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ORIGINAL RESEARCH

Association of Ambient Air Pollution and Pregnancy Outcomes Among Women with Assisted Reproductive Technology in Qingdao, China: A Retrospective Cohort Study

Shuyuan Chen[1,2,*], Zewei Yu[2,*], Yuquan Mao[1,3,*], Yangying Xu[2], Fanhui Meng[4], Duan Li[2], Xueyu Wang[5], Yupeng Jia[6], Xiaowen Liu[1], Yujie Li[2], Cuifang Hao[2], Xin Du[1,2]

[1]Department of Integrated Traditional Chinese and Western Medicine, Qingdao Medical College, Qingdao University, Qingdao, Shandong, 266000, People's Republic of China; [2]Reproductive Medicine Center, Women and Children's Hospital Affiliated to Qingdao University, Qingdao, Shandong, 266000, People's Republic of China; [3]The Department of Traditional Chinese Medicine of Qingdao University Affiliated Hospital, Qingdao, Shandong, 266000, People's Republic of China; [4]Qingdao Ecological and Agricultural Meteorological Center, Qingdao, Shandong, 266000, People's Republic of China; [5]The Oncology Department of Qingdao Fifth People's Hospital, Qingdao, Shandong, People's Republic of China; [6]School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, 430000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Cuifang Hao; Xin Du, Reproductive Medicine Center, Women and Children's Hospital Affiliated to Qingdao University, Qingdao, Shandong, 266000, People's Republic of China, Tel +86 17605321871; +86 19853279079, Email cuifang-hao@163.com; duxinsharontc@163.com

Background: Ambient air pollutants, a major global public health concern, have been widely documented in recent years as key risk factors for adverse reproductive system outcomes. Assisted reproductive technology (ART) has become an important therapeutic means for infertility, but its pregnancy outcomes are influenced by various environmental factors. Thus, we explored the effects of ambient air pollutants on populations undergoing ART.

Methods: The retrospective cohort study included 3478 infertility patients with fresh embryo transplantation residing in Qingdao City who underwent in vitro fertilization and intracytoplasmic sperm injection in China from 2021 to 2023. We employed multivariable logistic regression to assess the effects of contaminants on oocyte quality, embryonic development, and pregnancy outcomes. Stratified analysis was conducted to identify potential vulnerable subpopulations.

Results: Regression showed that NO_2 exposure showed negative association with biochemical pregnancy rates (aOR=0.967, 95% CI=0.935–0.999) and clinical pregnancy rates (aOR=1.044, 95% CI=1.001–1.088). CO exposure was positively correlated with cleavage rate (aOR=1.293, 95% CI=1.048–1.594) and day 3 high-quality embryo rate (aOR=1.462, 95% CI=1.054–2.028). $PM_{2.5}$ and NO_2 exposure were negatively associated with the number of oocyte retrieval and MII oocytes. WQS index was negatively correlated with MII oocyte count (aOR=0.916, 95% CI=0.857–0.978). BKMR analysis confirmed $PM_{2.5}$ correlated negatively with MII oocyte count. Stratified analyses revealed women aged ≥35 were more sensitive to NO_2, while those <35 were to O_3. Women with ≥7 oocytes were more sensitive to $PM_{2.5}$ and NO_2.

Conclusion: Ambient air pollutants exert significant negative effects on ART-related reproductive outcomes. Women aged ≥35 were more sensitive to NO_2, whereas those <35 were O_3. Women with ≥7 oocytes were more sensitive to $PM_{2.5}$ and NO_2. This study provides a scientific basis for the prevention of air pollution and clinical decision-making in ART population. It is necessary to develop personalized intervention strategies for sensitive populations and strengthen the environmental control of related pollutants.

Keywords: ambient air pollution, assisted reproduction technology, laboratory outcomes, MII oocytes, clinical pregnancy, Bayesian kernel machine regression, BKMR

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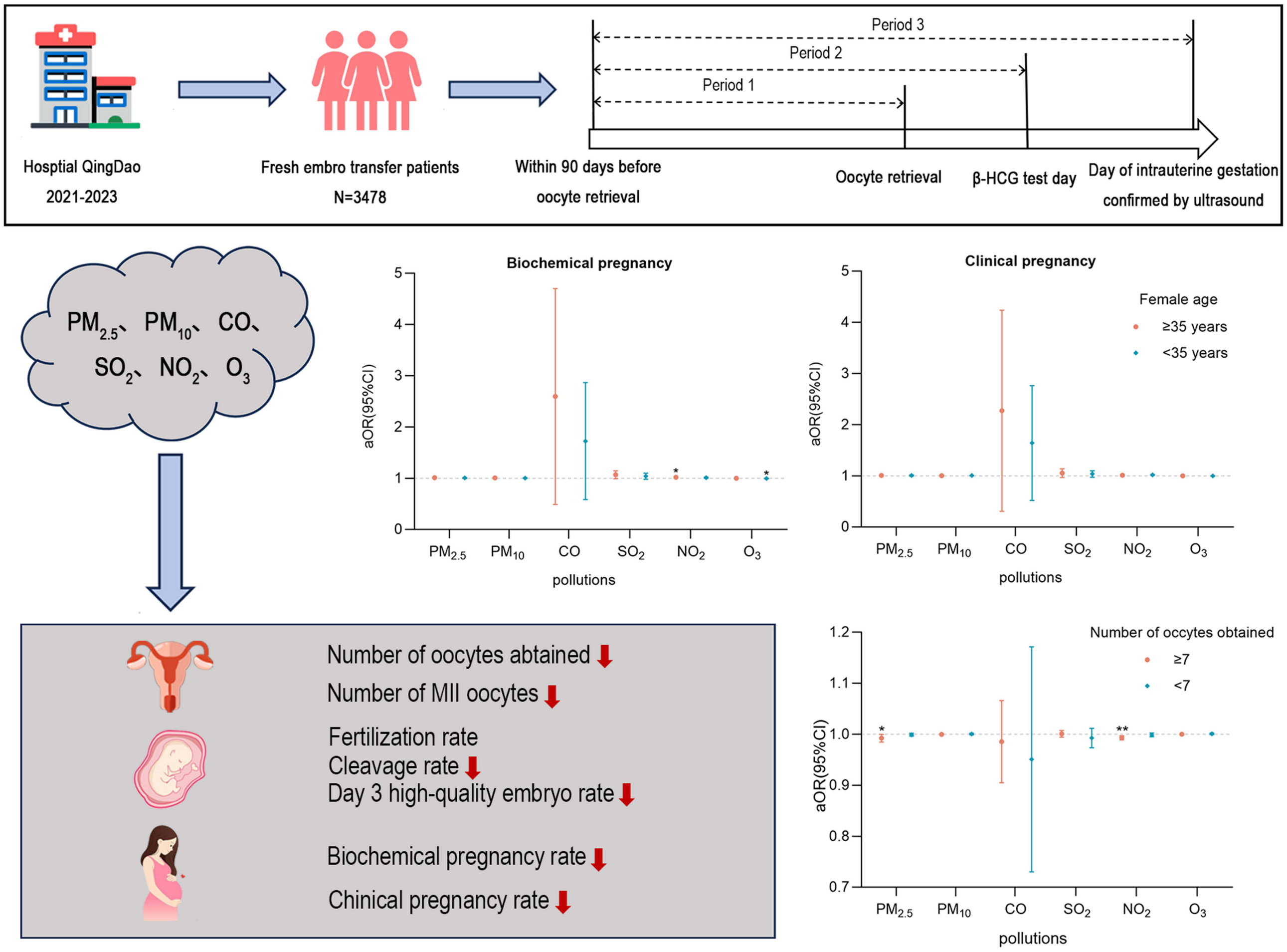
Graphical Abstract



Introduction

Infertility represents a significant global health challenge, with rising prevalence in recent decades. According to the WHO (2023), approximately 17.5% of adults worldwide experience infertility, equating to one in six individuals.[1] In China, infertility affects over 50 million people, accounting for 12%–15% of reproductive-age couples.[2] Assisted reproductive technology (ART), including in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and preimplantation genetic testing, has emerged as a critical solution for infertility management. However, accelerating industrialization has heightened exposure to environmental pollutants (eg, air pollution, heavy metals), extreme temperatures, and humidity, factors that may directly or indirectly compromise ART success rates, which not only reduces family well-being, but also increases medical burden. Therefore, exploring the relationship between air pollution and ART pregnancy outcomes is of great significance for the development of public health.

Qingdao, a coastal city on the Shandong Peninsula, is surrounded by the sea on three sides, with stretching mountains and lush vegetation. It has a temperate monsoon climate, and its urban area exhibits distinct maritime characteristics due to the direct regulation effect of the marine environment. Therefore, exploring the association between ambient air pollutants and ART pregnancy outcomes in this region can more representatively reflect the situation in coastal areas, fill the gap in relevant data for coastal regions, and provide a scientific basis for public environmental management and the establishment of pollutant concentration standards.

Ambient air pollution, which mainly includes fine particulate matter ($PM_{2.5}$ and PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and ozone (O_3), is an established risk factor for cardiovascular, respiratory, and neurological diseases.[3–5] Substantial evidence links air pollution to the reduced fertility and adverse ART outcomes, such as spontaneous abortion, preterm birth, and stillbirth.[6–8] During ART cycles, short-term $PM_{2.5}$ exposure may not significantly alter clinical pregnancy rates (CPR) but can impair embryo quality.[9] Similarly, high NO_2 and PM_{10} levels correlate with reduced high-quality embryo rates.[10] The mechanisms underlying pollution-induced reproductive toxicity remain incompletely understood. Proposed pathways include oxidative stress and inflammation triggered by pollutants like NO_2, O_3, $PM_{2.5}$, and black carbon.[11] Notably, O_3 exposure on the day preceding oocyte retrieval significantly reduces intrauterine pregnancy rates.[12] Recent studies further indicate that $PM_{2.5}$, SO_2, and O_3 negatively impact fresh embryo IVF outcomes, with effects modulated by temperature, humidity, and wind speed.[13]

To address these gaps, this retrospective cohort study analyzed women undergoing ART at Qingdao Women and Children's Hospital (2021–2023). We aimed to quantify the effects of $PM_{2.5}$, PM_{10}, CO, SO_2, NO_2 and O_3 exposure during critical ART windows on pregnancy outcomes and assess impacts on oocyte quality and embryonic development. Meanwhile, provide a scientific basis for improving ART outcomes, formulating public environmental health policies, and optimizing pollutant concentration standards in coastal areas.

Materials and Methods

Study Population

We retrospectively analyzed the clinical data of 3478 fresh embryo transfer patients residing in Qingdao City who underwent IVF/ICSI in the Reproductive Medicine Center of Women and Children's Hospital Affiliated to Qingdao University from January 2021 to December 2023. Inclusion criteria: ① Patients undergoing fresh cycle transfer with conventional IVF/ICSI; ② Female patients aged 21 to 50 years at the time of oocyte retrieval or embryo transfer; ③ Transfer of 1 or 2 cleavage-stage embryos or blastocysts, all of which were utilizable embryos. Exclusion criteria: ① Frozen embryo transfer; ② Cycles with cancelled embryo transfer; ③ Patients undergoing preimplantation genetic testing; ④ Cycles involving donor oocytes, cryopreserved oocytes, or oocyte retrieval failure; ⑤ Incomplete clinical data. As shown in Figure 1. All clinical data were extracted from the dedicated patient database of our center's reproductive medicine department before the patients entered the

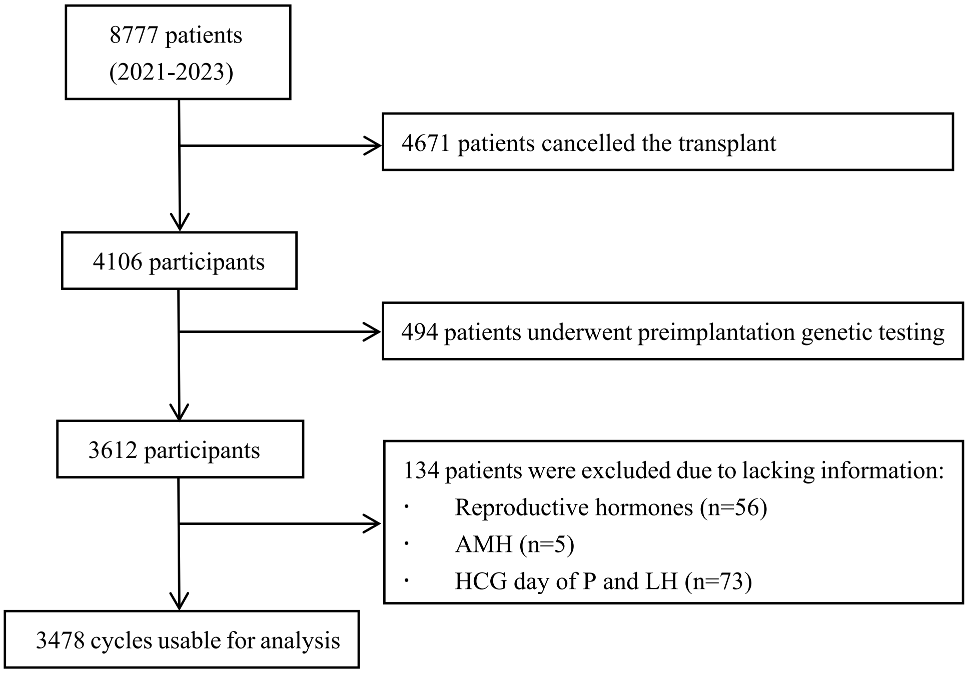


Figure 1 Flow chart of patients included in this study.
Abbreviations: AMH, anti-Müllerian hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; P, progesterone.

IVF/ICSI treatment cycle. This study was approved by the Ethics Committee of Women and Children's Hospital, Qingdao University (Approval number: QFELL-YJ-2023-120), and informed patient consent was waived due to its retrospective design.

IVF Procedure

In general, a complete IVF cycle comprises the following four steps: controlled ovarian stimulation, oocyte retrieval, embryo transfer, and pregnancy testing. The patient's ovarian reserve is first assessed to determine an optimal ovarian stimulation protocol. Commonly adopted protocols include gonadotropin-releasing hormone antagonist and agonist regimens, natural cycles, and other stimulation strategies (eg, luteal phase stimulation and direct stimulation protocols). When three or more dominant follicles with a mean diameter of ≥18 mm were identified, recombinant human chorionic gonadotropin (hCG) was administered to trigger final oocyte maturation. At 34–36 hours post-hCG administration, transvaginal ultrasound-guided oocyte retrieval was performed, and luteal phase support was subsequently initiated. IVF/ICSI was subsequently performed following clinical indications and sperm quality parameters, in accordance with the "Expert Consensus on Quality Control of Key Indicators in the Embryology Laboratory".[14] On post-oocyte retrieval Day 3 or Day 5, one or two embryos were transferred to the uterine cavity following morphological assessment. For Day 3 embryos, those with 7–9 blastomeres, uniform blastomere size, <10% fragmentation, and the absence of multinucleation were defined as high-quality embryos. Biochemical pregnancy was defined as a serum β-hCG concentration >5 mIU/mL on day 14 post-embryo transfer. Supernumerary embryos were cryopreserved for subsequent frozen embryo transfer. Clinical pregnancy was diagnosed as the visualization of a gestational sac via transvaginal ultrasound on day 35 post-embryo transfer, whereas ectopic pregnancy was defined as an ultrasound-confirmed gestational sac located outside the uterine cavity.

Assessment of Exposure to Ambient Air Pollutants

Six ambient air pollutants were included in the present study, namely fine $PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, and O_3. The concentration monitoring data of all air pollutants were officially obtained from the China National Air Quality Online Monitoring and Analysis Platform and the Qingdao Ecological and Agrometeorological Center. A total of 12 national controlled ambient air quality monitoring stations were enrolled for data collection, which comprehensively covered the medical treatment and residential areas of the study participants, including the main urban districts (Shinan District, Shibei District, Licang District, Laoshan District, Chengyang District, Huangdao District) and key functional zones (Jimo District, Jiaozhou City) of Qingdao city. All the above monitoring stations implemented continuous real-time hourly monitoring for 24 hours a day. Daily average concentrations of $PM_{2.5}$, PM_{10}, CO, SO_2, and NO_2 were calculated as the arithmetic mean of 24-hour hourly monitoring data at each station. For O_3, the maximum 8-hour daily average concentration was used for analysis in line with universal atmospheric ozone assessment standards, accounting for its diurnal photochemical properties. All pollutant concentration data were quality-controlled, with invalid values excluded prior to statistical analysis.

Using these data, we calculated the 24-hour average concentrations of air pollutants ($PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, and O_3) for three exposure periods. As shown in Figure 2, the exposure windows were defined as follows: Period 1, from 90 days pre-oocyte retrieval to the day of oocyte retrieval; Period 2, from 90 days pre-oocyte retrieval to the day of β-hCG testing; Period 3, from 90 days pre-oocyte retrieval to the day of ultrasound-confirmed clinical pregnancy.

Concomitant Variables

Potential risk factors influencing the pregnancy outcomes of IVF/ICSI were identified as confounding factors based on previous studies[15,16] and biological plausibility. For period 1, covariates included female age, body mass index (BMI), ovarian stimulation protocol, gonadotropin dose, duration of gonadotropin administration, anti-Müllerian hormone (AMH). For periods 2 and 3, covariates included female age, BMI, ovarian stimulation protocol, gonadotropin dose, duration of gonadotropin administration, AMH, number of embryos transferred, fertilization method, transferred embryo type, endometrial thickness on the day of embryo transfer, and the number of high-quality Day 3 embryos.

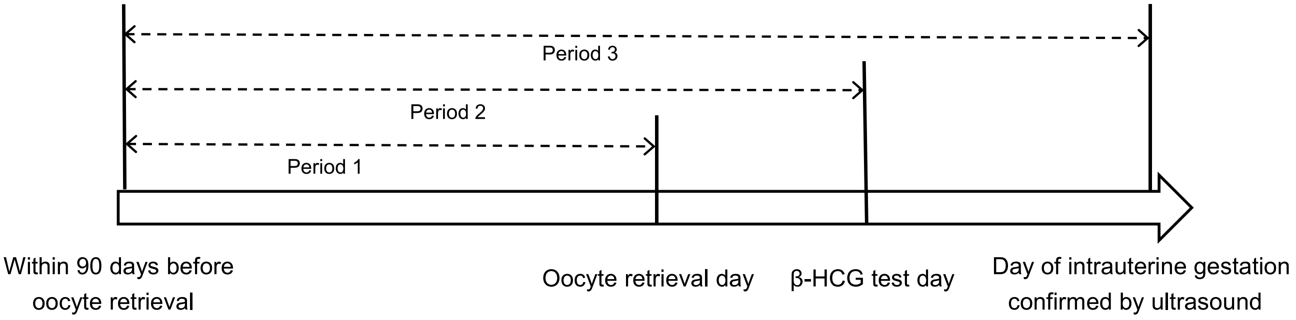


Figure 2 Timeline of IVF/ICSI stages defined for this study.
Abbreviations: ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; β-hCG, β-human chorionic gonadotropin.

Statistical Analysis

Normality was tested using the Kolmogorov–Smirnov test. Normally distributed data were reported as mean ± standard deviation (SD), and categorical variables as proportions or percentages (%). Ambient air pollutant concentrations across the three exposure periods were expressed as medians and interquartile ratio (IQR). Spearman correlation analysis was used to assess the exposure intensity of six air pollutants. A generalized linear model was employed to examine the associations between exposure to air pollutants and the number of oocytes obtained, number of metaphase II (MII) oocytes, fertilization rate (FR), cleavage rate (CR) and Day 3 high-quality embryo rate. The association between ambient air pollution and pregnancy onset (defined as pregnancy occurrence: 0 = pregnant, 1 = non-pregnant) was investigated using binary logistic regression analysis. Results were expressed as odds ratios (OR) and 95% confidence intervals (CI). After adjustment, adjusted odds ratio (aOR) and 95% CI. All covariates included in the adjustment are detailed in the Covariates section.

To account for the combined impact of mixed ambient air pollutant exposure and mitigate the confounding impact of multicollinearity on regression estimates, we performed supplementary analyses using the weighted quantile sum (WQS) regression model. The WQS model generates a composite WQS index by weighting the quantile values of each pollutant by their respective estimated weights and summing the weighted values. This index ranges from 0 to 1, with higher values representing greater combined exposure to the pollutant mixture. The WQS model was constructed using the R package “gWQS” with pollutants categorized into quartiles for scoring. To estimate the weights, the data were split into training and validation sets, with 40% used for training and 60% for validation.

The Bayesian Kernel Machine Regression (BKMR) model was employed to investigate the individual effects of air pollutants, their overall combined exposure effect, and the potential nonlinear exposure-outcome relationships. Posterior inclusion probabilities (PIP) were used to estimate the significance of each pollutant in relation to the outcome, with a PIP value closer to 1 indicating a stronger impact on the outcome. Single-pollutant exposure effects were analyzed by holding other components at the 25th, 50th and 75th percentiles, while concentration-response curves for each individual pollutant were plotted by fixing the other components at the 50th percentile.

Finally, stratified analysis was conducted to evaluate the effects of ambient air pollutants in different sensitive subgroups: age (<35 years vs. ≥35 years) and the number of retrieved oocytes (<7 vs. ≥7).

Statistical analyses were performed using SPSS 27.0 and R language 4.2.2. A two-sided $p < 0.05$ was deemed statistically significant. For missing data, the multiple imputation method was used to analyze the filled data.

Results

Participants Characteristics

In this study, we evaluated 3478 patients who underwent fresh embryo transfer. The detailed characteristics of the study population show in Table 1. The mean age of the participants was 33.60±4.63 years, mean BMI was 23.21±3.30 kg/m^2, and the mean duration of infertility was 3.50±2.59 years. The results revealed a biochemical pregnancy rate (BPR) of 60.44% (2094/3478) and a CPR of 53.34% (1855/3478). The FR was 62.45% (17,230/27,590) for IVF and 70.81% (4630/6539) for ICSI, respectively. The CR and Day 3 high-quality embryo rate were 96.01% (20,988/21,860) and 52.91% (11,566/21,860), respectively (Table S1).

Table 1 Baseline Characteristics of 3478 Infertility Patients Undergoing Fresh Embryo Transfer ART Cycles

Characteristic	Clinical Pregnancy (N=1855)	Non- Pregnancy (N=1623)	Total (N=3478)	Z/χ^2	p-value
Female age (years)[a]	32.65±4.08	34.71±4.97	33.61±4.63	−11.599	<0.001
<35	1287 (69.4)	869 (53.5%)	2156 (62.0%)		<0.001
≥35	568 (30.6%)	754 (46.5%)	1322 (38.0%)		<0.001
Duration of infertility (years)[a]	3.43±2.52	3.58±2.65	3.50±2.59	−1.559	0.119
BMI (kg/m^2)[a]	23.30±3.28	23.12±3.31	23.21±3.30	−1.635	0.102
Type of infertility[b]				21.630	<0.001
Primary infertility	1064 (57.4%)	803 (49.5%)	1867 (53.7%)		
Secondary infertility	791 (42.6%)	820 (50.5%)	1611 (46.3%)		
Reproductive hormones[a]					
FSH (mIU/ mL)	6.77±2.66	7.22±3.09	6.98±2.88	−4.107	<0.001
LH (mIU/ mL)	5.61±4.35	5.52±3.72	5.57±4.07	−0.833	0.405
E_2 (pg/ mL)	178.31±324.72	200.59±441.41	188.71±383.72	−2.700	0.007
P (mIU/ mL)	1.41±4.88	1.48±4.92	1.45±4.90	−0.556	0.578
AMH (ng/ mL)[a]	3.47±2.71	3.00±2.55	3.25±2.64	−7.197	<0.001
AFC counts (n)[a]	15.47±9.99	13.16±9.35	14.39±9.76	−8.046	<0.001
Ovarian stimulation protocol[b]				38.816	<0.001
GnRH agonist	288 (15.5%)	217 (13.4%)	505 (13.5%)		
GnRH antagonist	1547 (83.4%)	1337 (82.4%)	2884 (82.9%)		
Natural cycles	6 (0.3%)	35 (2.2%)	41 (1.2%)		
Other protocols	14 (0.8%)	34 (2.1%)	48 (1.4%)		
Dosage of gonadotropic (U)[a]	2247.43±756.37	2256.00±833.25	2251.43±793.07	−1.567	0.117
Duration of gonadotropin administration (days)[b]	9.16±1.71	8.83±2.17	9.01±1.94	−3.314	<0.001
HCG Day of LH	3.65±3.36	4.17±5.31	3.89±4.39	−2.857	0.004
HCG Day of E_2	6957.16±3836.88	6507.34±4028.84	6747.25±3933.47	−4.468	<0.001
HCG Day of P	1.90±0.97	1.95±1.09	1.92±1.03	−0.338	0.736
Endometrial thickness (mm)[a]	10.30±1.59	9.97±1.62	10.15±1.61	−6.221	<0.001
Day 3 number of high-quality embryos[a]	3.54±2.40	3.08±2.48	3.33±2.45	−7.286	<0.001
Number of high-quality blastocysts[a]	1.03±1.65	0.89±1.58	0.97±1.62	−3.434	<0.001
Number of embryos transferred[b]				90.289	<0.001
1	530 (28.6%)	715 (44.1%)	1245 (35.8%)		
2	1325 (71.4%)	908 (55.9%)	2233 (64.2%)		
Fertilization method[b]				0.996	0.318
IVF	1451 (78.2%)	1292 (79.6%)	2743 (78.9%)		
ICSI	404 (21.8%)	331 (20.4%)	735 (21.1%)		
Type of embryos transferred[b]				0.561	0.454
Embryo	1528 (82.4%)	1321 (81.4%)	2849 (81.9%)		
Blastocyst	327 (17.6%)	302 (18.6%)	629 (18.1%)		

Notes:[a]Data are given in mean ± SD.[b]Data are given in numbers (%).

Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; E_2, estradiol; FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; HCG, human chorionic gonadotropin; HRT, hormone replacement therapy; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; LH, luteinizing hormone; P, progesterone.

The Independent Influence of Individual Air Pollutants on Pregnancy Outcomes

We first calculated the average daily concentrations of six ambient air pollutants across the three exposure periods, as shown in Table 2. In period 2, the mean exposure concentrations were as follows: $PM_{2.5}$ 26.64 ± 9.96 μg/m^3, PM_{10} 54.64 ± 19.73 μg/m^3, CO 0.59 ± 0.13 mg/m^3, SO_2 7.59 ± 1.56 μg/m^3, NO_2 28.52 ± 7.97 μg/m^3, and O_3 104.34 ± 19.86 μg/m^3. During these exposure periods, the average daily levels of $PM_{2.5}$, PM_{10}, NO_2 and O_3 all exceeded the 2021 World Health Organization Air Quality Guidelines recommendations.[17]

Correlation analysis revealed a robust correlation between $PM_{2.5}$ and SO_2 (r = 0.96), $PM_{2.5}$ and PM_{10} (r = 0.95), NO_2 and SO_2 (r = 0.95), CO and SO_2 (r = 0.94), $PM_{2.5}$ and NO_2 (r = 0.93), $PM_{2.5}$ and CO (r = 0.89), PM_{10} and SO_2 (r = 0.87), and PM_{10} and CO (r = 0.80) in period 1 (all $p < 0.001$) (Figure S1). A strong correlation was additionally noted between these eight exposures in during both period 2 and period 3 (Figures S2 and S3).

We analyzed the effects of exposure to ambient air pollutants on the quality of oocytes and embryonic development during period 1. Our study found that exposure to ambient air pollutants $PM_{2.5}$ and NO_2 was significantly associated with reduced

Table 2 The Exposure Concentrations of Environmental Air Pollution in Period 1, Period 2 and Period 3

Air Pollutants	Mean	SD	Min	25%	Median	75%	Max	IQR
$PM_{2.5}$ (μg/m^3)								
Period 1	26.69	10.46	13.52	17.34	23.73	35.2	51.28	17.86
Period 2	26.64	9.96	13.89	17.48	24.07	35.15	48.58	17.67
Period 3	26.66	9.34	13.81	18.27	24.34	34.60	46.02	16.34
PM_{10} (μg/m^3)								
Period 1	54.75	20.72	26.3	36.11	50.7	71.9	97.89	35.79
Period 2	54.64	19.73	27.22	36.67	51.11	71.12	98.2	34.45
Period 3	54.53	18.43	27.65	37.59	52.68	69.13	96.94	31.54
CO (mg/m^3)								
Period 1	0.59	0.14	0.4	0.51	0.55	0.68	0.96	0.17
Period 2	0.59	0.13	0.41	0.5	0.56	0.68	0.91	0.18
Period 3	0.60	0.12	0.41	0.51	0.57	0.69	0.87	0.18
SO_2 (μg/m^3)								
Period 1	7.61	1.67	5.46	6.37	7.01	8.52	12.94	2.15
Period 2	7.59	1.56	5.45	6.43	7.12	8.5	12.05	2.07
Period 3	7.58	1.43	5.57	6.50	7.17	8.57	11.56	2.07
NO_2 (μg/m^3)								
Period 1	28.56	8.38	16.07	20.86	28.22	34.59	47.24	13.73
Period 2	28.52	7.97	16.73	21.04	28.53	34.43	46.51	13.39
Period 3	28.49	7.42	17.53	21.44	28.06	34.51	45.22	13.07
O_3 (μg/m^3)								
Period 1	104.30	20.97	56.42	88.52	111.68	120.51	138.14	31.99
Period 2	104.34	19.86	60.2	88.53	110.76	119.76	134.42	31.23
Period 3	104.34	18.64	64.12	88.60	109.16	118.06	132.42	29.46

Notes: Period 1, the average pollutant concentration from 90 days before oocyte retrieval to the day of oocyte retrieval. Period 2, the average pollutant concentration from 90 days before oocyte retrieval to the day of HCG testing day. Period 3, the average pollutant concentration from 90 days before oocyte retrieval to the day of ultrasound-confirmed clinical pregnancy.

Abbreviations: $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm; CO, carbon monoxide; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone.

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numbers of oocytes retrieved and MII oocytes. In the crude model, the reduced of oocyte and MII oocyte counts was 0.008%, 0.007%, 0.027% and 0.025% per IQR elevation in $PM_{2.5}$ (OR = 0.992, 95% CI = 0.986–0.999) and (OR = 0.973, 95% CI = 0.965–0.980), and NO_2 (OR = 0.993, 95% CI = 0.989–0.997) and (OR = 0.975, 95% CI = 0.971–0.980), respectively. However, the number of MII oocytes was reduced by 0.156% (OR = 0.844, 95% CI = 0.772–0.923) and 0.07% (OR = 0.930, 95% CI = 0.903–0.957) per IQR increase in CO and SO_2 exposure (Figure 3a). After adjusting for covariates, $PM_{2.5}$ (aOR = 0.982, 95% CI = 0.97–0.99) and (aOR = 0.992, 95% CI = 0.99–1.00), and NO_2 (aOR =0.963, 95% CI =0.95–0.97) and (aOR = 0.975, 95% CI = 0.97–0.98) continued to display negative correlations with the number of oocytes obtained and MII oocytes, respectively. Per IQR increase in CO (aOR = 0.853, 95% CI = 0.78–0.93) and SO_2 (aOR = 0.932, 95% CI = 0.97–0.98) exposure, a significant negative association with the number of MII oocytes, respectively (Figure 3b). Before adjusting for covariates, generalized linear regression analysis showed that per IQR increase in CO concentration was positively correlated with reductions in CR (OR = 1.178, 95% CI = 1.034–1.580) and Day 3 high-quality embryo rate (OR = 1.457, 95% CI = 1.050–2.021), respectively (Figure 3c). After covariate adjustment, elevated CO concentration remained significantly positively associated with reductions in CR (aOR = 1.293, 95% CI = 1.048–1.594) and Day 3 high-quality embryo rate

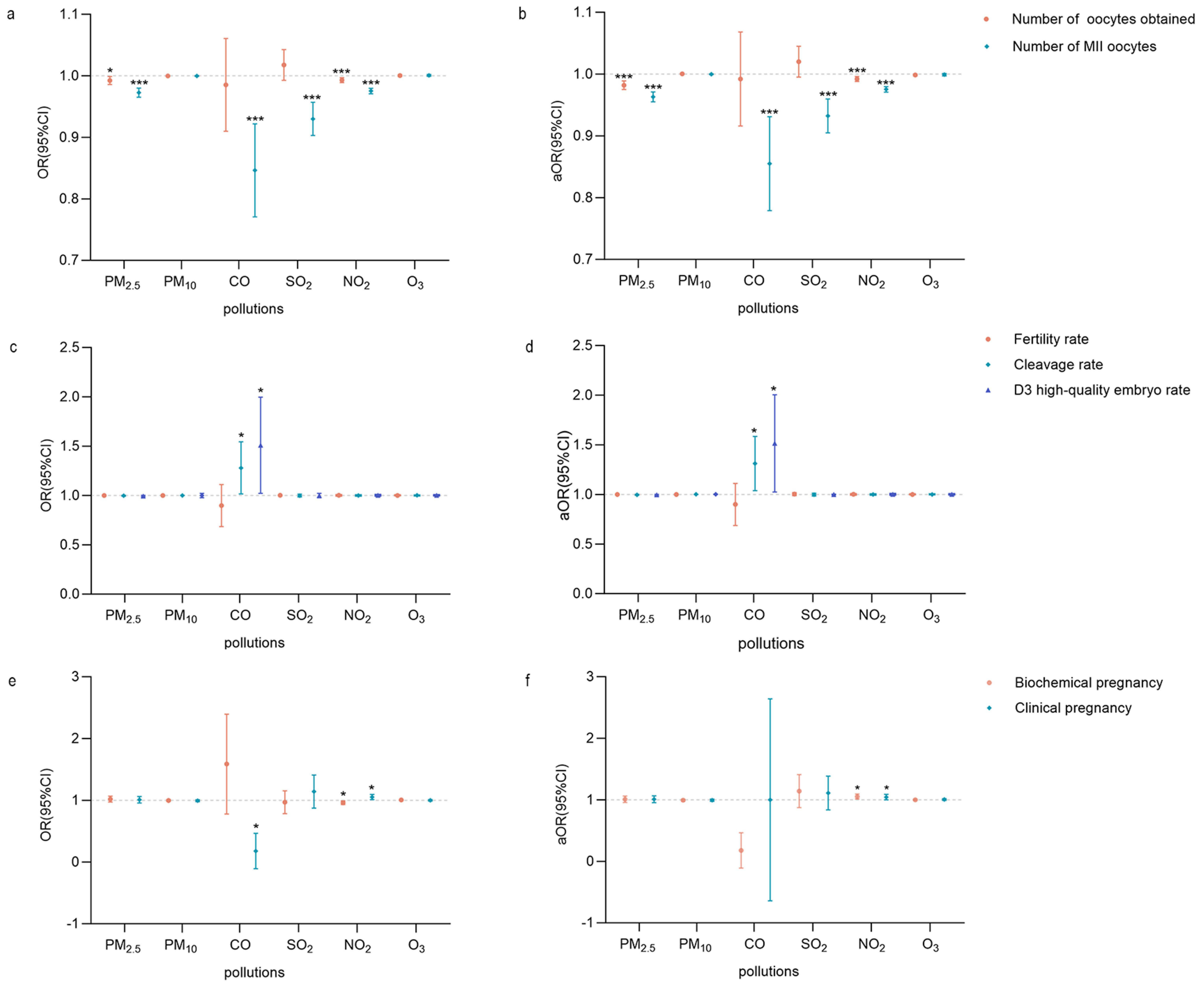

Figure 3 Associations between ambient air pollution exposure and pregnancy outcome, the quality of ovum and embryonic development. (**a, c** and **e**) The effects of air pollutants on oocyte quality, embryonic development and pregnancy outcomes before adjusting for covariates. (**b** and **d**) Adjusted covariates for female age, BMI, AMH, ovarian stimulation protocol, dosage of gonadotropic, duration of gonadotropic use. (**f**) Adjusted covariates for female age, BMI, AMH, ovarian stimulation protocol, dosage of gonadotropic, duration of gonadotropic use, endometrial thickness, Day 3 number of high-quality embryos, number of high-quality blastocysts, number of embryos transferred, fertilization method, type of embryos transferred. * $p < 0.05$, *** $p < 0.001$.

Abbreviations: AMH, anti-Müllerian hormone; aOR, adjusted odds ratios; BMI, body mass index; 95% CI, 95% confidence intervals.

(aOR = 1.462, 95% CI = 1.054–2.028), respectively. However, no significant correlation was observed between air pollutant exposure and the FR (Figure 3d).

In the crude model, elevated NO_2 concentration was negatively associated with BPR (OR= 0.961, 95% CI = 0.932–0.991) in period 2 (Figure 3e). After covariate adjustment, NO_2 exposure remained significantly negatively associated with BPR (aOR = 0.967, 95% CI = 0.935–0.999) in period 2 (Figure 3f). In the crude model, CPR was negatively associated with CO (OR = 0.022, 95% CI = 0.001–0.508) but positively associated with NO_2 (OR = 1.053, 95% CI = 1.011–1.096) in period 3 (Figure 3e). After covariate adjustment, CPR was probability associated only with NO_2 (aOR = 1.044, 95% CI = 1.001–1.088) (Figure 3f). Collectively, our findings indicated that NO_2 exposure was significantly associated with a reduced likelihood of a successful pregnancy during IVF/ICSI fresh embryo transfer cycles.

The Mixed Effects of Ambient Air Exposure and WQS on Component Weighting

The WQS regression model is more sensitive in screening pollutants associated with ART pregnancy outcomes. It can quantitatively reflect the weight of harmful effects of mixed pollutant exposure associated with ART pregnancy outcomes. Based on weighted quantile sum regression, we constructed a weighted mixture exposure index using weighted percentiles for predicting reproductive system outcomes. Since all exposures were associated with effects in the same direction, we created two types of weighted mixture exposure indices: positive and negative. After adjusting for all covariates, WQS index was negatively associated with the number of MII oocytes (aOR = 0.916, 95% CI = 0.857–0.978) in period 1. In the mixture effect, the pollutant with the greatest weight was NO_2 (90.1%), as delineated in Figure 4b, PM_{10}, SO_2 and O_3 had the lowest weights (nearly 0). WQS index showed that air pollutants were not associated with the number of oocytes retrieved, FR, CR and Day 3 high-quality embryo rate (Figure 4a and Figure 4c–e). Moreover, WQS index was also not associated with pregnancy outcomes after embryo transfer cycles in patients undergoing IVF/ICSI treatment across period 2 and period 3 (Figure 4f and g).

BKMR Model to Assess the Effects of Pollutants on the Reproductive System

The Gaussian prediction process in the BKMR model was used to analyze 3478 participants in the fresh embryo transfer population. The overall mixture effect showed no discernible trend in the association between air pollutants and the number of MII oocytes in period 1 (Figure 5a). The single-pollutant effects exhibited no significant association between air pollutants and the number of MII oocytes (Figure S4). Based on the PIP values used to identify significant variables,

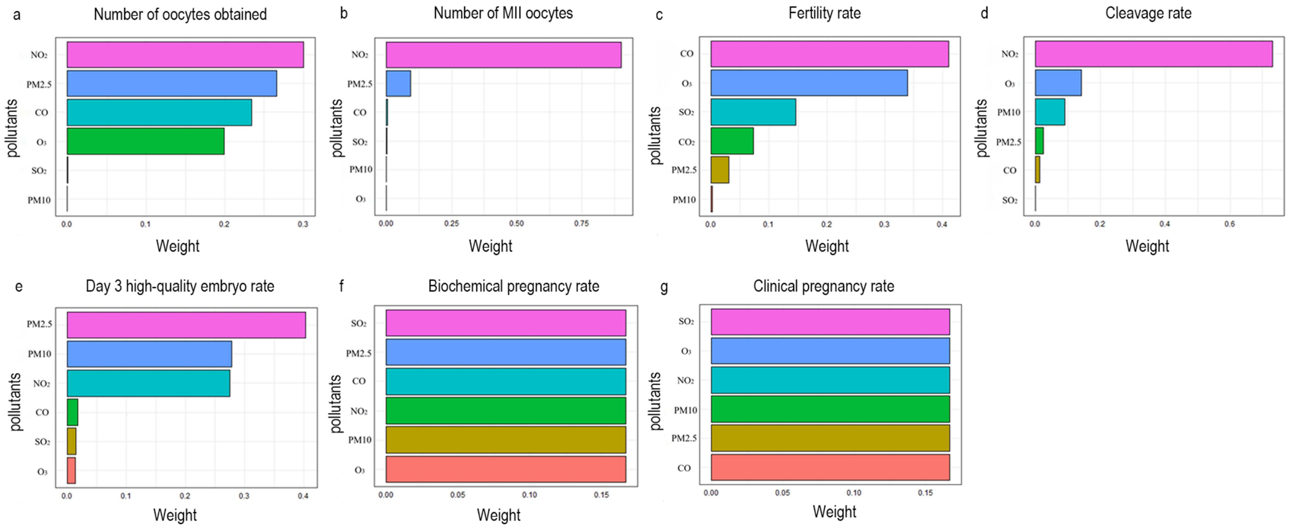

Figure 4 The impact of the WQS model on six pollutants. (**a** and **b**) Mixed effects of the adjusted WQS model on individual pollutant weights for oocyte quality. (**c–e**) Mixed effects of adjusted WQS models on embryo development individual pollutant weights. (**f** and **g**) Mixed effects of the adjusted WQS model on pregnancy rate with individual pollutant weights.

Abbreviation: WQS, weighted quantile sum.

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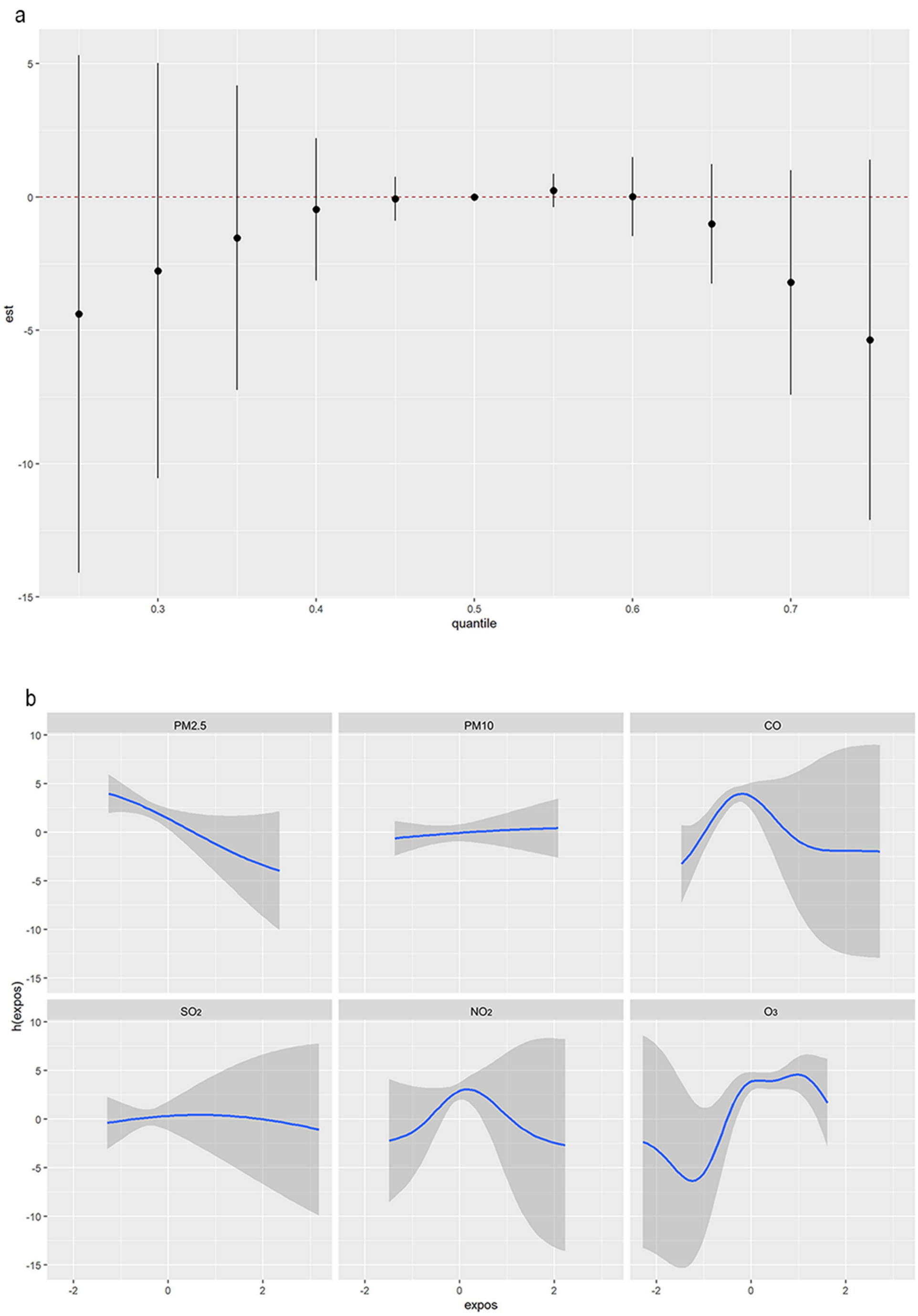

Figure 5 Joint effect of mixture on MII oocyte count (95% CI) and univariate exposure-response function for BKMR modeling. (**a**) Joint effect on MII oocyte count of all pollutants at particular percentiles compared to pollutants at their 50th percentile. (**b**) Univariate effect on MII oocyte count exposure–response function while fixing the concentrations of other pollutants at median values.

Note: est, estimate, representing the magnitude of the association between air pollutant exposure and MII oocyte count in the BKMR model.

Abbreviations: BKMR, bayesian kernel machine regression; MII, metaphase II.

the results showed that $PM_{2.5}$ (PIP = 1.00), CO (PIP = 1.00), SO_2 (PIP = 1.00), O_3 (PIP = 1.00), and NO_2 (PIP = 0.97) were the key variables associated with the number of MII oocytes (Figure S5). Concentration-response curves for individual pollutants showed a negative association between $PM_{2.5}$ and the number of MII oocytes, while CO and NO_2 exhibited an inverted U-shape association with the number of MII oocytes, and O_3 showed a non-linear association with the number of MII oocytes, with all other pollutants fixed at their median concentration (Figure 5b). In period 1, the overall effect analysis indicated a positive combined effect of ambient air pollutants on the number of oocytes retrieved, with the 50th percentile as the reference. This suggests an upward trend in the number of retrieved oocytes, although the difference did not reach statistical significance (Figure S6). The single-pollutant effects showed that SO_2 and $PM_{2.5}$ were negatively associated with the number of obtained oocytes (Figure S7). Concentration-response curve for individual pollutants indicated that SO_2 was positively associated with the number of obtained oocytes, while $PM_{2.5}$ was negatively associated with the number of obtained oocytes (Figure S8).

The overall mixed effect from the period 2 analysis showed that the estimated effect size was higher at 35% mixed concentration of ambient air pollutants than at 50% mixture concentration, accompanied by a significant decrease in BPR. With increasing percentile exposure concentrations, BPR decreased and tended to stable (Figure 6a). Figure S5

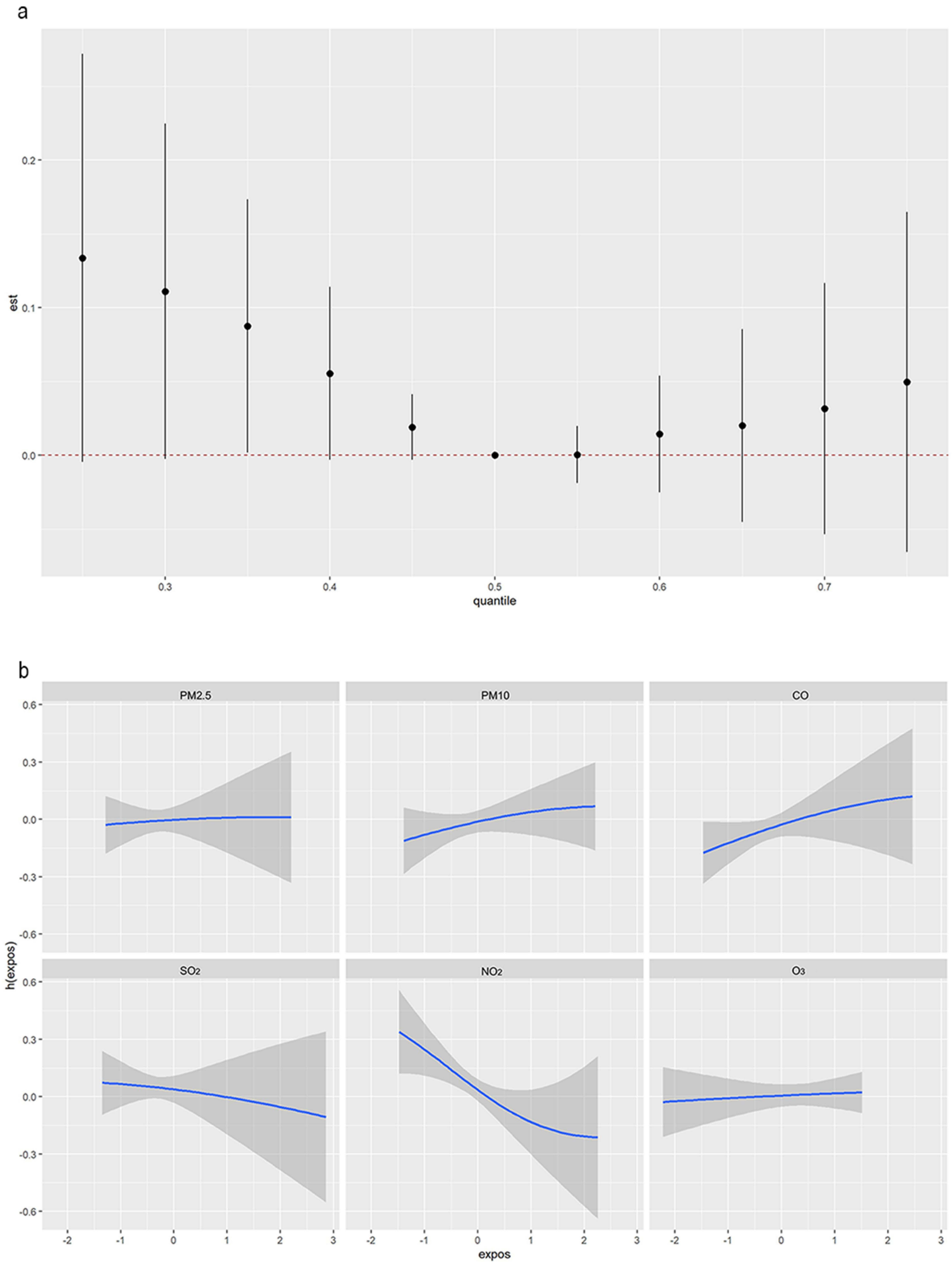

Figure 6 Joint effect of mixture on BPR (95% CI) and univariate exposure-response function for BKMR modeling. (**a**) Joint effect on BPR of all pollutants at particular percentiles compared to pollutants at their 50th percentile. (**b**) Univariate effect on BPR exposure–response function while fixing the concentrations of other pollutants at median values.

Abbreviations: BKMR, bayesian kernel machine regression; BPR, biochemical pregnancy rate; est, estimate.

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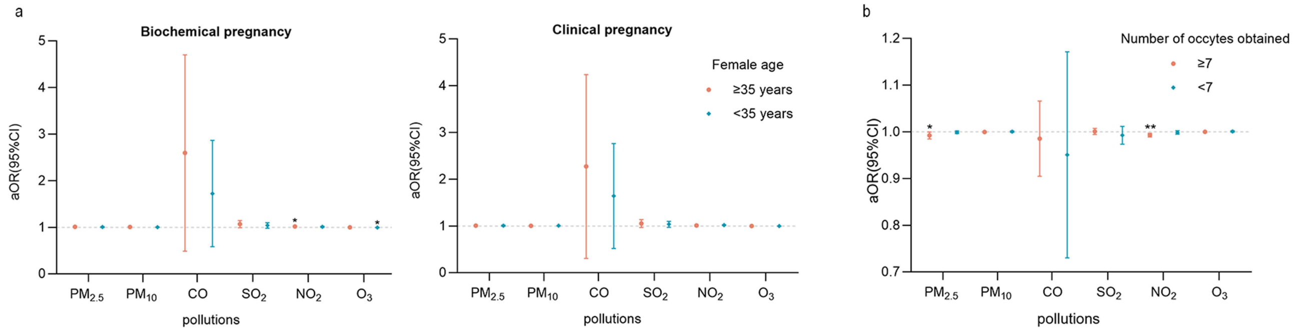

Figure 7 Stratified analysis to evaluate sensitive population. (**a**) Relationship between air pollutants and female age. Adjusted covariates for female age, BMI, AMH, ovarian stimulation protocol, dosage of gonadotropic, duration of gonadotropic use, endometrial thickness, Day 3 number of high-quality embryos, number of high-quality blastocysts, number of embryos transferred, fertilization method, type of embryos transferred. (**b**) Relationship between air pollutants and the number of oocytes obtained. Adjusted covariates for female age, BMI, AMH, ovarian stimulation protocol, dosage of gonadotropic, duration of gonadotropic use. *$p < 0.05$, **$p < 0.01$.
Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index.

shows that NO_2 (PIP = 1.00) played a leading role in the overall population mixing effect. Individual NO_2 exposure exhibited a negative association with BPR: the estimated effect size decreased from 25% to 50%, although the overall inhibitory effect remained significant (Figure S9). Concentration-response curves for single pollutants showed that NO_2 was negatively associated with BPR (Figure 6b). No significant association was found between pollutant exposure and CPR in the overall mixed effects, single-pollutant exposure, or concentration-response curve for individual pollutants during period 3 (Figures S10–S12).

Stratified Analysis to Evaluate Sensitive Population

Stratified analysis by female age showed that exposure to NO_2 and O_3 was associated with an increased risk of reduced biochemical pregnancy rates in both age groups (Figure 7a). Females aged ≥35 had increased sensitivity to NO_2 (aOR = 1.017, 95% CI: 1.002–1.031), while females aged <35 were more sensitive to O_3(aOR = 0.995, 95% CI: 0.991–1.000). Stratified analysis by the number of oocytes retrieved showed that participants with ≥7 oocytes were more sensitive to $PM_{2.5}$(aOR = 0.992, 95% CI: 0.985–1.000) and NO_2 (aOR = 0.993, 95% CI: 0.989–1.001), while no significant effect was observed among those with <7 oocytes (Figure 7b).

Discussion

This study demonstrates that female exposure to common air pollutants impacts their pregnancy outcomes in Qingdao. High NO_2 levels during fresh IVF/ICSI cycles could significantly increase the risk of adverse pregnancy outcomes, a finding consistent with the Shanghai report. NO_2 exposure was significantly negatively correlated with the biochemical pregnancy rate (aOR=0.86, 95% CI: 0.75–0.99).[18] Notably, women aged ≥35 years and those with ≥7 oocytes retrieved were more vulnerable to NO_2, while younger patients (<35 years) were more sensitive to O_3. These results suggest heterogeneity in the effects of air pollution on ART outcomes.

The BPR and CPR observed in this study were 60.44% and 53.34%, respectively. Previous studies have reported a relatively high BPR (66.5%) in the Yangtze River Delta region[19] and a relatively low CPR (43.9%) in the United States.[11] As the birthplace of ART, the United States is among the countries with the earliest development and most mature clinical application of ART worldwide. Its ART technologies have advanced rapidly since the birth of the first test-tube baby in the 1970s, with the standardized application of core technologies including ovulation induction, embryo culture and transfer leading the international forefront. Additionally, most ART research in the US is based on large-sample, multi-center long-term follow-up with more extensive inclusion criteria for study populations, yet the technical protocols of its research period have certain generational differences from the current mainstream ART protocols in China. In summary, clinical factors such as the age, BMI, controlled ovarian stimulation protocols, embryo transfer types and sample size of study populations, as well as disparities in the developmental stages of ART technologies, the maturity of clinically applied technologies and protocol differences across research periods among various countries, are all important reasons for the variations in research results worldwide.

$PM_{2.5}$ and PM_{10} are fine atmospheric particulate matter that pose a serious threat to human health. These particles adsorb toxic compounds (eg, polycyclic aromatic hydrocarbons, heavy metals) and induce ovarian oxidative stress and inflammation, which may directly damage the ovaries and the female reproductive system.[20,21] In agreement with Conforti et al,[22] we observed reduced oocyte quantity and quality after $PM_{2.5}$ exposure, and this effect was more severe in women with ≥7 oocytes retrieved. Animal studies have shown that $PM_{2.5}$ disrupts follicle development, reduces oocyte quality, and accumulates in ovarian tissue.[23] RNA sequencing further revealed that $PM_{2.5}$ exacerbates ovarian oxidative stress and inflammation via the NF-κB/IL-6 signaling pathway in mice.[24] Animal studies have further attributed fertility loss to ROS accumulation in oocytes and dysregulation of embryonic metabolism.[25]

NO_2 and O_3 as oxidative gaseous pollutants, exert oxidative capacity that induces cellular damage and elevates the risk of cardiovascular and respiratory mortality.[26,27] In recent years, its reproductive toxicity has also attracted increasing attention. A study in Shanghai found that NO_2 exposure during the early stages of pregnancy increases the risk of miscarriage (OR=1.68, 95% CI: 1.28–2.21).[28] Numerous clinical studies have confirmed that NO_2 exposure leads to adverse pregnancy outcomes (such as spontaneous abortion, low live birth rate, and fetal growth restriction) and is one of the risk factors.[7,11,29] Our study confirms previous findings and further demonstrates that NO_2 exposure exerts a more significant impact on adverse pregnancy outcomes in women aged ≥35. The main reason for this is that patients may be exposed to higher concentrations and for longer durations of pollution related to commuting. Previously, a study conducted in Chengdu, China, explored the relationship between ambient air pollutant exposure and IVF pregnancy outcomes. The results indicated that the concentrations of ambient air pollutants such as NO_2 were significantly negatively associated with the odds of biochemical pregnancy and clinical pregnancy,[30] this conclusion is consistent with the findings of our study.

On the other hand, females aged <35 were more sensitive to O_3. Multiple studies have reported an inverse association between O_3 exposure and adverse pregnancy outcomes,[8,31] which is highly consistent with the results of our stratified analysis. Animal experiments have shown that O_3 can induce oxidative stress. Long-term exposure to moderate levels of O_3 can lead to decreased follicle quality and progesterone levels, thereby impairing fertility.[32–34] Oocytes and embryos of women aged <35 are metabolically active with high mitochondrial activity, making them major producers of reactive oxygen species. As a potent oxidant, O_3 further induces oxidative stress, disrupting the "oxidation-antioxidation" balance. Meanwhile, their hypothalamic-pituitary-ovarian axis is precisely regulated, with superior reproductive hormone levels, a more robust immune system, and higher activity of implantation-related immune cells. However, this also renders them more sensitive to the endocrine disturbances caused by O_3, more prone to inducing inflammatory responses, interfering with immune tolerance mechanisms, and thereby hindering successful embryo implantation.[35,36]

In the atmosphere, SO_2 is oxidized to sulfuric acid mist and sulfate aerosols, acting as a major precursor of environmental acidification. SO_2 has been identified as a risk factor for preterm birth in pregnant women. It can cause premature birth in a dose-dependent manner. For every 100 $\mu g \cdot m^3$ increase in SO_2 concentration, pregnancy period shortens by approximately 0.75 weeks (12.6 h),[37] and SO_2 exposure also leads to low birth weight in newborns.[38,39] Huang et al[40] showed that the population attributable fraction of SO_2 exposure on live birth rate, biochemical pregnancy rate, and clinical pregnancy rate were 10.30% (95% CI: 3.09%, 17.00%), 10.20% (95% CI: 4.46%, 16.00%), and 10.30% (95% CI: 3.65%, 18.70%), suggesting that about 10% of adverse outcomes of ART pregnancies could be attributed to SO_2 exposure in the ART study population. The reproductive toxicity of air pollutants in ART population was further verified. Male exposure to CO 90 days prior to sperm retrieval increased the number of morphologically abnormal sperm and reduced testosterone levels.[41] Interestingly, we observed a positive association between CO and embryonic development indicators, a finding that warrants further mechanistic exploration.

The innovation and advantages of our research are mainly reflected in the following four aspects: First, the research area is unique. It is based on the coastal city of Qingdao, which has a temperate maritime monsoon climate in the north. This is the first time to explore the correlation between air pollution and ART outcomes under this climate background, filling the empirical gap in coastal areas and providing regional references for the study of air pollution reproductive toxicity in different geographical and climatic regions. Second, the in-depth subgroup analysis is the first to identify heterogeneous sensitivity to air pollution exposure in the ART population, clarifying differential pollutant susceptibility among women of different ages and with varying retrieved oocyte numbers, and providing a specific clinical basis for individualized protective strategies. Third, the research indicators are more targeted. It breaks through the limitation of most studies that only focus on pregnancy outcomes, systematically analyzing the impact of air pollution on the early stages of ART oocytes-embryo, supplementing key toxic evidence, and improving the chain of adverse outcome effects. Fourth, the analysis methods are comprehensive and advanced. It integrates multiple models to analyze the effects of single and mixed pollutants, clarifies the dominant role of NO_2, and through large sample stratified analysis, locks in sensitive populations, enhancing the reliability of the conclusion, and providing methodological references for similar studies.

Our study has several limitations. First, as a retrospective cohort study, it is susceptible to data quality issues and bias, although we excluded incomplete and inaccurate data. Second, exposure data for ambient air pollutants were obtained from air quality monitoring stations, and exposure heterogeneity may exist. Although we estimated each participant's average exposure over three periods (period 1: 90 days before oocyte retrieval until the day of retrieval; period 2: 90 days before oocyte retrieval until the day of hCG trigger; period 3: 90 days before oocyte retrieval until ultrasound-confirmed pregnancy), this approach may not accurately reflect individual-level exposure to air pollution. Finally, we did not account for other confounding factors, such as occupation, education level, home and work environments (eg, smoking or secondhand smoke exposure), and household fuel use, which may lead to biased or imprecise effect estimates. Future studies employing prospective cohorts with detailed information on these confounders are warranted to validate our findings.

From the perspective of public health strategy and policy intervention, our study has important guiding significance, and its social and policy implications are critical for human development, which warrants urgent attention. In clinical practice, ART centers should incorporate air pollution into their diagnosis and treatment evaluation system, which is not only a requirement for medical quality, but also a fundamental guarantee for patients' reproductive rights. More attention should be paid to susceptible populations such as those aged ≥35 years or with oocytes retrieved ≥7. Treatment strategies should be adjusted according to ambient air pollution levels. At the policy-making level, since NO_2 is mainly derived from vehicle emissions, urban traffic pollution control should be strengthened, such as optimizing public transportation and promoting new energy vehicles to reduce air pollutant concentrations. For $PM_{2.5}$, it is necessary to strengthen the control of industrial emissions and dust, especially in areas with a high density of ART clinics, and to incorporate reproductive health impacts into the development of air quality standards. At the public education and social participation level, it is necessary to dispel the misconception that "air pollution only affects respiratory health", and launch a universal campaign for reproductive health protection. Air pollution protection knowledge should be popularized among women undergoing ART, such as reducing outdoor activities on smoggy days and taking personal protection measures when traveling to and from the hospital; women undergoing ART should be listed as a key protected group; enterprises should implement flexible working arrangements, allowing them to work from home during pollution peak to reduce commuting exposure; meanwhile, attention should be paid to indoor air quality, and indoor air purification measures should be adopted to reduce exposure risks.

Conclusion

In conclusion, the study confirms the association between air pollution and pregnancy outcomes through a large sample ART cohort, filling the research gap in this field and providing novel insights for improving ART success rates and protecting reproductive health. Among women undergoing IVF/ICSI treatment, ambient exposure to NO_2 was associated with decreased pregnancy rates following ART. $PM_{2.5}$ and NO_2 exposure was negatively associated with decreased the number of oocytes and MII oocytes, after adjusting the covariates. Notably, CO and SO_2 exposure were inversely associated with the number of MII oocytes. CO exposure was significantly associated with decreased CR and day 3 high-quality embryo rates. The WQS index was negatively correlated with the number of MII oocytes. The concentration response curve of single pollutant in BKMR model showed that NO_2 was negatively correlated with BPR. Women aged ≥35 years exhibited greater susceptibility to NO_2 exposure, while those aged <35 years were more sensitive to O_3. Subgroups with ≥7 oocytes showed higher susceptibility to $PM_{2.5}$ and NO_2. Therefore, prospective studies are warranted to explore the underlying mechanisms and provide scientific evidence for the development of targeted reproductive health protection strategies and air pollution control policies.

Abbreviations

AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted reproductive technology; BKMR, Bayesian kernel machine regression; BMI, body mass index; BPR, biochemical pregnancy rate; CI, confidence intervals; CPR, clinical pregnancy rates; CR, cleavage rate; FR, fertilization rate; hCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; IQR, interquartile ratio; IVF, in vitro fertilization; MII, metaphase II; OR, odds ratios; PIP, posterior inclusion probabilities; SD, standard deviation; WQS, weighted quantile sum.

Data Sharing Statement

Data available from authors on request.

Ethics Approval and Written Informed Consent

This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the Women and Children's Hospital Affiliated to Qingdao University reviewed and proposed the use of human subjects in the above-mentioned study. The rights and the welfare of the participants were adequately protected. Owing to the retrospective design of this study, the patient-level data obtained do not require the patient's informed consent, the Ethics Committee of the Women and Children's Hospital Affiliated to Qingdao University waived the need for informed consent. We confirmed that all data were anonymized and kept confidentiality. The Ethics Committee of the Women and Children's Hospital Affiliated to Qingdao University has approved papers resulting from the project.

Consent for Publication

All authors agree to publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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