor, or diminished ovarian reserve on BP or CP. The detailed results for the eight individual centers are provided in Figure S8A−H. Such interaction effects may vary with the locations. For example, $PM_{2.5}$ exposure may have stronger adverse effect on BP and CP among the women with one embryo transfer (HN) (Figure S8D), younger age (LZ) (Figure S8E), fresh cycle (TJ) (Figure S8G), and ovulation disorder (YT) (Figure S8H), than those with two transferred embryos, older age, frozen cycle, and without ovulation disorder, respectively. For the TJ center, we can clearly observe that the women with fresh cycles seem to be more vulnerable during all the concerned periods for both BP and CP (Figure 3B,C), as well as for those with one transferred embryo in the HN center (Figure 3D,E).

In the above analysis, the population $PM_{2.5}$ exposure level was assigned by the reported residential address by the patients, of which the accuracy cannot be confirmed one-by-one due to the large population size. We assume that self-reported addresses with the distance from the hospital <20 km can be considered as acceptable information with high confidence level in China, resulting in a total of 39,187 cycles (noted as "P_{20km}"). Overall, the RR for P_{20km} had a trend similar to those by using all patients, but with larger variations with no statistically significance (Figure S9). Such results were overall consistent when the average $PM_{2.5}$ concentrations obtained from the four buffer radiuses of 1, 5, 10, and 20 km (Figure S10). Thus, we only use the $PM_{2.5}$ concentration of 1 km resolution for further analysis. To screen the sensitive exposure time window, a total of seven periods of the fresh cycle and five periods of the frozen cycle were defined according to the ovum development and IVF-ET treatment process (Figure 4A,B). Overall, we did not obverse significantly adverse effects of $PM_{2.5}$ on both BP and CP for these patients (Figure 4C,D).

■ DISCUSSION

To date, to the best of our knowledge, there have been 19 published studies about this issue conducted around the world; ten of them (52%) supported the adverse effect of $PM_{2.5}$

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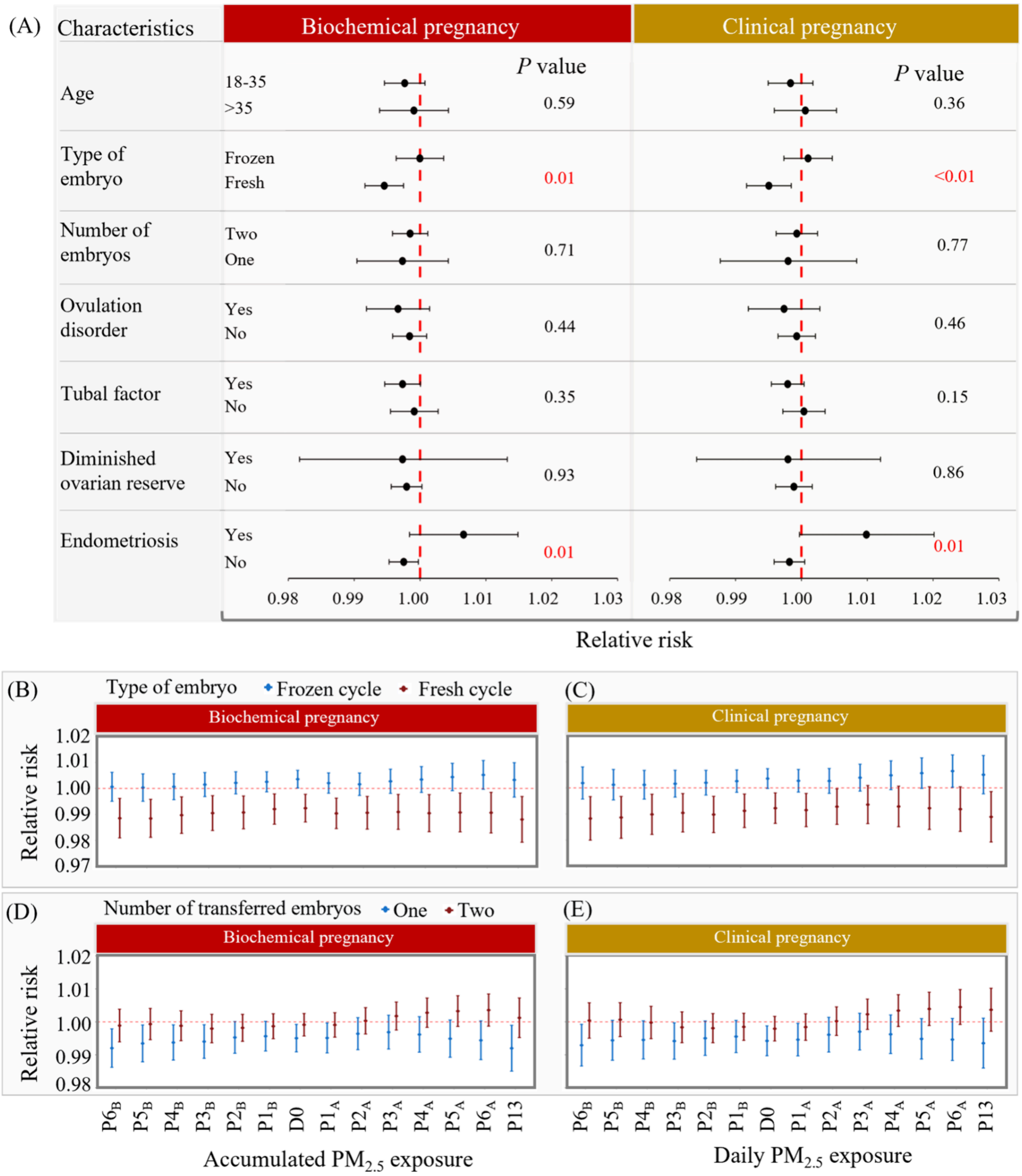

Figure 3. Interaction effects between $PM_{2.5}$ exposure and the clinical factors on the success odds of biochemical pregnancy (BP) and clinical pregnancy (CP). The results are presented as relative risk for every 10 $\mu g/m^3$ of $PM_{2.5}$ increase. (A) Pooled associations of $PM_{2.5}$ exposure with the CP and BP stratified by age, type of embryo transfer, number of transferred embryos, and infertility causes of ovulation disorder, tubal factor, diminished ovarian reserve, and endometriosis among the women undergoing *in vitro* fertilization and embryo transfer; (B and C) interaction effect between $PM_{2.5}$ and type of embryo for BP and CP in Tianjin Center, respectively; (D and E) interaction effect between $PM_{2.5}$ and number of transferred embryos for BP and CP in Henan Center, respectively. *P* value for the statistical testing of the interaction effect.

exposure on the pregnancy chance, while for the 12 studies conducted in China, seven of them (58%) did (Table S1). We considered that sample size should be the main influencing factor. Except for the largest sample size of 230,243 cycles in the study conducted in the United States,[19] the rest of them ranged form 486 in Spain[28] to 34,427 cycles in Korean.[29] Due to the relatively weak effect of $PM_{2.5}$ exposure on the VEP compared to the clinical factors, a small sample size should not have enough statistical power to ascertain their association. In addition, the heterogeneities of the women in their lifestyle and medical conditions are other important confounding factors. In our study, the adverse effects were mainly found in all of the patients in eight IVF centers, while not for the individual centers. Such a phenomenon cannot be well explained using the current data in our study. We considered that this variability can be caused by genetic, environmental, or socioeconomic confounders. Among the eight centers, the $PM_{2.5}$ exposure concentrations varied by regions (Figure 1D), as well as their toxic components based on previous studies.[30,31] Also, there are differences in the medical conditions between regions. For example, LZ has the highest clinical pregnancy rate of 57%, while GX has the lowest rate of 42%. Moreover, the basic population characteristics among the eight centers, e.g., age and lifestyle, also differ to a certain

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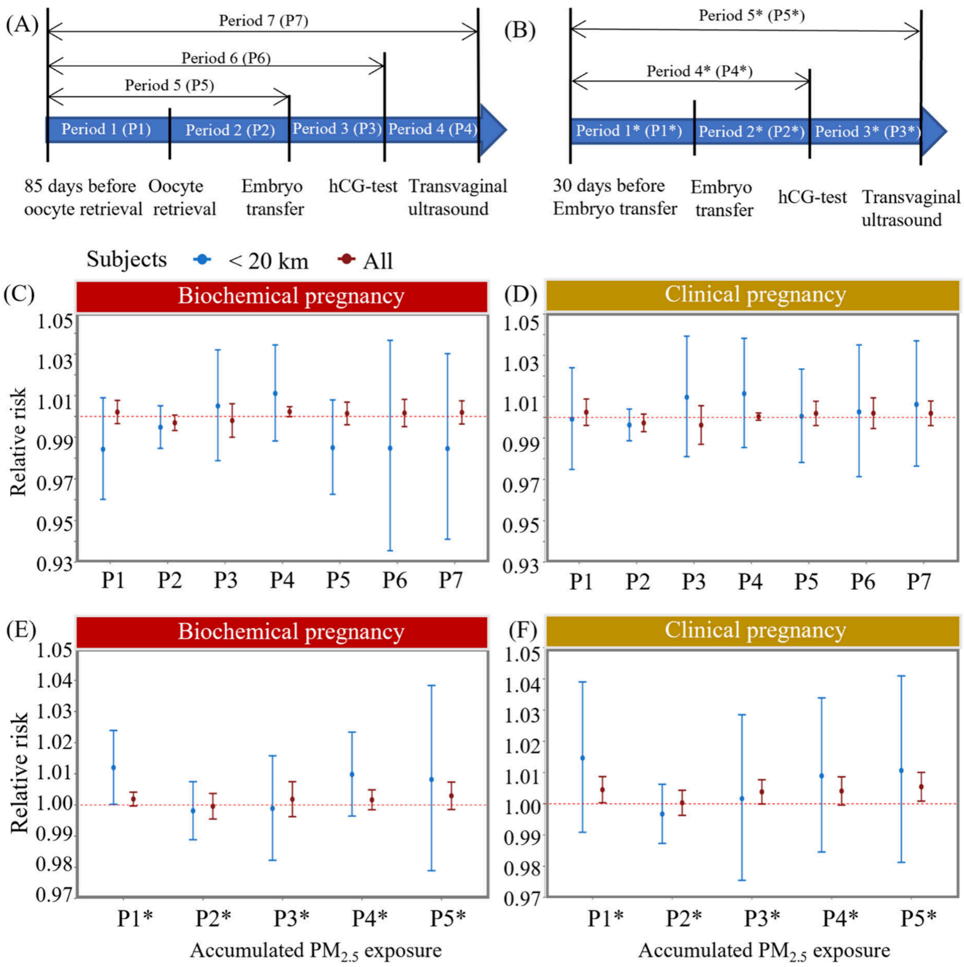

Figure 4. Pooled associations between $PM_{2.5}$ exposure and the two very early pregnancies of biochemical pregnancy (BP) and clinical pregnancy (CP). The results are presented as relative risk for every 10 $\mu g/m^3$ of $PM_{2.5}$ increase. The periods for assigning $PM_{2.5}$ exposure were separately defined for the fresh cycle with seven periods (A) and the frozen cycle with five periods (B). Two very early pregnancies were investigated, including BP (C) and CP (D) in fresh cycles, and BP (E) and CP (F) in frozen cycles.

extent. These factors may lead to regional susceptibility to $PM_{2.5}$ exposure, and further research is needed to explore these differences in depth.

According to their meta-analysis results, $PM_{2.5}$ exposure should be a risk factor to the VEP. We originally hypothesized that stronger associations may be observed among women with some reproductive diseases. However, such a phenomenon was not found for the women with diminished ovarian reserve, endometriosis, and obstruction of fallopian tubes, except for ovulation disorder only in the YT center. It is interesting to note that the women in the fresh cycle and with one-embryo transfer seemed to be more vulnerable to $PM_{2.5}$ exposure than those in the frozen cycle and with two-embryo transfer, respectively. A possible reason is that the women in the fresh cycle may be in high estrogen status due to the ovarian hyperstimulation, which may alter the endometrial receptivity and subsequently result in negative influence on the potential of embryonic implantation.[32] Compared with the women with one embryo transferred, those with two embryos have a higher success rate of clinical pregnancy and may be more resistant to $PM_{2.5}$ hazards.[33] It seems that $PM_{2.5}$ can play a modification role in deteriorating the embryo implantation conditions, indicating that some protection measures regarding $PM_{2.5}$ exposure should be taken for some specific groups of women.

We supposed that there should be a sensitive exposure time window for the effect of $PM_{2.5}$ exposure on the VEP. Previously, the average $PM_{2.5}$ concentrations in several time windows were frequently investigated from the months before COH to B-ultrasound examination for CP. According to the meta-analysis results for the previous qualified 14 studies, $PM_{2.5}$ values were only linked to reduced probabilities of BP during the period of 85 days before egg retrieval to the beginning of gonadotropin, while not for the others.[34] In our study, we only found the potential adverse effect of $PM_{2.5}$ exposure during the 2 weeks near the day of embryo transfer on BP. It can be partly explained by the findings from the animal study that $PM_{2.5}$ can cause ovarian injury, which is close the day of embryo transfer.[8] However, due to the complex processes of oocyte development during the period before COH, such association cannot be well explained with high certainty. We considered that the vulnerable exposure period of $PM_{2.5}$ should exist near the day of embryo transfer.

A severe decline in child births has occurred over the past half century, which will lead to considerable population declines, particularly in industrialized regions,[1] as well as for China with an obviously decreasing birth rate in the past 10 years.[11] Especially, more deaths than births happened in 2022 in China (https://www.stats.gov.cn/), indicating the high demand for increasing the birth rate. It has been reported that

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missed abortion in the first trimester is related to maternal air pollution exposure.[35] We further proposed that the VEP of 2−3 weeks gestational weeks was also interfered with by $PM_{2.5}$ exposure. This should be considered by related policy-makers to reduce the $PM_{2.5}$ exposure among women seeking pregnancy. Our study may have the following limitations: First, we were unable to obtain the activity trajectories of the study participants, which limited our ability to accurately assess the $PM_{2.5}$ exposure level. Second, the study population consists of individuals with infertility, which differs from the general population and may limit the generalizability of the findings. Third, the socioeconomic variables in the medical records system are limited, which prevented a more in-depth exploration of their influence. As we know that female reproductive health can be affected by various risk factors, like metal(loid)s,[36] multiple endocrine-disrupting chemicals,[37] and per- and polyfluoroalkyl substances,[38] future studies should be conducted under the framework of exposome.[39,40] Our study also had some obvious strengths. First, our study adopted a large population size from the eight typical provinces to address the epidemiological evidence of the association between $PM_{2.5}$ exposure and VEP. Hence, the geographical heterogeneity, sensitive exposure window, and vulnerable population of this association can be ascertained. Second, various sensitivity analyses and statistical methods were conducted to confirm the reliability of our findings, and the conservative conclusions were finally obtained. Various resolutions of $PM_{2.5}$ distribution in China of 1, 5, 10, and 20 km were used. Also, a natural cubic smooth function was adopted to control for underlying time trends of both BP and CP. Taking AH center for example (Figure S11), very strong adverse effects of $PM_{2.5}$ exposure on the VEP were observed without adjusting the time trend. We concluded that increased exposure to ambient $PM_{2.5}$ near the embryo transfer day was negatively associated with odds of VEP. Such effects, as well as the vulnerable women, varied with locations. Overall, this effect seems relatively weak but nonnegligible due to the issues of global decreasing fertility rate and severe $PM_{2.5}$ pollution.

■ ASSOCIATED CONTENT

Data Availability Statement

The original data are confidential due to the regulation of human genetic resources. However, some demo data to reproduce the main study results can be downloaded on the Github Web site: https://github.com/ExposomeX/Data-and-Code-for-PM2.5-IVF-Manuscript.git. More information can be obtained by contacting the corresponding author: Dr. Bin Wang (binwang@pku.edu.cn).

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00107.

> Descriptions of the IVF-ET procedures at each center, the participant recruitment process, a summary of previous literature, center-specific results, and the results of various sensitivity analyses (Tables S1−S5 and Figures S1−S11) (PDF)

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Author Contributions

#CL, YG, HL, XM, YY, HB, CH, XH, and HZ have equal contributions to this study.

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