Association between ambient air pollution and in vitro fertilization pregnancy outcomes in Taiyuan: A retrospective study in a heavy polluted city in northern China

Suming Xu

Children's Hospital of Shanxi and Women Health Center of Shanxi <https://orcid.org/0000-0003-2916-6824>

Chunqing Sun

Shanxi Medical University

Xingyu Bi

Children's Hospital of Shanxi and Women Health Center of Shanxi

Dan Feng

Shanxi Medical University

Lei Zhang

Children's Hospital of Shanxi and Women Health Center of Shanxi

Chunfang Wang

Shanxi Medical University

Yaoqin Wang

Children's Hospital of Shanxi and Women Health Center of Shanxi

Xueqing Wu (✉ xueqingwu416@126.com)

Children's Hospital of Shanxi and Women Health Center of Shanxi <https://orcid.org/0000-0001-5044-9832>

Research

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Abstract

Background

Globally, air pollution has a significant impact on human health. However, the effects of air pollution on pregnancy outcomes in patients undergoing in vitro fertilization (IVF) have not been fully understood. In this study, we analyzed the effects of air pollution on IVF pregnancy outcomes in Taiyuan, which is a heavy polluted city in northern China.

Methods

516 patients who underwent first fresh IVF cycle were enrolled in the retrospective study from January 1, 2015 to May 31, 2020. We collected medical record data from the electronic medical record system and daily average air pollution data from air quality monitoring station. Logistic regression was used to analyze the relationship between six atmospheric pollutants ($PM_{2.5}$, PM_{10} , O_3 , NO_2 , SO_2 , CO) and air quality index (AQI) and IVF pregnancy outcomes (biochemical pregnancy and clinical pregnancy) in different exposure periods.

Results

The results indicated that exposure to NO_2 was negatively associated with the odds of biochemical pregnancy and clinical pregnancy, whereas exposure to O_3 presented positive association. Furthermore, we also found that AQI was negatively associated with IVF pregnancy outcomes.

Conclusions

Our findings suggested that exposure to ambient air pollution during any period may have an impact on IVF pregnancy outcomes, and poor air quality is more likely to reduce clinical pregnancy rates.

Introduction

With the rapid industrialization, urbanization and motorization, air pollution problems are becoming more and more serious, and the effect of air pollution on health has attracted more attention. Air pollutant is a complex mixture of gaseous components, solid and liquid suspended particles in the air [1], mainly includes particulate matter $\leq 10 \mu m$ in aerodynamic diameter (PM_{10}), particulate matter $\leq 2.5 \mu m$ in aerodynamic diameter ($PM_{2.5}$), sulfur dioxide (SO_2), carbon monoxide (CO), nitrogen dioxide (NO_2) and ozone (O_3). Several studies have shown that air pollution has a variety of negative effects on human health, such as cardiovascular diseases [2, 3], respiratory diseases [4, 5], type 2 diabetes mellitus [6], mental disease [7, 8], and so on. In recent years, more evidences showed that there was a correlation between ambient air pollution and human reproductive outcomes, such as infertility, preeclampsia, miscarriage and preterm delivery [9, 10].

Infertility is a global problem. It is reported that about 10% of the world's population are infertile [11]. Among couples of childbearing age in China, the incidence of infertility has reached 25%, and it is on the rise [12]. With the development of human assisted reproductive technology (ART), it has become an important mean for treatment of infertility. More than 7 million children have been born worldwide since 1978 using ART [13]. Previous studies had reported that both long-term and short-term exposure to air pollutants were associated with decreased probability of the rate of implantation, biochemical pregnancy, clinical pregnancy, and live birth [14–17]. However, the present results are inconsistent. Taiyuan is a typical resource-based city with high pollution, which is rich in coal resources. The relationship between air pollution and pregnancy outcomes in other areas could not directly reflect the status in Taiyuan due to its unique air pollution characteristics. Hence, it was of great significance and urgency to further investigate the effects of ambient air pollutants on IVF pregnancy outcomes in Taiyuan.

Air quality index (AQI) is an index that is used for reporting daily the air quality of the environment where we live [18]. However, no studies reported the effects of AQI on IVF pregnancy outcomes. To further investigate the impact of six ambient air pollution (PM_{10} , $PM_{2.5}$, SO_2 , CO , NO_2 and O_3) and AQI on IVF pregnancy outcomes, we conducted a retrospective study. The women who received IVF treatment at Center of Reproductive Medicine of Children's Hospital of Shanxi and Women Health Center of Shanxi in Taiyuan were enrolled into the study from 2015 to 2020. Our results would be helpful to further understand the impact of air pollution on pregnancy outcomes of patients underwent IVF in a heavy polluted city in northern China, and provide some theoretical support for the prevention and treatment of infertility patients.

Materials And Methods

Study design and subjects

Clinical data from patients who underwent the first fresh IVF cycle were obtained at the Center of Reproductive Medicine of Children's Hospital of Shanxi and Women Health Center of Shanxi between January 1, 2015 and May 31, 2020. In this study, the participants were collected depending on the patients' residential location. We assumed that they did not relocate during IVF treatment. Additional selection criteria include: 1) patients underwent their first fresh cycle, 2) patients used the conventional controlled ovarian hyperstimulation (COH) protocols, and 3) patients' complete medical record data were accessible. Finally, we included 516 IVF patients for analysis.

IVF procedure

In general, IVF procedure is divided into four stages: COH, oocyte retrieval, embryo transfer, and pregnancy test. Firstly, COH protocol was carried out to induce ovulation according to the ovarian response, age and ovarian reserve, in order to promote the development of follicles. Human chorionic gonadotrophin (hCG) was injected when two or more dominant follicles reached 18 mm or more in diameter. Oocyte retrieval was conducted through transvaginal ultrasound-guided follicle aspiration. Oocytes were fertilized by a conventional IVF or ICSI methods. Embryo transfer was performed 3–5 days after oocyte retrieval. Luteal support was started on the day of oocyte retrieval. Biochemical pregnancy is diagnosed by a serum β -hCG greater than 30 mIU/ml at 2 weeks (14 days) after the embryo transfer. Clinical pregnancy is diagnosed by a gestational sac with fetal heart beat during ultrasound examination after five weeks (35 days) of embryo transfer.

Air pollution data

The daily air pollution data in Taiyuan were obtained from air quality online analysis platform between January 1, 2015 and May 31, 2020 (<http://www.aqistudy.cn/historydata>). The air pollution data mainly include the concentration of six air pollutants ($PM_{2.5}$ in $\mu g/m^3$, PM_{10} in $\mu g/m^3$, SO_2 in $\mu g/m^3$, NO_2 in $\mu g/m^3$, CO in mg/m^3 , O_3 in $\mu g/m^3$) and AQI. Based on these data, we calculated average ambient air pollutant concentration during long-term exposure to air pollutants (period 1, period 2 and period 3) and IVF treatment cycle (period 4, period 5, period 6, and period 7). As shown in Fig. 1, these stages are the following: period 1 (85 days before the oocyte retrieval to ultrasound to determine pregnancy), period 2 (85 days before the oocyte retrieval to serum hCG test), period 3 (85 days before the oocyte retrieval to oocyte retrieval), period 4 (gonadotropin (Gn) start to oocyte retrieval; period 5 (oocyte retrieval to embryo transfer), period 6 (embryo transfer to serum hCG test), and period 7 (embryo transfer to ultrasound to determine pregnancy).

Statistical analysis

Descriptive analyses were presented as count (%) for categorical variables or as mean $\pm$ standard deviation (SD) for continuous variables, respectively. Air pollutants were summarized by the median and quartiles (25th–50th–75th quartile). Spearman correlation analysis was performed to examine the correlation among the pollutants. Univariate and multivariate logistic regression analyses was used to evaluate the associations between ambient air pollution exposures and IVF pregnancy outcomes. Odd ratios (ORs) and 95% confidence intervals (CIs) were used to report the result. For multiple logistics analysis, we divided the exposure levels of air pollutants in different expose periods into four groups (Q1: low levels, Q2: medium levels, Q3: high-medium levels, Q4: high levels) according to the quartile, and Q1 group was used as a control, adjusting for age, BMI, duration of infertility, type of infertility, causes of infertility, IVF/ICSI, basal follicle-stimulating hormone (FSH), basal luteinizing hormone (LH), basal estradiol (E2), number of oocytes retrieved for analysis. All statistical analyses were performed using SPSS 22. A p-value of < 0.05 was considered statistically significant.

Results

Study population characteristics

This retrospective population-based cohort study consisted of 516 patients with IVF from January 1, 2015 to May 31, 2020 in Taiyuan. The descriptive statistics of study population was given in Table 1. Among the 516 women, 297 (57.6%) occurred primary infertility and 219 (42.4%) occurred secondary infertility. In addition, 382 (74.0%) underwent IVF and 134 (26.0%) underwent ICSI. Their mean age, mean BMI and mean duration of infertility were 31.48 years, 22.83 kg/m^2 and 3.5 years, respectively. The main causes of infertility were tubal and uterine factor 270 (52.3%). Their mean basal hormone levels (FSH, LH and E2) and mean number of oocytes retrieved were 8.77 mIU/ml, 4.64 mIU/ml, 70.96 pg/ml, and 10.78, respectively. For IVF outcomes, the biochemical pregnancy rate and clinical pregnancy rate were 255 (49.4%) and 217 (42.1%), respectively.

Air pollution exposure characteristics

The average ambient air pollutant concentration for six air pollutants and AQI during different exposure periods were exhibited in Table 2. In addition, we used the Spearman's correlation to examine the correlations among the pollutants. The results showed that concentrations of the air pollutants examined (PM_{10} , $PM_{2.5}$, SO_2 , CO, NO_2) were positively correlated (Rang: 0.23 to 0.89), and the correlations had highly significant in statistics ($P < 0.01$). However, the concentration of O_3 was negatively correlated (Rang: -0.13 to -0.80) with significant difference ($P < 0.01$).

Association between air pollution and pregnancy outcomes

As shown in Table 3, we performed univariate logistic regression analysis of the relationship between 6 air pollutants and AQI and IVF pregnancy outcomes (see Additional file 1 and 2). We found that 6 air pollutants and AQI were not associated with the IVF pregnancy outcomes ($P \geq 0.05$). Similarly, we explored the estimated effects by air pollutants quartiles during different expose periods with Q1 as the reference, adjusting for age, BMI, duration of infertility, type of infertility, causes of infertility, IVF/ICSI, basal FSH, basal LH, basal E2, number of oocytes retrieved. It indicated that there was a certain relationship between air pollutants to exposure and IVF pregnancy outcomes.

The result of biochemical pregnancy was shown in Table 3. During period 4, medium levels (Q2) and high levels (Q4) of NO_2 were significantly associated with reduced odds of biochemical pregnancy. High levels (Q4) of NO_2 exposure during period 7 was significantly associated with reduced odds of biochemical pregnancy and decreased in a dose-dependent manner as exposure levels quartiles increasing (P for trend = 0.031). On the contrary, medium levels O_3 (Q2) during period 4 and 5 and high-medium levels O_3 (Q3) during period 5 were associated with increased odds of biochemical pregnancy.

The results for the clinical pregnancy rate was shown in Table 4. High-medium levels NO_2 (Q3) during period 1, 3 and 6 and medium levels (Q2) during period 4 were significantly associated with reduced odds of clinical pregnancy. In contrast, high-medium levels O_3 (Q3) during period 1 and 5 were

associated with increased odds of clinical pregnancy. For AQI, high-medium levels (Q3) during period 1 and high levels (Q4) during period 4 were significantly associated with reduced odds of clinical pregnancy. The odds of clinical pregnancy showed a decreasing trend (P for trend = 0.005) with AQI quartiles increasing during period 4.

Discussion

With the deterioration of air quality in recent years, more and more people pay attention to the health effects of air pollution. In this retrospective study, we explored the association between 6 air pollutants and AQI and IVF pregnancy outcomes during long-term exposure (period 1, period 2 and period 3) and IVF treatment cycle (period 4, period 5, period 6, and period 7) in Taiyuan. The results suggested that lower pregnancy outcomes in IVF cycles might be linked with worse air environment. The results further supported previous studies that air pollution exposure had the negative influences on IVF pregnancy outcomes.

Previous studies have explored the relationship between air pollution and IVF pregnancy outcomes. A study from three IVF laboratories in the Northeastern United States found that the increase of NO_2 concentration was significantly associated with a low chance of pregnancy and live birth [17]. And another study, Boulet et al. reported that exposure to O_3 was weakly positively associated with implantation rate and live birth rate, while exposure to $\text{PM}_{2.5}$ was not associated with any of IVF treatment outcomes [16]. Perin et al. indicated that high levels of ambient PM during the follicular phase had a higher risk of pregnancy loss in Brazilian women undergoing IVF [19]. Choe et al. showed that increase of PM_{10} , NO_2 and CO were associated with a decreased probability of intrauterine pregnancy in Korea women after adjusting for individual risk factors [20]. Also from South Korea, Kang et al. showed that exposure to NO_2 , PM_{10} , and $\text{PM}_{2.5}$ were associated with decreased pregnancy rates in women undergoing fresh IVF-ET treatment from a large, long-term database [15]. Additionally, there have been related reports in China. In Xiamen, Wang et al. retrospectively analyzed the effect of outdoor air pollution on IVF outcomes of frozen-thawed embryo transfer (FET) and fresh embryo transfer in the same period. They found that exposure to high levels of SO_2 and O_3 were significantly associated with low live birth rates in frozen embryo transfers but had no effect on fresh embryo transfer [21]. In Shenyang, Qiu et al. observed that an inter quartile range (IQR) increasing of O_3 during Gn start to oocyte retrieval and one day before oocyte retrieval was associated with a lower intrauterine pregnancy rate, while there was an inverse association of intrauterine pregnancy with CO two days prior to oocyte retrieval [22]. In Chengdu, Zeng et al. found that exposure of $\text{PM}_{2.5}$, PM_{10} , NO_2 , SO_2 and CO were negatively associated with the odds of biochemical pregnancy and clinical pregnancy except O_3 , particularly < 35 years younger women [14]. The inconsistency of the above conclusions could be explained as follows: 1) the composition, levels and sources of air pollution vary due to different countries and regions; 2) the individual susceptibility is different due to different genetic backgrounds and lifestyles; 3) most of the above studies are retrospective cohort studies, which may increase the possibility of selection bias, failure to control for selection bias potential confounding factors and sample size.

Taiyuan, is a typical heavy industry city characterized by coal-burning pollution, mainly comes from the exhaust emissions of the heavy industries and coal-fired heating in winter [5]. With the rapid development of urbanization, motor vehicle exhaust emissions have become one of the main sources of air pollution in Taiyuan city [23]. Additionally, Taiyuan is surrounded on the three sides by mountains that inhibit the dispersion of pollutants. The special basin terrain character and temperature inversion in winter make it difficult to disperse air pollutants. Therefore, the air pollution characteristics of Taiyuan was formed that the dominated pollutant by particulate matter and SO_2 , accompanied by a large amount of NO_2 and O_3 . Similar to the above results, we also found that air pollutants were associated with reduced biochemical pregnancy rates and clinical pregnancy rates among IVF patients in Taiyuan.

NO_2 is a traffic-related air pollutants that was mainly released from vehicle emission and coal combustion [24]. In this study, we found that there was a significant negative correlation between exposure to NO_2 and biochemical and clinical pregnancy, while exposure to O_3 had the inverse relationship. The results of this study are similar to Zeng's [14]. In addition, Slama et al. reported that high concentrations of $\text{PM}_{2.5}$ and NO_2 were associated with lower pregnancy rates in women [25]. In Balb/c mice, Mohallem et al. also found that the failure rate of implantation increased and the live birth rate decreased exposed to high levels of NO_2 and $\text{PM}_{2.5}$ [26]. In addition, O_3 is a secondary pollutant that is not emitted directly into the atmosphere, but is produced by photochemical reactions between NO_2 and hydrocarbons [27]. Therefore, the rise of O_3 reflects good air quality to some extent. This not only explains that O_3 is positively correlated with pregnancy outcome, but also explains that O_3 is negatively correlated with other pollutants and AQI.

AQI as a quantitative index is to describe air quality status. The higher the AQI value, the more serious the air pollution and it has greater risk to human health [28]. At present, there were no data to analyze the relationship between AQI and IVF pregnancy outcomes. In the study, we found that there was a dose-dependent relationship between AQI and clinical pregnancy rate, and the clinical pregnancy rate decreased with AQI quartiles increase. The results showed that the worse the air quality, the lower the clinical pregnancy rate.

In this study, AQI was firstly used to explore the relationship between air quality and IVF pregnancy outcomes. As a heavy polluted city in northern China, we further explored the effect of air pollutants during different exposure periods on IVF pregnancy outcomes in Taiyuan.

However, certain limitations of this study should be mentioned. First, the level of individual air pollution exposure in this study do not accurately represent individual exposure level. In this study, the data of averaging daily pollutant concentrations was collected from an air pollution monitoring station. In addition, it is difficult to directly measure individual air pollution exposure due to its expensive cost and the patients' compliance. Furthermore, we only conducted the single-pollutant models based on six air pollutants, without the additive and/or interactive effects of two or more pollutants. As an environmental evaluation indicator based on six pollutants, we explore the relationship between AQI and IVF pregnancy outcomes. Third, the number of participants and potential confounders were limited due to retrospective study. Therefore, a prospective study with a large sample size will be more conducive to draw more reliable conclusions.

Conclusions

In summary, our findings suggested that air pollution has a certain impact on IVF pregnancy outcomes, especially NO₂ and O₃. In addition, the results of AQI further indicated that poor air quality was more likely to reduce clinical pregnancy. Thus, to strengthen the protection of IVF infertility patients from air pollutants is beneficial to increase the biochemical pregnancy rate and clinical pregnancy rate.

Abbreviations

IVF: in vitro fertilization; ART: assisted reproductive technology; COH: controlled ovarian hyperstimulation; hCG: human chorionic gonadotrophin; PM₁₀: particulate matter ≤ 10 µm in aerodynamic diameter; PM_{2.5}: particulate matter ≤ 2.5 µm in aerodynamic diameter; SO₂: sulfur dioxide; CO: carbon monoxide; NO₂: nitrogen dioxide; O₃: ozone; AQI: air quality index; BMI: body mass index; CI: confidence interval; OR: odds ratio

Declarations

Acknowledgements

Not applicable.

Authors' contributions

All authors read and approved the final manuscript. SX, YW designed the study. SX, CS and LZ analyzed the data. CS and DF collected the data. SX drafted the manuscript. XB, CW and YW revised the manuscript. XW coordinated the study and revised the manuscript.

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Availability of data and materials

The data used during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Children's Hospital of Shanxi and Women Health Center of Shanxi.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Center of Reproductive Medicine, Children's Hospital of Shanxi and Women Health Center of Shanxi, Taiyuan, Shanxi, China. ² The Second Hospital of Shanxi Medical University, Shanxi Medical University, Taiyuan, Shanxi, China. ³ Laboratory Animal Center, Shanxi Medical University, Taiyuan, Shanxi, China.

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Tables

Table 1 The descriptive statistics of the study population in Taiyuan, China, 2015–2020 (n = 516)

Characteristics	Mean ± SD/N (%)
Age (years)	31.48 ± 4.12
BMI (kg/m ²)	22.83 ± 3.17
Duration of infertility (years)	3.50 ± 2.80
Type of infertility	
Primary infertility	297 (57.6)
Secondary infertility	219 (42.4)
Causes of infertility	
Tubal and Uterine factor	270 (52.3)
Endometriosis	24 (4.7)
Ovulatory dysfunction	12 (2.3)
Male factor	97 (18.8)
Unexplained	80 (15.5)
Both factor	22 (4.3)
Others	11 (2.1)
IVF/ICSI	
IVF	382 (74.0)
ICSI	134 (26.0)
Basal hormone levels	
Basal FSH (mIU/ml)	8.77 ± 2.76
Basal LH (mIU/ml)	4.64 ± 2.36
Basal E2 (pg/ml)	70.96 ± 26.88
Number of oocytes retrieved	10.78 ± 5.26
IVF outcomes	
Biochemical pregnancy	255 (49.4)
Clinical pregnancy	217 (42.1)

Note: Data are presented as mean ± SD or n (%)

SD, standard deviation; BMI, body mass index; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol

Table 2 The summary statistics of air pollutants and their pairwise correlations in different exposure periods

Exposure period	Air pollutant	Percentiles							Spearman correlation coefficient						
		Mean	SD	Min	Max	25th	50th	75th	PM _{2.5}	PM ₁₀	SO ₂	CO	NO ₂	O ₃	AQI
P1	PM _{2.5}	57.75	18.13	22.00	134.00	45.12	52.04	68.85	1.00						
	PM ₁₀	118.52	25.06	45.62	268.00	101.67	114.51	132.29	0.89	1.00					
	SO ₂	41.30	29.30	9.81	183.44	22.11	32.14	51.88	0.73	0.64	1.00				
	CO	1.39	2.82	0.77	46.22	0.93	1.16	1.38	0.72	0.57	0.91	1.00			
	NO ₂	46.91	9.60	14.00	91.00	39.14	45.88	53.77	0.69	0.74	0.23	0.29	1.00		
	O ₃	93.24	35.27	32.23	227.00	63.86	91.71	118.20	-0.76	-0.63	-0.72	-0.77	-0.43	1.00	
	AQI	101.42	17.78	45.26	255.00	89.33	101.44	109.58	0.68	0.74	0.35	0.32	0.74	-0.29	1.00
P2	PM _{2.5}	57.69	18.62	26.22	131.97	44.16	52.31	67.77	1.00						
	PM ₁₀	118.10	25.37	60.41	202.45	102.54	115.93	131.41	0.88	1.00					
	SO ₂	41.66	30.76	8.78	210.25	21.17	30.67	52.02	0.77	0.62	1.00				
	CO	1.22	0.36	0.77	2.28	0.95	1.15	1.42	0.73	0.53	0.92	1.00			
	NO ₂	46.74	9.55	25.68	69.70	38.42	45.70	53.32	0.66	0.76	0.23	0.26	1.00		
	O ₃	92.42	36.21	27.31	172.01	60.60	87.72	120.36	-0.78	-0.61	-0.73	-0.77	-0.42	1.00	
	AQI	100.65	17.12	62.14	169.60	89.36	99.75	109.21	0.70	0.75	0.40	0.38	0.73	-0.31	1.00
P3	PM _{2.5}	57.86	20.14	24.06	174.00	43.99	51.92	68.79	1.00						
	PM ₁₀	117.95	27.58	59.33	268.00	101.93	116.00	131.57	0.85	1.00					
	SO ₂	43.08	36.15	8.12	354.00	20.93	30.26	54.47	0.79	0.58	1.00				
	CO	1.24	0.47	0.77	6.80	0.96	1.13	1.44	0.73	0.45	0.91	1.00			
	NO ₂	46.72	10.18	25.53	120.00	37.41	45.95	52.90	0.66	0.76	0.26	0.27	1.00		
	O ₃	92.05	37.29	26.02	185.00	59.12	90.77	120.39	-0.76	-0.56	-0.72	-0.74	-0.42	1.00	
	AQI	100.55	19.40	60.81	230.00	88.89	98.22	109.37	0.69	0.75	0.41	0.38	0.71	-0.29	1.00
P4	PM _{2.5}	57.87	28.24	23.15	187.50	39.52	50.00	67.82	1.00						
	PM ₁₀	120.80	38.17	44.92	257.44	95.96	116.53	143.72	0.86	1.00					
	SO ₂	39.61	37.80	5.64	227.58	17.22	29.26	44.80	0.73	0.66	1.00				
	CO	1.17	0.43	0.65	2.95	0.86	1.06	1.39	0.74	0.55	0.86	1.00			
	NO ₂	47.34	11.96	22.86	81.17	38.06	46.26	54.24	0.63	0.69	0.38	0.41	1.00		
	O ₃	94.07	45.43	0.50	221.00	60.45	92.10	123.48	-0.59	-0.48	-0.67	-0.69	-0.42	1.00	
	AQI	101.72	28.45	46.62	227.67	83.00	96.26	113.93	0.70	0.70	0.41	0.44	0.57	-0.14	1.00
P5	PM _{2.5}	58.72	32.73	16.00	222.75	36.31	49.75	69.38	1.00						
	PM ₁₀	120.77	46.11	35.00	331.00	86.44	112.00	150.75	0.86	1.00					
	SO ₂	38.21	37.42	4.25	272.50	15.75	27.00	43.13	0.63	0.64	1.00				
	CO	1.18	0.46	0.50	3.15	0.85	1.05	1.38	0.74	0.59	0.79	1.00			
	NO ₂	47.63	14.42	17.50	96.75	37.00	45.50	57.69	0.65	0.72	0.45	0.48	1.00		
	O ₃	96.16	49.62	0.00	243.25	56.25	93.75	128.06	-0.42	-0.35	-0.61	-0.56	-0.32	1.00	
	AQI	103.33	34.96	41.75	267.00	78.25	97.63	119.25	0.72	0.72	0.35	0.48	0.57	-0.16	1.00
P6	PM _{2.5}	59.18	30.36	24.69	214.64	40.53	48.61	68.95	1.00						
	PM ₁₀	122.24	40.91	53.13	282.78	95.14	117.73	143.25	0.87	1.00					

	SO ₂	39.70	39.29	5.93	247.56	16.53	27.64	47.07	0.72	0.69	1.00				
	CO	1.19	0.47	0.62	3.23	0.87	1.05	1.36	0.74	0.58	0.85	1.00			
	NO ₂	47.97	13.03	26.92	89.33	38.27	45.71	55.54	0.66	0.72	0.42	0.45	1.00		
	O ₃	95.37	47.66	9.33	213.17	51.88	94.93	128.73	-0.64	-0.56	-0.72	-0.70	-0.46	1.00	
	AQI	104.32	30.37	51.13	258.36	84.20	98.94	115.53	0.64	0.64	0.34	0.43	0.53	-0.13	1.00
P7	PM _{2.5}	58.64	26.36	27.44	199.33	41.54	49.64	67.13	1.00						
	PM ₁₀	120.68	36.15	57.39	264.92	97.59	118.90	134.86	0.88	1.00					
	SO ₂	40.16	38.42	6.25	228.25	17.59	26.04	47.83	0.81	0.70	1.00				
	CO	1.20	0.45	0.67	3.03	0.86	1.05	1.42	0.80	0.58	0.88	1.00			
	NO ₂	47.68	11.84	30.08	83.42	37.90	45.74	56.59	0.70	0.76	0.43	0.46	1.00		
	O ₃	95.97	47.57	22.06	198.36	50.40	96.67	135.72	-0.80	-0.69	-0.78	-0.76	-0.54	1.00	
	AQI	104.12	25.30	62.81	241.58	89.26	98.22	115.93	0.55	0.56	0.35	0.39	0.56	-0.22	1.00

P1, period 1; P2, period 2; P3, period 3; P4, period 4; P5, period 5; P6, period 6; P7, period 7; PM₁₀, particulate matter ≤ 10 µm in aerodynamic diameter; PM_{2.5}, particulate matter ≤ 2.5 µm in aerodynamic diameter; SO₂, sulfur dioxide; CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; AQI, air quality index; SD: standard deviation

Table 3 Risk analysis between air pollutants quartiles and biochemical pregnancy outcome during each exposure period

Air pollutant	Exposure period	P1	P2	P3	P4	P5	P6	P7
		AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
PM _{2.5} (µg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	0.886 (0.359 2.187)	0.948 (0.382 2.354)	0.575 (0.229 1.441)	1.731 (0.666 4.502)	0.983 (0.386 2.502)	1.353 (0.555 3.295)	0.978 (0.403 2.375)
	Q3	0.805 (0.316 2.050)	1.183 (0.435 3.215)	0.836 (0.305 2.295)	1.894 (0.738 4.865)	0.642 (0.254 1.624)	1.675 (0.631 4.447)	1.290 (0.513 3.243)
	Q4	0.653 (0.243 1.754)	0.742 (0.264 2.087)	0.715 (0.264 1.942)	0.621 (0.228 1.696)	0.537 (0.200 1.438)	0.696 (0.271 1.789)	0.490 (0.182 1.316)
	P for trend	0.386	0.695	0.798	0.401	0.125	0.504	0.279
PM ₁₀ (µg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	0.938 (0.389 2.262)	0.881 (0.361 2.149)	1.280 (0.533 3.072)	1.958 (0.793 4.829)	1.224 (0.502 2.987)	0.690 (0.280 1.700)	0.758 (0.307 1.867)
	Q3	0.728 (0.280 1.893)	1.096 (0.413 2.909)	1.454 (0.558 3.785)	1.632 (0.620 4.297)	0.751 (0.311 1.810)	1.745 (0.705 4.316)	1.324 (0.550 3.187)
	Q4	0.687 (0.261 1.808)	0.596 (0.219 1.617)	0.782 (0.294 2.075)	0.528 (0.203 1.374)	0.825 (0.324 2.099)	0.701 (0.274 1.790)	0.581 (0.221 1.526)
	P for trend	0.362	0.422	0.728	0.159	0.446	0.986	0.566
SO ₂ (µg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	0.589 (0.229 1.513)	1.014 (0.394 2.613)	0.906 (0.338 2.430)	0.628 (0.236 1.666)	0.777 (0.293 2.062)	0.968 (0.366 2.557)	1.199 (0.455 3.163)
	Q3	0.730 (0.245 2.175)	0.857 (0.296 2.479)	1.422 (0.495 4.086)	1.259 (0.489 3.238)	0.843 (0.324 2.194)	1.117 (0.451 2.765)	0.954 (0.367 2.480)
	Q4	0.805 (0.302 2.140)	1.149 (0.432 3.055)	1.107 (0.406 3.020)	0.876 (0.342 2.244)	1.005 (0.373 2.707)	1.007 (0.391 2.593)	0.712 (0.258 1.967)
	P for trend	0.937	0.8	0.655	0.907	0.892	0.915	0.39
CO (mg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	0.554 (0.209 1.472)	0.710 (0.254 1.984)	0.729 (0.266 1.999)	0.582 (0.206 1.646)	0.936 (0.351 2.496)	0.682 (0.259 1.800)	0.733 (0.278 1.936)
	Q3	0.677 (0.239 1.913)	0.725 (0.258 2.038)	0.694 (0.250 1.923)	0.879 (0.317 2.437)	0.472 (0.171 1.307)	0.582 (0.222 1.528)	1.101 (0.402 3.011)
	Q4	0.791 (0.292 2.139)	0.873 (0.312 2.444)	1.007 (0.358 2.828)	0.491 (0.168 1.438)	0.540 (0.187 1.564)	0.550 (0.201 1.509)	0.552 (0.192 1.589)
	P for trend	0.944	0.957	0.863	0.361	0.097	0.245	0.462
NO ₂ (µg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	0.734 (0.309 1.740)	0.959 (0.402 2.287)	1.069 (0.431 2.647)	0.333 (0.132 0.838)	0.486 (0.205 1.154)	1.027 (0.394 2.678)	0.521 (0.218 1.249)

Q3	0.501 (0.206 1.216)	0.670 (0.273 1.644)	0.671 (0.284 1.584)	1.189 (0.494 2.862)	0.668 (0.286 1.560)	0.677 (0.302 1.517)	0.445 (0.181 1.098)
Q4	0.440 (0.170 1.135)	0.480 (0.191 1.209)	0.646 (0.261 1.597)	0.352 (0.133 0.932)	0.662 (0.249 1.757)	0.682 (0.267 1.741)	0.374 (0.141 0.990)
P for trend	0.054	0.095	0.24	0.283	0.417	0.287	0.031
O ₃ (µg/m ³)							
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
Q2	2.313 (0.910 5.881)	1.336 (0.538 3.319)	1.169 (0.481 2.844)	2.608 (1.046 6.504)	3.261 (1.237 8.595)	1.965 (0.776 4.975)	2.409 (0.913 6.359)
Q3	2.040 (0.817 5.096)	1.148 (0.457 2.886)	1.143 (0.458 2.853)	1.875 (0.743 4.735)	2.739 (1.026 7.310)	2.236 (0.846 5.911)	1.998 (0.734 5.437)
Q4	1.472 (0.566 3.832)	1.391 (0.562 3.442)	1.143 (0.473 2.763)	1.743 (0.688 4.421)	2.175 (0.787 6.010)	1.998 (0.737 5.418)	2.008 (0.695 5.802)
P for trend	0.472	0.56	0.783	0.385	0.234	0.19	0.35
AQI							
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
Q2	1.362 (0.552 3.364)	1.007 (0.413 2.454)	1.698 (0.679 4.250)	1.774 (0.691 4.554)	0.950 (0.406 2.219)	1.379 (0.587 3.242)	1.696 (0.714 4.030)
Q3	0.684 (0.280 1.675)	1.320 (0.538 3.237)	1.556 (0.625 3.871)	0.941 (0.366 2.421)	1.020 (0.408 2.554)	0.846 (0.339 2.112)	0.844 (0.343 2.079)
Q4	0.881 (0.354 2.193)	0.667 (0.269 1.656)	0.855 (0.344 2.123)	0.476 (0.190 1.192)	0.640 (0.250 1.636)	0.878 (0.341 2.260)	0.808 (0.320 2.040)
P for trend	0.481	0.561	0.742	0.059	0.419	0.589	0.403

AOR, adjusted odds ratio; CI: confidence interval; P1, period 1; P2, period 2; P3, period 3; P4, period 4; P5, period 5; P6, period 6; P7, period 7; PM₁₀, particulate matter ≤ 10 µm in aerodynamic diameter; PM_{2.5}, particulate matter ≤ 2.5 µm in aerodynamic diameter; SO₂, sulfur dioxide; CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; AQI, air quality index; Q1, the first quartile; Q2, the second quartile; Q3, the third quartile; Q4, the fourth quartile.

Adjusting for age, BMI, duration of infertility, type of infertility, causes of infertility, IVF/ICSI, basal FSH, basal LH, basal E2 and number of oocytes retrieved.

Table 4 Risk analysis between air pollutants quartiles and clinical pregnancy outcome during each exposure period

Air pollutant	Exposure period	P1	P2	P3	P4	P5	P6	P7
		AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
PM _{2.5} (µg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	1.342 (0.545 3.307)	1.136 (0.450 2.867)	0.431 (0.166 1.115)	1.815 (0.688 4.787)	0.600 (0.237 1.521)	1.432 (0.579 3.540)	1.825 (0.734 4.535)
	Q3	0.850 (0.329 2.199)	1.027 (0.370 2.850)	0.622 (0.223 1.735)	2.149 (0.826 5.592)	0.517 (0.204 1.312)	1.519 (0.568 4.064)	2.019 (0.791 5.155)
	Q4	0.842 (0.313 2.265)	0.843 (0.298 2.384)	0.529 (0.192 1.459)	0.674 (0.238 1.910)	0.646 (0.245 1.702)	0.967 (0.371 2.523)	1.037 (0.387 2.783)
	P for trend	0.503	0.658	0.465	0.55	0.356	0.898	0.852
PM ₁₀ (µg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	0.956 (0.396 2.310)	0.554 (0.223 1.376)	0.795 (0.326 1.939)	1.962 (0.788 4.882)	1.122 (0.456 2.763)	0.948 (0.375 2.399)	1.237 (0.492 3.106)
	Q3	0.641 (0.241 1.703)	0.737 (0.277 1.960)	0.810 (0.312 2.102)	1.533 (0.589 3.993)	1.196 (0.493 2.899)	2.291 (0.920 5.705)	2.031 (0.842 4.901)
	Q4	0.782 (0.298 2.055)	0.483 (0.175 1.330)	0.567 (0.212 1.517)	0.487 (0.178 1.332)	1.035 (0.399 2.685)	1.009 (0.388 2.628)	0.920 (0.342 2.475)
	P for trend	0.446	0.274	0.294	0.144	0.892	0.475	0.703
SO ₂ (µg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	1.096 (0.423 2.841)	1.796 (0.670 4.814)	1.968 (0.689 5.617)	1.035 (0.380 2.820)	1.254 (0.466 3.371)	1.980 (0.734 5.339)	2.602 (0.946 7.159)
	Q3	1.400 (0.465 4.215)	1.780 (0.600 5.285)	2.698 (0.902 8.066)	2.016 (0.778 5.228)	1.425 (0.530 3.829)	2.081 (0.809 5.348)	2.088 (0.763 5.715)
	Q4	1.293 (0.477 3.504)	1.936 (0.700 5.359)	2.113 (0.734 6.080)	1.386 (0.530 3.622)	1.439 (0.525 3.939)	1.628 (0.605 4.381)	1.522 (0.524 4.423)
	P for trend	0.561	0.286	0.221	0.344	0.47	0.357	0.735
CO (mg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	1.160 (0.436 3.090)	1.734 (0.599 5.019)	1.919 (0.674 5.459)	1.229 (0.433 3.484)	1.302 (0.494 3.429)	0.981 (0.374 2.573)	1.463 (0.532 4.022)
	Q3	1.197 (0.427 3.353)	1.458 (0.506 4.206)	1.219 (0.427 3.478)	1.757 (0.627 4.924)	0.638 (0.226 1.804)	0.925 (0.348 2.455)	2.208 (0.774 6.297)
	Q4	1.291 (0.475 3.506)	1.646 (0.568 4.769)	1.881 (0.651 5.439)	0.649 (0.218 1.935)	0.914 (0.320 2.610)	0.860 (0.317 2.331)	1.429 (0.479 4.267)
	P for trend	0.63	0.543	0.477	0.494	0.42	0.741	0.439
NO ₂ (µg/m ³)								
	Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Q2	0.661 (0.253	0.571 (0.233	0.825 (0.324	0.340 (0.133	0.648 (0.270	1.055 (0.395	0.884 (0.371

	1.478)	1.402)	2.098)	0.871)	1.557)	2.813)	2.107)
Q3	0.380 (0.152 0.950)	0.473 (0.187 1.197)	0.381 (0.153 0.949)	1.003 (0.426 2.363)	0.817 (0.350 1.907)	0.409 (0.174 0.962)	0.725 (0.293 1.793)
Q4	0.507 (0.196 1.307)	0.436 (0.171 1.113)	0.527 (0.210 1.322)	0.428 (0.163 1.122)	0.643 (0.240 1.720)	0.612 (0.237 1.580)	0.758 (0.295 1.947)
P for trend	0.069	0.065	0.064	0.351	0.454	0.086	0.463
O₃ (µg/m ³)							
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
Q2	2.230 (0.860 5.782)	1.739 (0.693 4.363)	1.507 (0.617 3.681)	2.422 (0.972 6.034)	2.045 (0.769 5.442)	1.306 (0.514 3.316)	1.657 (0.629 4.368)
Q3	2.899 (1.136 7.396)	1.470 (0.579 3.735)	1.369 (0.545 3.439)	1.565 (0.615 3.983)	3.184 (1.175 8.627)	1.788 (0.680 4.703)	1.616 (0.594 4.395)
Q4	0.828 (0.298 2.298)	1.089 (0.430 2.758)	0.911 (0.368 2.257)	0.857 (0.329 2.232)	1.041 (0.365 2.974)	0.946 (0.349 2.565)	0.863 (0.296 2.520)
P for trend	0.999	0.941	0.831	0.543	0.732	0.949	0.679
AQI							
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
Q2	0.897 (0.363 2.215)	0.782 (0.316 1.934)	1.057 (0.422 2.645)	1.727 (0.669 4.456)	0.987 (0.420 2.321)	0.937 (0.397 2.213)	1.334 (0.558 3.189)
Q3	0.293 (0.112 0.768)	0.630 (0.258 1.535)	0.708 (0.278 1.800)	0.671 (0.258 1.741)	0.991 (0.391 2.513)	0.680 (0.268 1.721)	0.464 (0.181 1.185)
Q4	0.689 (0.275 1.726)	0.479 (0.189 1.210)	0.576 (0.228 1.456)	0.306 (0.115 0.814)	0.532 (0.203 1.395)	0.471 (0.178 1.250)	0.521 (0.200 1.358)
P for trend	0.127	0.106	0.176	0.005	0.236	0.11	0.051

AOR, adjusted odds ratio; CI, confidence interval; P1, period 1; P2, period 2; P3, period 3; P4, period 4; P5, period 5; P6, period 6; P7, period 7; PM₁₀, particulate matter ≤ 10 µm in aerodynamic diameter; PM_{2.5}, particulate matter ≤ 2.5 µm in aerodynamic diameter; SO₂, sulfur dioxide; CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; AQI, air quality index; Q1, the first quartile; Q2, the second quartile; Q3, the third quartile; Q4, the fourth quartile.

Adjusting for age, BMI, duration of infertility, type of infertility, causes of infertility, IVF/ICSI, basal FSH, basal LH, basal E2 and number of oocytes retrieved.

Figures

Figure 1

Timeline of an IVF cycle and the observed exposure time point for current study.

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