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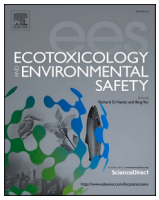

Exposure to ambient particulate matter and reproductive outcomes among women undergoing in vitro fertilization/intracytoplasmic sperm injection: A prospective cohort study in China

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ABSTRACT

Limited evidence is available regarding the association between ambient particulate matter exposure and reproductive outcomes in women undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatments. In this prospective cohort study, we included 1237 women who underwent IVF/ICSI procedures in Hubei, China, between 2018 and 2020. We performed multivariate regression models to estimate the associations between exposure to particulate matter with diameters of $\leq$ 2.5 microns ($PM_{2.5}$), $\leq$ 10 microns (PM_{10}), and 2.5–10 microns ($PM_{2.5-10}$) and ten pregnancy outcomes: the number of mature oocytes, number of zygotes with two pronuclei, maturation rate, fertilization rate, cleavage rate, best-quality embryos rate, ovarian sensitivity index, implantation, clinical pregnancy, and live birth. We found that exposure to particulate matter was associated with declines in maturation rate and fertilization rate but showed no significant associations with clinical pregnancy outcomes. Specifically, each interquartile range increase in $PM_{2.5}$ was associated with a 1.01 % (95 % CI: 0.17 %, 1.84 %) reduction in the maturation rate and a 1.42 % (95 % CI: 0.29 %, 2.55 %) decrease in the fertilization rate. These associations were particularly pronounced during the follicle maturation stage (from 10 days before oocyte retrieval to retrieval day). Our findings provide novel evidence that exposure to ambient particulate matter may adversely affect early reproductive outcomes among women undergoing IVF/ICSI.

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1. Introduction

Infertility has become a significant public health concern in the 21st century, affecting approximately 17.5 % of couples of reproductive ages. It is defined as the inability to achieve a successful pregnancy after one year of unprotected sexual intercourse, or due to impaired reproductive capacity in one or both partners (Carson and Kallen, 2021; Inhorn and Patrizio, 2015; Penzias et al., 2021). In vitro fertilization (IVF), a cornerstone of assisted reproductive technology (ART), plays an increasingly vital role in addressing these reproductive health challenges.

The success of an IVF cycle largely depends on the quality of oocytes, embryos, and endometrial receptivity, all of which are highly susceptible to environmental risk factors (Younglai et al., 2005). Animal studies have suggested that exposure to particulate matter (PM) can induce apoptosis in ovarian granulosa cells, decrease oocyte count, and impair embryonic development (Januário et al., 2010; Liao et al., 2020; Luderer et al., 2022). However, epidemiological evidence in humans remains limited.

Most existing epidemiological studies on PM exposure among women undergoing IVF have focused on adverse clinical pregnancy outcomes and have reported associations between PM exposure and lower rates of pregnancy success such as implantation or live birth (Carré et al., 2017; Dai et al., 2021; Gaskins et al., 2019; Jiang et al., 2024; Lan et al., 2024; Li et al., 2022). However, fewer studies have examined early reproductive outcomes, such as oocyte maturation or cleavage rates, or identified critical exposure windows. This focus is understandable from a clinical perspective, as pregnancy outcomes are directly aligned with the ultimate goals of infertility treatment and are well documented in medical records and ART registries. Nevertheless, it may obscure the potential toxic effects of environmental pollutants on earlier stages of oocyte development.

Importantly, IVF provides a unique opportunity to evaluate oocyte quality at multiple stages of folliculogenesis—a prolonged process that spans approximately 12 months from primordial follicle activation to ovulation (Baerwald et al., 2012; Gougeon, 1986, 1984). It takes at least 270 days for primordial follicles to develop into preantral follicles, and another 85 days to reach the preovulatory stage. Investigating distinct windows of exposure during this developmental timeline may offer critical insights into the biological mechanisms underlying reproductive toxicity and inform strategies for precision prevention.

Therefore, we aimed to estimate the association between exposure to PM with a diameter of $\leq$ 2.5 microns ($PM_{2.5}$), $\leq$ 10 microns (PM_{10}), and 2.5–10 microns ($PM_{2.5–10}$) and ten reproductive outcomes, including early IVF outcomes such as maturation rate, and pregnancy outcomes like live birth, among 1237 women undergoing their first fresh or frozen IVF cycle in Hubei Province, China. Additionally, we investigated the susceptible windows for the relationship between PM exposure and IVF outcomes.

2. Methods

2.1. Study population

Participants were recruited from the TREE study, a prospective cohort described in detail elsewhere (Yao et al., 2023). Couples undergoing intrauterine insemination were excluded, as embryo laboratory outcomes could not be assessed for these individuals. Briefly, the TREE cohort originally enrolled 1701 women aged over 20 years who underwent IVF or intracytoplasmic sperm injection (ICSI) at the Reproductive Center of Tongji Hospital, Hubei, China, between 2018 and 2020. To minimize confounding effects from multiple treatment cycles, only first cycles were included in the analysis. We additionally excluded 263 participants with incomplete or unclear residential address, residency outside Hubei Province, or residency in Hubei for less than one year, 21 participants without embryo transfer following oocyte retrieval, 14 participants undergoing preimplantation screening and genetic testing, 2 participants with frozen embryo transfer more than 6 months, and 3 participants lacking detailed clinical or reproductive outcome data. After applying these criteria, the final analysis included 1237 women (Fig. S1). Participants were prospectively followed from ovarian stimulation through to either live birth or failure at any stage (such as no available embryos, implantation failure, or clinical pregnancy failure). The median duration of follow-up was 8.9 months (IQR 1.4–9.3). The study protocol was approved by the Institutional Review Board of Tongji Medical College, and all participants provided written informed consent.

2.2. Exposure assessment

The residential geographic addresses of participants were geocoded to obtain longitude and latitude coordinates. Daily concentrations of $PM_{2.5}$ and PM_{10} were estimated using the China High Air Pollutant (CHAP) dataset, which has a spatial resolution of 1 km $\times$ 1 km. The CHAP dataset is a high-quality air pollution resource generated by integrating artificial intelligence and big data, accounting for spatial and temporal heterogeneity driven by meteorological conditions, surface characteristics, and emission sources. The resulting exposure estimates represent ambient PM concentrations at a granular 1 km $\times$ 1 km grid. The accuracy of the CHAP dataset has been validated through stringent ten-fold cross-validation, yielding R^2 values of 0.92 for $PM_{2.5}$ and 0.86 for PM_{10} (Wei et al., 2021a, 2021b). Concentrations of $PM_{2.5–10}$ were obtained by subtracting $PM_{2.5}$ from PM_{10} (Charron and Harrison, 2005).

We calculated residential-level average PM concentrations during both the entire oocyte development period and three critical developmental windows (Fig. S2). Exposure during the entire oocyte development period was defined as the one year before oocyte retrieval, representing long-term exposure across the follicle initiation, follicle growth and selection, and follicle maturation stage. The specific critical stages of oocyte development included follicle initiation stage: from primordial follicle to preantral follicle stage (from one year to 85 days before oocyte retrieval, approximately 9 months), growth and selection stage: from preantral to antral follicle stage (from 85 days to 10 days prior to oocyte retrieval, approximately 75 days), and maturation stage: from antral follicle to preovulatory follicle stage (from 10 days before oocyte retrieval to retrieval day, approximately 11 days). These three exposure windows correspond to key biological stages in oocyte development (Gougeon, 1986; Hafez and Hafez, 2000).

2.3. Outcome assessment

All participants in the cohort followed a standard protocol for IVF/ICSI at the center, detailed elsewhere (Deng et al., 2023). Briefly, ovarian stimulation (8–13 days) was performed using long-agonist, short-agonist, or antagonist regimens according to the infertility diagnosis. Following oocyte retrieval, embryologists assessed both the total number and maturity of oocytes. Fertilization was carried out in the laboratory; for suboptimal semen quality, ICSI was used, involving the injection of a single sperm into an oocyte. Embryologists transferred embryos with the highest morphological grading to the uterus, and blood hCG levels were measured two weeks post-transfer to confirm pregnancy.

This study included ten outcome parameters, categorized as early IVF outcomes and clinical pregnancy outcomes. Early IVF parameters included the number of mature oocytes, number of 2PN zygotes, maturation rate, fertilization rate, cleavage rate, and best-quality embryos rate. Specifically, the mature oocyte count refers to the number of retrieved oocytes reaching the Metaphase II stage, displaying the first polar body, and capable of fertilization. The count of retrieved oocytes that were successfully fertilized and exhibited two pronuclei in the zygote refers to the number of 2PN zygotes. The maturation rate and fertilization rate were calculated as the ratio of mature oocytes or 2PN

zygotes to total retrieved oocytes. The proportion of zygotes dividing into embryos by 44 ± 1 h post-insemination on day 2 was used to calculate the cleavage rate. The best-quality embryo rate was calculated as the proportion of embryos meeting best quality criteria (four cells on day 2, or seven to nine cells on day 3, with no multinucleation and less than 20 % fragmentation) relative to all 2PN zygotes (Prevention, 2011). All definitions for early IVF outcomes adhere to the Vienna Consensus criteria (ESHRE Special Interest Group of Embryology; Alpha Scientists in Reproductive Medicine, 2017). To account for ovarian response, the ovarian sensitivity index (OSI) was calculated as the total number of oocytes retrieved divided by the total gonadotropin dose, multiplied by 1000 (Huber et al., 2013).

Clinical pregnancy outcomes included implantation, clinical pregnancy, and live birth. Implantation was assessed by measuring blood β-hCG levels two weeks after embryo transfer; a positive result was considered evidence of successful implantation. Clinical pregnancy was confirmed by the presence of a gestational sac on ultrasound imaging, performed six weeks after embryo transfer. Live birth was defined as the delivery of at least one live infant at or beyond 28 weeks of gestation (Zhang et al., 2022).

2.4. Covariates

Covariate data were collected using standardized questionnaires, including sociodemographic characteristics (household income and educational attainment), lifestyle factors (smoking and drinking status), and medical and reproductive history. Additional information such as causes of infertility and ovarian stimulation protocols, was extracted from medical records.

Age was categorized into three groups: < 30, 30–34, and ≥ 35 years (Somigliana et al., 2016). Body mass index (BMI) was divided into four categories based on Chinese-specific cutoff points (Wu et al., 2023). Passive smoking was defined as exposure to secondhand smoke for more than 15 min per day (Yao et al., 2023). Alcohol consumption was defined as drinking alcohol at least once per week. Due to the low prevalence of active smoking in this cohort (n = 39), secondhand smoke exposure was used as a proxy for tobacco exposure.

2.5. Statistical analyses

We used a directed acyclic graph (Fig. S3) to guide the selection of potential confounders. Baseline characteristics were summarized as means (standard deviations) for continuous variables and proportions for categorical variables. Comparisons between the analytic sample and the entire TREE cohort (n = 1701) used Chi-square tests or Student's t-tests as appropriate.

In the models, we adjusted for age (< 30, 30–34, ≥ 35 years), BMI (< 18.5, 18.5–23.9, 24–27.9, ≥ 28.0 kg/m^2), monthly household income (< 5000, 5001–10,000, ≥ 10,001 yuan), educational attainment (before high school, high school, college or higher), passive smoking (yes versus no), alcohol consumption (yes versus no), causes of infertility (female, male, mixed, or unexplained factors), controlled ovarian stimulation protocol (GnRH, antagonist, others), and season of oocyte retrieval or season of embryo transfer (spring, summer, autumn, and winter). The season of oocyte retrieval was adjusted for early IVF outcomes; the season of embryo transfer was adjusted for clinical pregnancy outcomes.

We performed multivariate regression models to examine associations between $PM_{2.5}$, PM_{10}, and $PM_{2.5–10}$ exposures during the entire oocyte development period (one year before oocyte retrieval to the retrieval day) and ten outcome parameters, with the aforementioned covariates. Linear regression was used for continuous outcomes (maturation, fertilization, cleavage rate, best-embryos rates, and OSI), logistic regression for binary outcomes (implantation, clinical pregnancy, and live birth), and Poisson regression for count outcomes (number of mature oocytes and 2PN zygotes). Results for the number of mature oocytes, 2PN zygotes, maturation, fertilization, cleavage, and best-quality embryos rates were expressed as percentage changes (%). Implantation, clinical pregnancy, and live birth outcomes were expressed as odds ratio (OR), while the ovarian sensitivity index (OSI) was presented as absolute changes. Effect estimates were calculated per interquartile range (IQR) increase in PM exposure or by comparing the highest three quartiles to the lowest.

To explore the exposure-response relationships for the association between PM exposure and outcome parameters, restricted cubic splines (RCS) functions with knots at the 10th, 50th, and 90th percentiles of PM exposure were included in the models, and nonlinearity was evaluated using likelihood ratio tests (Li et al., 2024).

To identify potential susceptible exposure windows, the main analyses were repeated for each of the three critical periods of oocyte development.

To identify susceptible subpopulations, we conducted stratified analysis by age (< 30, 30–34, and ≥ 35 years), BMI (< 24.0 versus ≥ 24.0 kg/m^2), alcohol consumption (yes versus no), COS protocols (long GnRH versus non-long GnRH), passive smoking status (yes versus no), and infertility causes (female versus non-female factors). We included cross-product terms between PM exposure and stratified variables in the models to formally test for interaction, and reported the corresponding *P* values for interaction (Han et al., 2024).

We conducted several sensitivity analyses to confirm the robustness of our findings. First, we constructed two-pollutant models to assess the independent effects of PM, adjusting for gaseous air pollutants with Spearman correlations < 0.80 (Table S3) (Sun et al., 2019, 2016). Second, to avoid model misspecification and inappropriate assumptions of linear regression, we used generalized linear models with a binomial distribution and logit link for proportional outcomes. Third, to address potential influence of higher oocyte counts, we restricted the analyses to participants without polycystic ovary syndrome (PCOS). Fourth, we limited the analysis to nulliparous participants to control for potential changes in reproductive health or residential location resulting from prior childbearing experiences (Wesselink et al., 2023).

We conducted all analyses in R software (version 4.3.1). Two-sided tests were used throughout, and a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Descriptive statistics

The women included in the analysis (n = 1237) had an average age of 30.9 years and a mean BMI of 22.1 kg/m^2 (Table 1). The majority were never drinkers (75.5 %), never smokers (95.2 %), with 60.1 % having completed at least a high school education. Female factors were the primary cause of infertility (56.5 %). Most participants underwent oocyte retrieval in the summer (41.6 %) or autumn (39.3 %). Among the 1149 women who had available embryos and underwent embryo transfer, 665 (57.9 %) achieved implantation, 592 (51.5 %) achieved clinical pregnancy, and 513 (48.5 %) achieved live birth. Baseline characteristics were comparable to the overall TREE cohort, except for differences in COS protocols (Table S1). The median (IQR) exposure levels to $PM_{2.5}$, PM_{10}, and $PM_{2.5–10}$ during the year preceding oocyte retrieval were 45.6 (4.84), 73.7 (6.99), and 28.2 (4.02) μg/m^3, respectively, with similar air pollution levels observed across different exposure windows (Table S2).

3.2. Main analyses

Exposure to $PM_{2.5}$, PM_{10}, and $PM_{2.5–10}$ during the entire oocyte development stage was associated with decreases in oocyte maturation and fertilization rate (Table 2). For example, for each IQR increase in $PM_{2.5}$, there was a 1.01 % (95 % CI: 0.17 %, 1.84 %) decrease in the maturation rate and a 1.42 % (95 % CI: 0.29 %, 2.55 %) reduction in fertilization rate. Similarly, each IQR increase in $PM_{2.5–10}$ was associated

Table 1
Demographic and clinical characteristics of the included study participants (n = 1237).

Characteristics	Mean (SD) or N (%)[a]
Demographic characteristics	
Age, mean (SD), years	30.9 (4.8)
BMI, mean (SD), kg/m^2	22.1 (3.1)
Education level	
Less than high school	494 (39.9 %)
High school	277 (22.4 %)
College and above	466 (37.7 %)
Household income, Yuan/month	
< 5000	632 (51.1 %)
5001–10,000	403 (32.6 %)
≥ 10,001	202 (16.3 %)
Active smoking	
Yes	59 (4.8 %)
No	1178 (95.2 %)
Passive smoking	
No	625 (50.5 %)
Yes	612 (49.5 %)
Alcohol consumption	
No	934 (75.5 %)
Yes	303 (24.5 %)
Clinical characteristics	
Causes of infertility	
Female factors	699 (56.5 %)
Male factors	135 (10.9 %)
Mixed factors	295 (23.9 %)
Unexplained	108 (8.7 %)
Season of oocyte retrieval	
Spring [March–May]	125 (10.1 %)
Summer [June–August]	515 (41.6 %)
Autumn [September–November]	486 (39.3 %)
Winter [December–February]	111 (9.0 %)
Season of embryo transfer[b]	
Spring [March–May]	82 (7.1 %)
Summer [June–August]	465 (40.5 %)
Autumn [September–November]	448 (39.0 %)
Winter [December–February]	154 (13.4 %)
COS protocols	
GnRH Agonist	740 (59.8 %)
Antagonist	388 (31.4 %)
Others	109 (8.8 %)
Fertilization methods	
IVF	782 (63.2 %)
ICSI	348 (28.1 %)
IVF + ICSI	107 (8.7 %)
OSI, mean (SD)	6.0 (4.8)
Number of mature oocytes, mean (SD)	10.3 (6.3)
Maturation rate, mean (SD), %	84.1 (16.5)
Number of 2PN zygotes, mean (SD)	7.4 (5.0)
Fertilization rate, mean (SD), %	60.0 (22.3)
Cleavage rate, mean (SD), %	94.2 (5.0)
Best-quality embryos rate, mean (SD), %	71.8 (29.2)
Implantation success[b]	665 (57.9 %)
Clinical pregnancy[b]	592 (51.5 %)
Live birth[b]	513 (48.5 %)

Abbreviations: BMI, body mass index; SD, standard deviation; COS, controlled ovarian stimulation; IVF, in vitro Fertilization; ICSI, Intracytoplasmic Sperm Injection. OSI, ovarian sensitivity index.

[a] Baseline characteristics were summarized as means with standard deviations for continuous variables or proportions for categorical variables.

[b] n = 1149 participants with available embryos and embryo transfer.

with a 1.95 % (95 % CI: 0.98 %, 2.93 %) decline in maturation rate and a 2.57 % (95 % CI: 1.24 %, 3.89 %) reduction in fertilization rate. Compared to women residing in areas with the lowest (first quartile) $PM_{2.5–10}$ level, those in the second, third, and fourth quartiles showed changes in fertilization rate of − 3.03 % (95 % CI: − 6.57 %, 0.50 %), − 2.85 % (95 % CI: − 6.39 %, 0.69 %), and − 4.70 % (95 % CI: − 8.32 %, − 1.07 %), respectively.

No significant associations were found between PM exposure and clinical pregnancy outcomes during the entire oocyte development stage (Table 3). For example, exposure to $PM_{2.5}$ across the entire or specific critical stages was not associated with risks of implantation or live birth.

To explore the exposure-response relationships for the association between PM exposure and oocyte outcome parameters, we used RCS functions with three knots for each PM exposure in the models. Overall, the association between PM_{10} and oocyte outcomes appeared linear. For $PM_{2.5}$ and $PM_{2.5–10}$, the exposure-outcome curves displayed nonlinear patterns (Fig. 3). Specifically, the numbers of mature oocytes and 2PN zygotes plateaued and then declined at higher levels of $PM_{2.5–10}$ exposure, while both maturation and fertilization rates displayed L-shaped relationships with $PM_{2.5}$.

3.3. Stratified analyses

In stratified analyses (Tables S4–S6), the associations between PM exposure and oocyte quality were generally consistent across subgroups defined by age and BMI, but effects were more pronounced among non-passive smokers and non-drinkers. For example, with each IQR increase in PM_{10} exposure, the change in oocyte maturation rate was 0.13 % (95 % CI: − 1.37 %, 1.64 %) among non-passive smokers, compared to a − 1.59 % (95 % CI: − 2.45 %, − 0.74 %) among passive smokers (*P* for interaction = 0.05). Significant effect modification by BMI was observed for some outcomes. For example, with each IQR increase in $PM_{2.5}$ exposure, the number of 2PN zygotes decreased by 5.45 % (95 % CI: 1.70 %, 9.15 %) in participants with BMI ≥ 24 kg/m^2, whereas no significant association was found in those with BMI < 24 kg/m^2 (*P* for interaction < 0.01).

3.4. Exposure windows

To identify susceptible exposure windows, we repeated the main analyses across different developmental periods (Fig. 1 **and** Fig. 2). The reductions in early reproductive outcomes associated with PM were most pronounced during the follicle maturation stage. For example, per IQR increase in $PM_{2.5}$, the reduction in cleavage rate was 0.10 % (95 % CI: − 1.41 %, 1.20 %) during the follicle initiation stage, 2.23 % (95 % CI: 0.26 %, 4.20 %) during the growth and selection stage, and 4.55 % (95 % CI: 2.65 %, 6.45 %) during the maturation stage.

3.5. Sensitivity analyses

Our findings were robust in several sensitivity analyses. Results remained consistent in two-pollutant models (Table S9 and Table S10), when applying generalized linear models with a binomial distribution and logit link for proportional outcomes (Table S11), and when analyses were restricted to participants without PCOS and those without previous births (Tables S12–S15).

4. Discussion

In this prospective study conducted in Hubei Province, China, involving 1237 women undergoing their first IVF cycle, exposure to PM was associated with reductions in maturation and fertilization rates, but not with clinical pregnancy outcomes. The most susceptible exposure windows were the follicle maturation stage, approximately 10 days before oocyte retrieval. These associations were more pronounced among non-passive smokers and non-drinkers.

Fewer studies have assessed the effects of PM exposure on fertilization and embryo quality (Shi et al., 2021; Zeng et al., 2020). For instance, Deng et al. reported that $PM_{2.5}$ exposure during the follicle growth and selection stage was associated with reduced total and mature oocyte yields in a cohort of 8048 women (Deng et al., 2024). Similarly, a study in Georgia, USA, found that PM_{10} exposure during the 85 days prior to oocyte retrieval was associated with lower oocyte thaw survival rates (LaPointe et al., 2024a), while another US study reported that exposure to $PM_{2.5}$ during the same exposure window led to

Table 2
Percentage changes in early IVF outcomes associated with an interquartile range increase in particulate matter (PM) exposure among 1237 women during the entire oocyte development period.

Particulate matter	Adjusted % Change (95 % CI)[a]					
	Number of mature oocytes	Number of 2PN zygotes	Maturation rate	Fertilization rate	Cleavage rate	Best-quality embryos rate
$PM_{2.5}$, μg/m^3						
Q1 (< 42.11)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2 (42.11 – 45.56)	− 3.13 (− 8.28, 2.02)	− 4.02 (− 10.11, 2.07)	**− 4.40 (− 7.05, − 1.75)**	**−5.35 (− 8.94, − 1.76)**	− 1.20 (− 4.23, 1.82)	− 1.43 (− 6.03, 3.17)
Q3 (45.57 – 46.95)	− 1.42 (− 6.55, 3.70)	− 1.07 (− 7.11, 4.97)	− 1.81 (− 4.46, 0.85)	− 3.23 (− 6.83, 0.37)	− 1.43 (− 4.47, 1.61)	1.10 (− 3.51, 5.72)
Q4 (≥ 46.96)	6.14 (− 1.09, 11.19)	4.74 (− 1.24, 10.73)	− 1.01 (− 3.66, 1.64)	− 2.86 (− 6.45, 0.73)	− 2.11 (− 5.14, 0.92)	− 2.24 (− 6.85, 2.36)
Continuous $PM_{2.5}$ exposure (per IQR increase)[b]	0.48 (− 1.13, 2.11)	− 0.04 (− 1.94, 1.88)	**− 1.01 (− 1.84, − 0.17)**	**− 1.42 (− 2.55, − 0.29)**	− 0.29 (− 1.24, 0.67)	− 0.34 (− 1.78, 1.11)
P for trend[c]	0.05	0.08	0.87	0.25	0.18	0.56
PM_{10}, μg/m^3						
Q1 (< 69.36)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2 (69.36 – 73.74)	**− 5.70 (− 10.81, − 0.59)**	**− 6.64 (− 12.66, − 0.63)**	− 2.30 (− 4.92, 0.33)	− 3.54 (− 7.10, 0.01)	− 1.36 (− 4.36, 1.63)	1.30 (− 3.26, 5.85)
Q3 (73.75 – 76.35)	2.13 (− 2.88, 7.14)	− 0.04 (− 5.96, 5.88)	− 1.96 (− 4.61, 0.68)	− 3.37 (− 6.96, 0.21)	0.04 (− 2.98, 3.06)	0.09 (− 4.50, 4.68)
Q4 (≥ 76.36)	1.79 (− 3.29, 6.87)	0.22 (− 5.78, 6.22)	− 1.78 (− 4.43, 0.88)	− 3.58 (− 7.18, 0.01)	− 1.20 (− 4.22, 1.83)	− 0.77 (− 5.38, 3.83)
Continuous PM_{10} exposure (per IQR increase)[b]	− 0.09 (− 1.53, 1.36)	− 0.90 (− 2.59, 0.81)	**− 1.21 (− 1.96, − 0.47)**	**− 1.65 (− 2.65, − 0.64)**	− 0.32 (− 1.17, 0.53)	− 0.29 (− 1.58, 1.01)
P for trend[c]	0.10	0.42	0.25	0.05	0.66	0.63
$PM_{2.5–10}$, μg/m^3						
Q1 (< 25.77)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2 (25.77 – 28.25)	− 0.84 (− 5.90, 4.21)	− 0.93 (− 6.88, 5.02)	− 1.17 (− 3.78, 1.44)	− 3.03 (− 6.57, 0.50)	− 0.23 (− 3.21, 2.75)	3.43 (− 1.10, 7.96)
Q3 (28.26 – 29.80)	4.29 (− 0.67, 9.25)	3.65 (− 2.19, 9.50)	− 2.51 (− 5.12, 0.10)	− 2.85 (− 6.39, 0.69)	0.36 (− 2.63, 3.34)	2.35 (− 2.18, 6.88)
Q4 (≥ 29.81)	− 0.11 (− 5.25, 5.03)	− 3.34 (− 9.44, 2.77)	− 2.47 (− 5.14, 0.21)	**− 4.70 (− 8.32, − 1.07)**	− 1.13 (− 4.18, 1.93)	− 0.37 (− 5.01, 4.27)
Continuous $PM_{2.5–10}$ exposure (per IQR increase)[b]	− 1.07 (− 2.95, 0.82)	**− 2.60 (− 4.81, − 0.37)**	**− 1.95 (− 2.93, − 0.98)**	**− 2.57 (− 3.89, − 1.24)**	− 0.48 (− 1.60, 0.64)	− 0.30 (− 1.99, 1.40)
P for trend[c]	0.53	0.62	**0.04**	**0.02**	0.58	0.77

Abbreviations: IVF, in vitro fertilization; 2PN, two distinct pronuclei; COS, controlled ovarian stimulation; Q, quartiles; IQR, interquartile range; CI, confidence interval; Ref, Reference; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; $PM_{2.5–10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm.

[a] We used linear regression for continuously scaled outcome variables (i.e., maturation rate, fertilization rate, cleavage rate, and the best-quality embryos rate), and Poisson regression models for oocyte count (i.e., number of mature oocytes and 2PN zygotes). Data are presented as percent change (%) adjusted for age, BMI, alcohol use, passive smoking status, education level, household income, COS protocols, season of oocyte retrieval, and infertility causes.

[b] An IQR increase in $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$ exposure at the residential address is 4.84, 6.99, and 4.02 μg/m^3, respectively.

[c] *P* for trend was derived by calculating the quartiles number (1–4) of exposure as a continuous variable in the models.

decreased total and mature oocyte numbers (LaPointe et al., 2024b). Our findings are consistent with these prior studies, demonstrating that ambient PM exposure is associated with impaired early IVF outcomes. However, none of these studies assessed exposure throughout the entire oocyte development period, potentially underestimating the cumulative effects of long-term PM exposure. To our knowledge, our study is the first to comprehensively estimate the association between ambient PM exposure and pregnancy outcomes in women undergoing IVF procedures during the entire oocyte development period and across three key stages of folliculogenesis. Our findings suggest that reducing exposure to high ambient PM levels during critical follicular development stages may be beneficial. Specifically, we found that exposure to ambient particulate matter was associated with reduced oocyte maturation and fertilization rates during all three stages, with the strongest effects during the maturation stage.

Several biological mechanisms have been proposed to explain the association between PM exposure and compromised early IVF outcomes. First, PM exposure increases oxidative stress and reduces meiotic competency, potentially triggering apoptosis or premature removal of granulosa cells and oocytes (Liao et al., 2020; Wang et al., 2021). Second, exposure to $PM_{2.5}$ may decrease follicular reserve by promoting follicle atresia and over-activating primordial follicles, thereby reducing the number of available follicles (Zhou et al., 2020). Third, PM exposure elevates levels of proapoptotic and apoptotic factors, further compromising follicular integrity (Liao et al., 2020; Tiwari et al., 2015). Fourth, exposure to PM induces intracellular toxicity by increasing reactive oxygen species levels and causing DNA damage (Alfaro-Moreno et al., 2002). Collectively, these mechanisms may underlie the adverse effects of PM exposure on early IVF outcomes.

Compared to earlier developmental windows, the follicle maturation stage appears to be particularly sensitive to PM exposure. Although the underlying mechanisms remain incompletely understood, two lines of evidence support this hypothesis. First, the follicle maturation stage is characterized by crucial events in nuclear and cytoplasmic maturation, which are highly hormone-dependent and involve the acquisition of developmental competence (Telfer et al., 2023). $PM_{2.5}$ contains various endocrine-disrupting components that may interfere with follicle-stimulating hormone (FSH) and locally produced insulin-like growth factors (IGFs), disrupting these pathways and damaging granulosa cell function (Chen et al., 2025). Second, once follicles enter the antral stage, they undergo exponential growth, with rapid increases in follicular fluid volume and cavity size. Enhanced vascularization and

Table 3
Effect estimates of pregnancy outcomes associated with an interquartile range (IQR) increase in particulate matter (PM) among 1149 women during the entire oocyte development period.

Particulate matter	Adjusted absolute change (95 % CI)[a]	Adjusted OR (95 % CI)[a]		
	Ovarian Sensitivity Index	Implantation	Clinical pregnancy	Live birth
$PM_{2.5}$, μg/m^3				
Q1 (< 42.11)	Ref.	Ref.	Ref.	Ref.
Q2 (42.11 – 45.57)	0.03 (− 0.64, 0.71)	1.24 (0.88, 1.76)	1.34 (0.95, 1.89)	1.30 (0.92, 1.83)
Q3 (45.58 – 46.95)	0.06 (− 0.62, 0.74)	1.08 (0.76, 1.54)	1.20 (0.85, 1.70)	1.15 (0.81, 1.63)
Q4 (≥ 46.96)	0.50 (− 0.18, 1.17)	1.02 (0.72, 1.44)	1.27 (0.90, 1.79)	1.29 (0.91, 1.82)
Continuous $PM_{2.5}$ exposure (per IQR increase)[b]	0.08 (− 0.13, 0.29)	1.04 (0.93, 1.16)	1.08 (0.96, 1.20)	1.08 (0.97, 1.20)
P for trend[c]	0.16	0.88	0.29	0.27
PM_{10}, μg/m^3				
Q1 (< 69.44)	Ref.	Ref.	Ref.	Ref.
Q2 (69.44 – 73.74)	− 0.34 (− 1.01, 0.32)	0.81 (0.57, 1.14)	0.96 (0.68, 1.36)	0.98 (0.69, 1.38)
Q3 (73.75 – 76.33)	0.41 (− 0.27, 1.08)	1.31 (0.92, 1.87)	1.43 (1.01, 2.03)	1.36 (0.96, 1.93)
Q4 (≥ 76.34)	0.32 (− 0.35, 1.00)	0.80 (0.56, 1.13)	0.97 (0.69, 1.37)	0.92 (0.65, 1.31)
Continuous PM_{10} exposure (per IQR increase)[b]	0.08 (− 0.11, 0.27)	1.02 (0.92, 1.12)	1.05 (0.96, 1.16)	1.05 (0.95, 1.15)
P for trend[c]	0.11	0.74	0.58	0.87
$PM_{2.5–10}$, μg/m^3				
Q1 (< 25.81)	Ref.	Ref.	Ref.	Ref.
Q2 (25.81 – 28.25)	− 0.06 (− 0.73, 0.60)	1.00 (0.71, 1.42)	1.15 (0.82, 1.62)	1.11 (0.79, 1.56)
Q3 (28.26 – 29.78)	0.49 (− 0.18, 1.16)	1.03 (0.73, 1.45)	1.18 (0.84, 1.67)	1.06 (0.75, 1.50)
Q4 (≥ 29.79)	0.37 (− 0.31, 1.06)	0.84 (0.59, 1.19)	0.99 (0.70, 1.40)	0.94 (0.66, 1.33)
Continuous $PM_{2.5–10}$ exposure (per IQR increase)[b]	0.11 (− 0.14, 0.36)	0.99 (0.87, 1.12)	1.04 (0.91, 1.18)	1.02 (0.89, 1.15)
P for trend[c]	0.12	0.38	0.99	0.66

Abbreviations: IVF, in vitro fertilization; Q, quartiles; IQR, interquartile range; CI, confidence interval; OR, Odds Ratio; Ref, Reference; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; $PM_{2.5–10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm.

[a] We used linear regression for continuously scaled outcome variables (i.e., ovarian sensitivity index), and logistic regression for dichotomous measures (i.e., implantation, clinical pregnancy, and live birth). Data are presented as absolute change for OSI and odds ratios for implantation, clinical pregnancy, and live birth after adjusting for age, BMI, alcohol use, passive smoking status, education level, household income, COS protocols, infertility causes, and season of oocyte retrieval or embryo transfer.

[b] An IQR increase in $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$ exposure at the residential address is 4.83, 6.89, 3.97 μg/m^3, respectively.

[c] *P* for trend was derived by calculating the quartiles number (1–4) of exposure as a continuous variable in the models.

increased blood flow at this stage may allow PM components and their metabolites to more readily cross the blood-follicle barrier and accumulate in follicular fluid, increasing the likelihood of direct oocyte exposure to pollutants (Bongaerts et al., 2023).

The OSI is a measure of ovarian responsiveness. In our study, we found no significant association between PM exposure and OSI. This contrasts with a prior analysis of 781 IVF cycles in the southeastern US, which found that $PM_{2.5}$ exposure during the three months before stimulation and during the stimulation period was associated with lower OSI (LaPointe et al., 2024b). The discrepancy between these findings may reflect differences in ovarian stimulation regimens across countries and regions, which could influence physiological responses to environmental exposures. Additionally, ambient PM concentrations and compositions vary substantially between geographical areas and over time, potentially contributing to inconsistencies across studies. Our study was conducted at a single reproductive center in Hubei, China, where participants shared similar ethnic and regional backgrounds and were exposed to relatively homogeneous air pollution levels. These characteristics inherently limit the generalizability of our findings to populations in other regions or with different demographic and environmental contexts. Given the limited number of relevant studies, our findings should be interpreted with caution, and future multi-center studies in diverse settings are needed to clarify the underlying causes of these discrepancies.

Although prior studies have reported associations between PM exposure and adverse clinical pregnancy outcomes (Liu et al., 2023; Zhang et al., 2022; Quraishi et al., 2019), we did not observe such associations in our study. This discrepancy may partly reflect methodological factors, including our relatively small sample size, which limited power to detect clinically meaningful differences, as well as our exclusive focus on first-cycle IVF participants. In contrast, previous studies included repeated cycles involving women with underlying reproductive disorders, who may be more vulnerable to environmental stressors. Other contributing factors may include regional variability (Liu et al., 2009), differences in population characteristics (Patel et al., 2016), clinical protocols (Shrestha et al., 2015), and residual confounding. Beyond these considerations, biological mechanisms may also explain the null findings. Clinical pregnancy outcomes are strongly influenced by endometrial receptivity and embryonic genetic quality, which can overshadow subtle environmental effects (Makker and Singh, 2006). In addition, maternal physiological adaptations during gestation, such as rising estrogen levels in the second and third trimesters that promote angiogenesis and enhance uteroplacental blood flow, may buffer early insults (Albrecht and Pepe, 2010). The placenta may further counteract PM-induced oxidative stress and inflammation through antioxidant enzyme systems and exosomal signaling pathways (Ghafourian et al., 2022).

We observed that the association was more pronounced among non-passive smokers and non-drinkers. Smokers, having already been exposed to cumulative air pollution and tobacco-related toxins, may exhibit a lower relative risk increase from additional ambient air pollution exposure (von Lewinski et al., 2024). In contrast, non-smokers, with lower baseline exposure to pollutants, may have less oxidative stress adaptation and thus be more sensitive to the effects of PM exposure. Similarly, non-drinkers appeared more vulnerable than drinkers. This difference may be attributed to potential protective mechanisms induced by moderate alcohol consumption, such as improved cardiovascular or anti-inflammatory response (Bektas et al., 2016). Alternatively, alcohol's systemic effects could mask the reproductive impacts of PM by altering metabolic or hormonal pathways, complicating the detection of PM-specific effects among drinkers (Cebral et al., 1998;

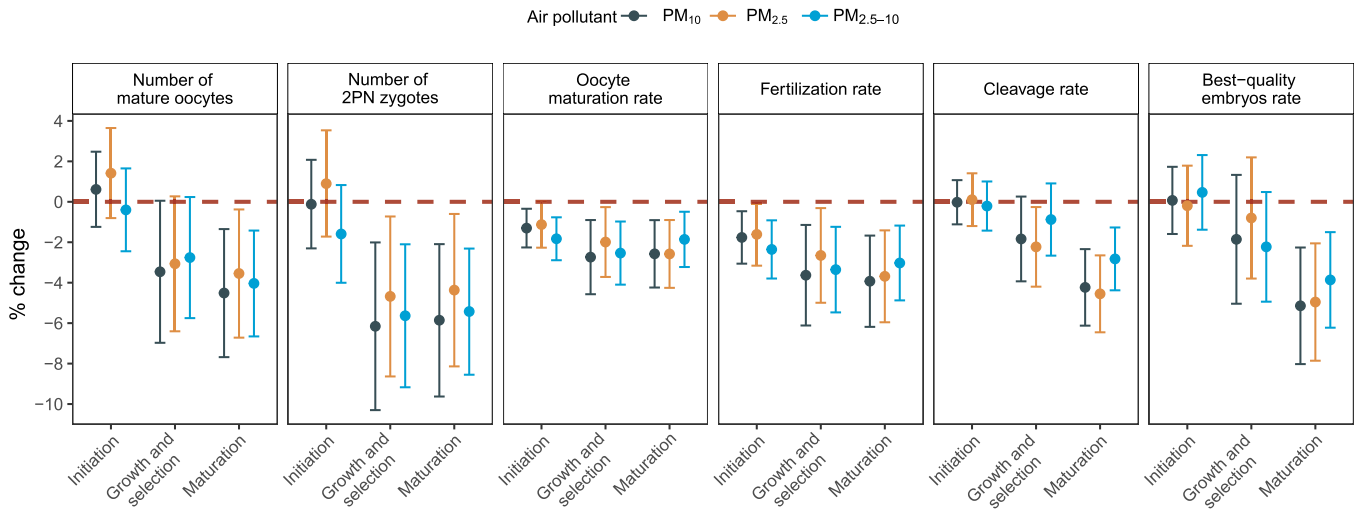

Fig. 1. Percent changes of early IVF outcomes associated with an interquartile range (IQR) increase in particulate matter (PM) during three key critical stages of oocyte development. The specific critical stages of oocyte development included follicle initiation stage: from primordial to preantral follicle stage (from one year to 85 days before oocyte retrieval, approximately 9 months), growth and selection stage: from preantral follicle to antral follicle (from 85 days to 10 days before oocyte retrieval, approximately 75 days), and maturation stage: from antral follicle to preovulatory follicle stage (from 10 days before oocyte retrieval to retrieval day, approximately 11 days). Corresponding numeric data are reported in Table S7.

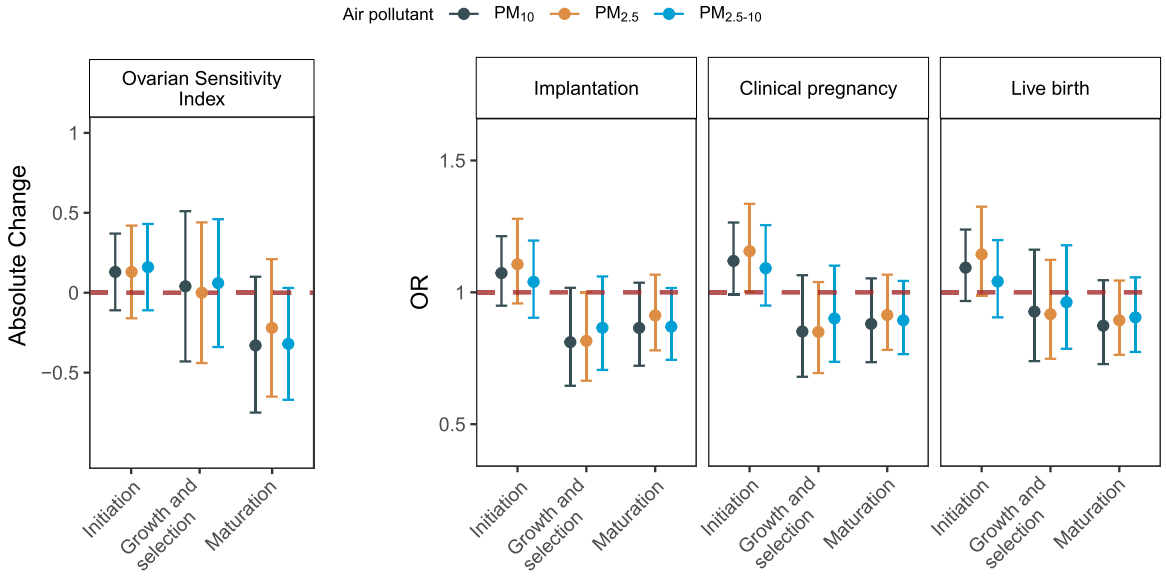

Fig. 2. Effect estimates of pregnancy outcomes associated with an interquartile range (IQR) increase in particulate matter (PM) during three key critical stages of oocyte development. The specific critical stages of oocyte development included follicle initiation stage: from primordial to preantral follicle stage (from one year to 85 days before oocyte retrieval, approximately 9 months), growth and selection stage: from preantral follicle to antral follicle (from 85 days to 10 days before oocyte retrieval, approximately 75 days), and maturation stage: from antral follicle to preovulatory follicle stage (from 10 days before oocyte retrieval to retrieval day, approximately 11 days). Corresponding numeric data are reported in Table S8.

Ozbakir and Tulay, 2021).

Several limitations should be noted. First, while we found associations between PM exposure and reductions in maturation and fertilization rates, we could not fully distinguish whether these effects were driven by adverse impacts on maternal or paternal factors (Wu et al., 2022; Zhang et al., 2023). Nevertheless, the strongest associations between PM exposure and early IVF outcomes occurred before the interaction of male gametes, suggesting a predominantly maternal effect. Second, we relied on outdoor ambient PM concentrations as a proxy for personal exposure but did not account for indoor particulate matter exposure sources, such as solid and cooking fuel use, or individual activity patterns such as time spent at the workplace or lifestyle factors such as physical activity levels. These limitations may have introduced exposure misclassification. However, as these exposure misclassifications are likely nondifferential (Meldrum et al., 2016), they may have biased our findings toward a null association. Third, our study population was limited to women undergoing IVF treatment in a single province of China so the findings may not be applicable to other populations or regions. Fourth, we used an integrated measure of ambient PM exposure to reflect total PM concentrations rather than specific pollution sources. Future studies should further clarify the impacts of different sources of PM, such as traffic, industrial, or biomass emissions.

5. Conclusions

In summary, this prospective study of 1237 women undergoing IVF/

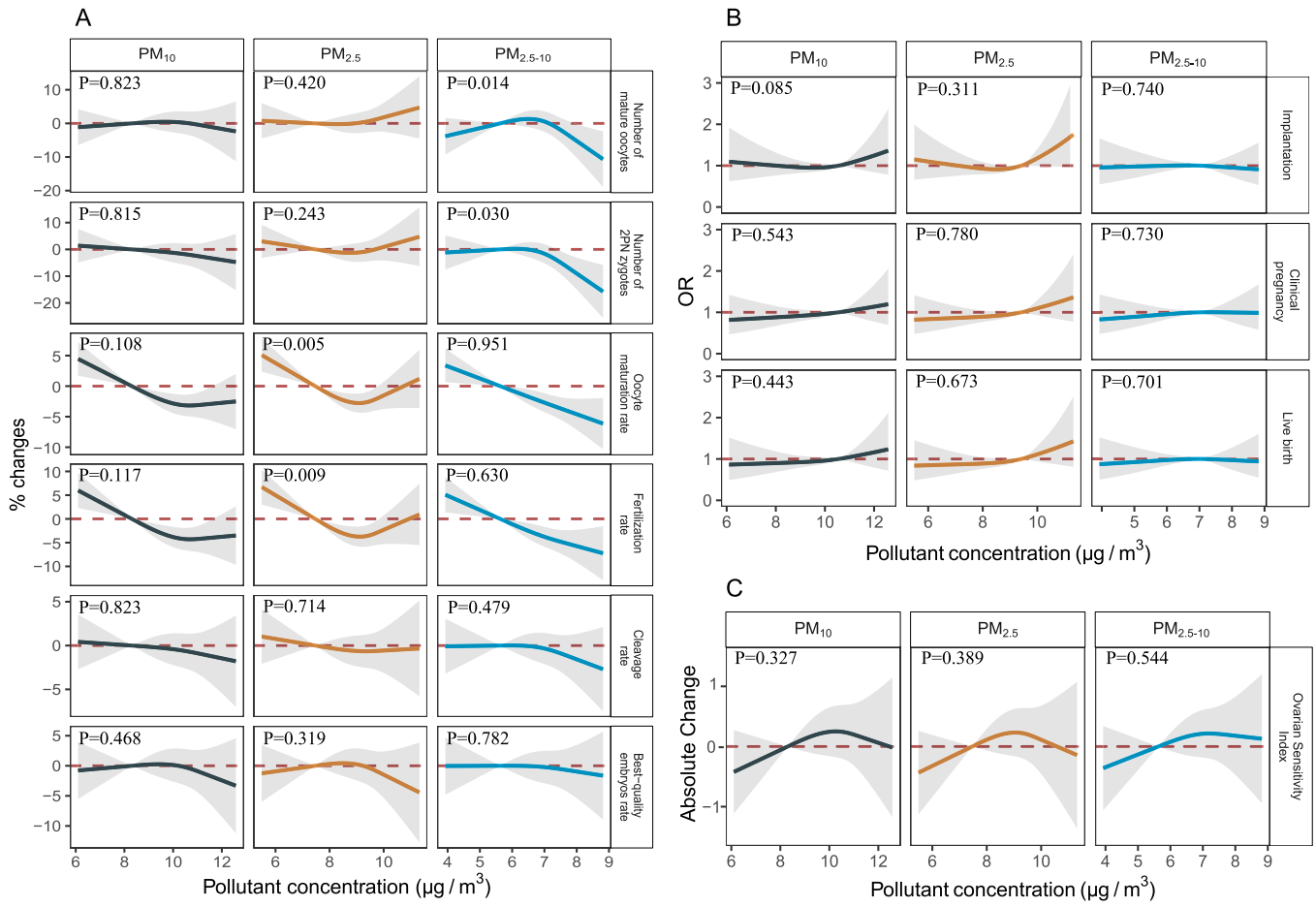

Fig. 3. Exposure-response relationship between exposure to particulate matter (PM) and ten pregnancy outcome parameters, including early IVF outcomes (A), clinical pregnancy outcomes (B), and ovarian sensitivity index (C). *P* values represent the statistical significance of nonlinearity.

ICSI treatment found that exposure to PM was associated with adverse reproductive outcomes, particularly reductions in maturation and fertilization rates. The strongest associations were observed during the follicle maturation stage. This study provides novel evidence that PM exposure may adversely affect key early reproductive parameters in women undergoing IVF/ICSI.

CRediT authorship contribution statement

Jiayi Liu: Writing – original draft, Methodology, Formal analysis, Data curation. **Jie Yin:** Writing – review & editing, Methodology. **Ze Han:** Writing – review & editing, Data curation. **Yangchang Zhang:** Writing – review & editing, Investigation. **Shi Zhao:** Writing – review & editing, Conceptualization. **Chunrong Li:** Writing – review & editing. **Yan Gong:** Writing – review & editing. **Wangnan Cao:** Writing – review & editing, Supervision, Conceptualization. **Qiang Zeng:** Writing – review & editing, Supervision, Data curation. **Shengzhi Sun:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Funding acquisition, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.119049.

Data availability

Data will be made available on request.

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