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The Impact of Ambient Air Pollutants on Birth Outcomes Using ARMA Model: Yazd Mother and Birth Cohort Study

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ABSTRACT

Introduction: The present study examines the association between ambient air pollution and harmful consequences at birth in Yazd, Iran during 2017-2020.

Materials and Methods: This time series study by the autoregressive (AR) and moving average (MA) or ARMA model was conducted in Yazd, Iran. Birth information including fetal sex, birth weight, birth height, and head circumference as well as preterm birth (PTB) and abortion was collected from mother and birth cohort databases. Data on air pollutants concentrations in the corresponding gestational period were obtained from fixed air monitors of Yazd Municipal Environmental Monitoring Center. The time series model statistical test was performed to find the relation between ambient air pollution and harmful consequences at birth.

Results: 2131 singleton live births were monitored for 3 years. In ARMA models, the ratio of girl births to total births (Coef: 7.943, 95% CI: 2.797, 13.089), preterm delivery (Coef: 2.915, 95% CI: 0.224, 5.606), and spontaneous abortion (Coef: 44.751, 95% CI: 26.872, 62.629) was associated with NO_2 exposure. Distributed mismatch models also suggested associations between the Air Quality Index (AQI) in pregnant women with a sex-premature birth relationship (Coef: 0.001, 95% CI: 0.000, 0.001).

Conclusion: Exposure to air pollution, even at low levels, may increase the risk of sex ratio in singletons, premature birth, and spontaneous abortion. However, the results of the present study could not definitively show the relationship between air quality and other birth problems. More research studies are required to investigate the present findings.

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Introduction

Air pollution is an important risk factor for the overall global burden of disease (GBD). For example, in the UK, about 40,000 deaths occur annually due to exposure to outdoor air pollution[1]. Although air quality has improved significantly in

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recent decades, air pollution remains the environmental factor with the greatest impact on health in developing countries. Strict environmental regulations and technological advances have greatly contributed to a significant reduction in pollution levels in industrialized countries[2]. However, environmental regulations related to air pollution are very controversial. Concentration limits set by governments have been unable to completely provide the specific level of exposure to population safety [3].

The environmental protection agency (EPA) has established the Air Quality Index (AQI) for six criteria pollutants under the Clean Air Act (CAA) [4, 5]. Human short-term exposure to large amounts of SO_2 gas, depending on individual sensitivity, may cause reversible effects on lung function. Also, exposure to very high concentrations of NO_2 can lead to severe lung damage. A high concentration of ozone gas causes changes in lung function, inflammation of the airways, and increased responsiveness of the airways to bronchoconstrictors. Respiratory and cardiovascular hospitalizations and other health variables were observed at levels lower than 100 mg/m^3 of particulate matter (PM_{10}, $PM_{2.5}$), defined as the average daily concentration of PM_{10} [6].

In developing countries, 18% of the GBD is related to pregnancy complications [7]. A significant effect of inhalation of air pollutants during pregnancy and birth periods could be low birth weight (LBW) [8], intrauterine growth retardation (IUGR), and preterm birth (PTB)[9] have been shown by similar studies [1, 10].

Birth outcomes are important, since they are important indicators of the infants' health and affect their future health status. In addition, the embryonic term is a critical period of development, and the organ systems of the fetal body are rapidly multiplying cells or changing metabolic capabilities. Sensitive vitamins (sensitive period of growth) can be vulnerable to environmental toxins. Studies have shown that exposure to air pollutants changes the endothelial function of the fetus, causes inflammation and insulin resistance, and also increases high blood pressure and coronary heart disease[11-13].

Many environmental factors, including air pollution, harm fetal growth [14]. Delay in growth and development in the womb can increase the risk of many chronic disease including cardiovascular diseases risk and cognitive development in the future [14, 15]. In recent years, the number of studies on the impact of exposure to air pollution on birth outcomes has increased. Hooven et al. have shown that exposure to PM_{10} and NO_2 pollutants in the third trimester of pregnancy leads to a smaller fetal head circumference [10]. Qian et al. have proved the relationship between air pollutants and PTB[16].

PTB is the main cause of child mortality. Furthermore, surviving preterm infants are at risk of short-term health complications, including acute problems of the respiratory system, digestive system, infectious diseases, central nervous system disorders, hearing and vision problems, as well as long-term neurological disabilities such as cerebral palsy and learning disabilities, and also suffer from chronic diseases in adulthood [17].

Many studies have shown that inhaling air pollution raises the risk of PTB (23% or 3.4 million PTBs worldwide in 2010) responsible for $PM_{2.5}$ particles. It has been hypothesized that it is more difficult to detect the relationship between air pollution and PTB than other outcomes such as LBW, which can be related to the duration of exposure to polluted air during the entire pregnancy or the third trimester in PTBs, and the presence of seasonal cycles in the incidence of PTB [18]. Limitd studies exist on the relation between ambient air pollution and infant or fetal mortality. The latest ones have shown that infant mortality in countries with low air pollution is 19% lower than in countries with high concentrations of air pollution [4].

Although there have been many studies on air pollutants' effects on vulnerable groups, challenges in this field are still felt. The city of Yazd has a very low self-purification capacity due to its vegetation. On the other hand, due to the establishment of large mines around the city, it is considered one of the major industrial poles in the country. Therefore, this study aimed to demonstrate the impact of air pollution on birth consequences in Yazd, Iran during 2017-2020.

Materials and Methods

Study area and data gathering

Yazd city is situated on the edge of Iran central desert and has an unfavorable climate and nature. Yazd is one of the most important cities in Iran in terms of industries and mines, which have developed a lot in recent decades. The exclusion criteria were smoking status, alcohol consumption, history of genital diseases, and intentional abortion. Large populations, vehicle traffic, industrial settlements, and the presence of natural factors, aggravate air pollution. This cross-sectional study was conducted in the form of modeling data from the mother and child cohort study.

Outcomes definition and assessment

Pregnant mothers and birth outcomes data were obtained from the medical and hospital records of the individuals in the mother and child cohort data of Shahid Sadoughi University of Medical Sciences (2017 to 2020). The mentioned outcome areas included term sex ratio, LBW, fetal height and head circumference size, premature delivery, and spontaneous abortion. The sex ratio was the ratio of girls' births to total births. The term LBW is defined as a birth that occurred on or after the 37th week of gestation with a weight less than 2500 g [19]. Premature delivery is defined as a birth that occurred before 37 weeks of gestation [20]. The criteria of head circumference were considered to be ≤ 32.5 cm, and neonates with height ≤ 44 cm. Spontaneous abortion is defined as the loss of pregnancy naturally before twenty weeks of gestation [21].

Exposure estimation

Daily concentrations of five criteria air pollutants including sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3), and coarse particles (PM_{10}) during 2017-2020 were obtained from two fixed air monitors of Yazd Municipal Environmental Monitoring Center. Monitoring stations are located in the central areas of each city (Natural Resources Department and Environment Organization). The average monthly level of pollutants was calculated for the stations, separately. The amount of AQI was calculated using Equation 1:

$$I_P = \frac{I_{Hi} - I_{Lo}}{BP_{Hi} - BP_{Lo}} (C_P - BP_{Lo}) + I_{Lo} \qquad (1)$$

where I_P is the AQI for pollutant (P), C_P is the measured concentration of pollutant (P), BP_{Hi} is a breakpoint that is greater than or equal $C_P\,(t)$, BP_{Lo} is breakpoint that is less than or equal to C_P, I_{Hi} and I_{Lo} are AQI value corresponding to BP_{Hi} and BP_{Lo} , respectively [22].

Then, the AQI was calculated and compared for all months of the year. Finally, the highest AQI value was selected as the AQI value of Yazd city during 2017-2020.

Data analysis

The data were primarily analyzed using appropriate descriptive indices such as mean and standard deviation, as well as trend charts. Also, the time series model statistical test (ARMA model) was used to study the relationship between air pollution and the consequences of birth problems during study periods (2017 to 2020). The autoregressive (AR) and moving average (MA) or ARMA model is one of the important methods for studying time series. Yule, Slutsky, Walker, and Yaglom formulated the concept of AR and MA models [23]. The ARMA model expresses the conditional mean Y_t as a function of both past observations Y_{t-1}, Y_{t-p}, and past innovations $\in_{t-1}$, $\in_{t-p}$. In this model, the number of past observations that Y_t depends on p is the AR degree. The number of past innovations that Y_t depends on, is the MA degree [24]. To increase the interquartile range for each pollutant exposure, correlation coefficient and confidence intervals (Cis = 95%) were also investigated.

Ethical Issue

This study was approved by the Ethics committee of Shahid Sadoughi University of Medical Sciences (ID: IR.SSU.SPH.REC.1399.189).

Results

In this study, the effect of ambient air pollution on adverse pregnancy and birth outcomes was investigated and the ARMA model was used for data analysis. The changes in the AQI of Yazd city during 2017-2020 were analyzed and the results are illustrated in Figure 1. Average amount of AQI was at or below 100 and the air quality of Yazd has been in satisfactory condition during these years. However, in some cases, the AQI was higher than the standard; for example, its value was between 137 and 129, in January 2017 and October 2019, respectively, which was unhealthy for sensitive groups of people. Most of the problems caused by air pollution in Yazd are related to particles. The level of PM_{10} is above the limit of 50 µg/m³ most of the time.

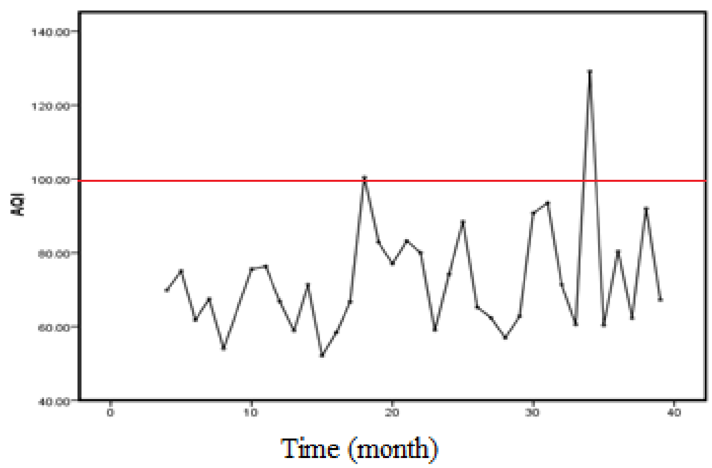

Figure 1: Changes in the Ambient Quality Index of YAZD during 2017-2020

Distribution of birth outcomes and covariates through changes in the mean and standard deviation are presented in Table 1. There were 2113 singleton live births, of which 193 PTBs were enrolled in the cohort study. During this term, 237 spontaneous abortions happened.

Table 1: Characteristics of birth outcomes in Yazd city (2017-2020)*

Year	Girl by total born	Premature delivery	LBW	Fetal height ≤ 44cm	Small head size ≤ 32.5 cm	Spontaneous abortion
2017	0.52 (0.16)	0.12 (0.09)	0.06 (0.04)	0.02 (0.02)	0.044 (0.05)	5 (3.30)
2018	0.50 (0.04)	0.09 (0.04)	0.08 (0.04)	0.01(0.01)	0.06(0.03)	5.83 (3.37)
2019	0.49 (0.06)	0.087 (0.05)	0.09 (0.07)	0.03(0.02)	0.07 (0.04)	3.58(0.99)
2020	0.53 (0.05)	0.16 (0.09)	0.05 (0.009)	0.01(0.01)	0.08(0.03)	6.33(5.5)

*The numbers in the table: the mean (standard deviation) of the monthly ratio of birth outcomes in Yazd city as year

Table 2 shows the coefficient and the 95% confidence intervals (95%CI) of the ARMA models for the rate of birth outcomes and air pollution exposure using mean concentrations of all the five inhaled pollutants (CO, NO_2, O_3, SO_2, and PM_{10}) and the AQI. According to the results of the statistical analysis obtained from the ARMA model, there was a significant relationship between the ratio of a girl born to total birth with the mean concentration of NO_2 (Coef:7.943, 95%CI:2.797,13.089) and AQI (Coef:0.001, 95%CI:0.000,0.001), but there was no correlation between this ratio and other air pollutants). Premature delivery was related to the mean concentration of NO_2 (Coef: 2.915, 95%CI: 0.224, 5.606) and AQI (Coef:0.001, 95%CI:0.000,0.001). However, inhalation of other pollutants has not been significantly linked to preterm birth. Also, increasing the risk of preterm delivery had a significant relationship with the AQI index during pregnancy (Coef: 0.001, 95%CI: 0.000, 0.0001). There was also a significant relationship between spontaneous abortion and the mean concentration of NO_2 (Coef: 44.751, 95%CI: 26.872, 62.629) and O_3 (Coef: -4.124, 95%CI: -8.031, -0.218) in the air. However, there was no relationship between this ratio and exposure to other air pollutants (CO, $PM_{10,}$ and SO_2) and AQI.

Table 2: The relationship between air pollution and AQI of YAZD city with birth consequences by ARMA model during (2017-2020)

	Girl to total born		Premature delivery		LBW		Fetal height ≤ 44cm		Small head size ≤ 32.5 cm		Spontaneous abortion	
Exposure	**Coef.**	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% CI**	**Coef.**	**95% CI**
NO_2	7.943	**(2.797, 13.089)**	2.915	**(0.224, 5.606)**	-2.607	(-6.519, 2.384)	0.119	(-1.713, 1.952)	-.039	(-2.234, 2.157)	44.751	**(26.872, 62.629)**
CO	-0.010	(-0.059, 0.039)	-0.006	(-0.02, 0.009)	0.013	(-0.008, 0.034)	0.005	(-0.006, 0.016)	0.001	(-0.009, 0.012)	0.020	(-0.145, 0.185)
O_3	-0.724	(-2.916, 1.469)	0.202	(-0.603, 1.008)	-0.349	(-2.634, 1.935)	0.011	(-0.253, 0.274)	-0.345	(-1.231, 0.541)	-4.124	(-8.031,-0.218)
SO_2	0.617	(-18.780, 20.013)	2.157	(-2.375, 6.688)	-4.000	(-9.735, 1.735)	1.387	(-2.373, 5.146)	-1.967	(-5.218, 1.284)	-14.520	(-83.822, 54.872)
PM_{10}	0.000	(-0.003, 0.003)	0.000	(-0.001, 0.001)	-0.000	(-0.001, 0.001)	-0.000	(-0.001, 0.000)	0.000	(-0.000, 0.001)	0.001	(-0.007, 0.008)
AQI	0.001	**(0.000, 0.001)**	0.001	**(0.000, 0.001)**	-0.001	(-0.001, 0.000)	-0.000	(-0.000, 0.000)	-0.000	(-0.001, 0.000)	-0.003	(-0.005, 0.000)

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Discussion

The daily concentrations of ambient air pollutants related to five air quality criteria including SO_2, NO_2, CO, O_3, and PM_{10} recorded from two air pollution monitoring stations were obtained from the Environment Agency. Then, the monthly mean level of each pollutant was calculated.

Based on the results, the air quality of Yazd city during 2017-2020 was generally at a moderate level and the AQI was below 100, but the AQI of Yazd city was unhealthy for sensitive groups in January 2017 and October 2019 and was very unhealthy in March and February 2017. PM_{10} had the highest concentration of pollutants in the air. The concentration of PM_{10} in most of the urban areas in Yazd was above the limit of 50 µg/m³ (24-h average), which can be due to desert dust storms. Yazd is often affected by the atmospheric transport of desert dust from drylands around the city. It represents a real threat to air quality and population health in source areas, and its implications extend to downstream areas. Barnaba et al. evaluated the effect of desert dust on particulate matter AQI in Italy. They found that in Italy, desert dust contributes to exceeding PM_{10} limit fixed by the EU and WHO [25]. In addition to the contribution of natural resources, the industrial nature of Yazd city and transfer traffic also have a significant role in shaping air pollution, especially particles. Although economic development has been achieved at the expense of the environment over the past decades, many rigorous environmental policies have been adopted by relevant organizations in the field of reducing air pollution, while progress still needs to be made on cutting back greenhouse gas emissions.

In the present study, according to the available data, 2113 singleton live births, 193 premature births, and 237 spontaneous abortions were considered in the analyses. Evaluating the impact of exposure to different chemical pollutants on human health is a big challenge. The lack of measured data and appropriate methodological approaches remain two main obstacles. In this study, the effect of air pollutant on birth and pregnancy consequences was investigated and ARMA model was used for data analysis.

Based on data analysis, there was a significant relationship between the ratio of a girl born with total birth with the mean concentration of NO_2 and AQI, while no relationship was observed with other air pollutants. Although the number of studies conducted in the field of the relationship between infant gender and exposure to environmental pollutants is very limited, previous research on environmental pollutants suggested that fluctuations in sex ratios of births might provide a useful early warning of possible health effects of toxins or other environmental stressors. According to the analyses of the sex ratios of Williams et al. [26], a study in residential areas at risk of airborne pollution from incinerators showed locations with statistically significant excesses of female births. In a small industrial town in central Scotland, the possible role of air pollution was associated with an abnormally high sex ratio of births [27]. Research in populations and wildlife has shown a fewer male births, but the mechanism by which environmental risks may change the gender relationship remains unclear [28].

Based on the result of this study, exposure to CO, SO_2, O_3, and PM_{10} throughout pregnancy was not associated with preterm delivery (birth before 37 weeks of gestation). However, increased risk for premature delivery, significantly related to AQI and NO_2 concentration during the pregnancy. The evidence for the association between PTB and air pollutants is conflicting. The findings of several studies showed that the increased risk of PTB is consistent with exposure to air pollution during pregnancy [29-31], while it was not observed in some other studies.

The time series study of the relationship between LBW at birth with exposure to CO, NO_2, O_3, and PM_{10} as well as AQI index during pregnancy demonstrated that there was no relationship between

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air pollution and AQI index with a birth weight loss. In many studies, inhalation of air pollutants during pregnancy was associated with LBW [32, 33]. The results of Chen et al. showed that exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO before and during pregnancy was strongly implicated with an increased risk of LBW [34]. In the study by Bergstra et al., the higher exposure to PM_{10}, NOX, SO_2, and VOC during pregnancy was significantly associated with lower birth weight [35]. Gray et al. predicted concentrations of $PM_{2.5}$ and O_3 pollutants which were associated with a greater effect on LBW and increase in LBW risk [36]. Researchers have hypothesized that exposure to particles may directly modulate trophoblast proliferation, due to the interaction between these pollutants and placental growth factor receptors [37, 38]. Such reactions may interfere with placental fetal oxygen and nutrient exchange and subsequently disrupt the growth of the fetus [19]. However, some surveys were similar to the findings of the present work [39, 40]. A study also showed that there was a relationship between O_3 and LBW [19]. Currently, more research is required to gain a better understanding of the effects of air pollution on LBW, including the identification of susceptible populations, the effects of multiple pollutants, the influence of different climate types, time symmetries, and different study designs.

The results of investigating the relationship between height and head circumference of newborns with air pollutants in pregnancy showed that there was no relationship between exposure to CO, NO_2, O_3, and PM_{10} as well as AQI during pregnancy with height and head circumference of the newborn. Similar studies have been conducted to investigate the relationship between the height and head circumference of infants and exposure to environmental and indoor air pollutants. In the cross-sectional analysis of Hooven et al., PM_{10} and NO_2 amounts were both associated with a smaller fetal head circumference in the third trimester of pregnancy, but mean levels of PM_{10} and NO_2 during pregnancy were not associated with newborn head circumference and length [10]. The results of a similar study by Franklin et al. showed that exposure to NO_2 had no significant relationship with height and head circumference of newborns [41], which is consistent with the results of the present study.

The effects of environmental pollution on fetal spontaneous abortion are still unclear. Spontaneous abortion records were collected from Yazd mother and child cohort study (237 abortions) and their relationship with exposure levels to CO, NO_2, O_3, and PM_{10} as well as AQI was studied between 2017 and March 2020. The results showed that there was a significant relationship between O_3 pollutants and spontaneous abortion. Many studies have examined the relationship between air pollutants and the risk of spontaneous abortion, with considerable heterogeneity among the results. The degree of heterogeneity varied significantly depending on the pollutant, consequences, and duration of exposure. A time series study in Italy reported that with an increase in exposure to 10 $\mu g/m^3$ PM_{10} and ozone, the risk of spontaneous abortion increased by 20% and 34%, respectively [42]. A case-control study failed to confirm an association with PM_{10}, but showed that exposure to total suspended particulate (TSP) in the first 14 weeks of pregnancy during the heating period (December to May) doubled the risk of spontaneous abortion (OR = 2.04, 95 % CI 1.01–4.13) [43]. A case-control study in Iran showed that CO, NO_2, O_3, and PM_{10} had a strong effect on spontaneous abortion, but no association was found between SO_2 and spontaneous abortion [44]. However, a time-series study in Ahvaz reported no association between spontaneous abortion and CO exposure [45], and a Kuhurt study found null results [46]. A study in Croatia showed that the frequency of abortion was lower when the local coal plant was closed (P-value < 0.05) [47]. However, some other studies failed to support the above findings [42, 45, 46]. Studies showed inconclusive results; therefore, more studies have to be conducted in this field.

Lack of a relationship between air pollutants and pregnancy consequences in present study may be due to low levels of those pollutants, limitations of individual exposure assessment, or lack of association. Lomelin et al. reported that assessing the relationship between adverse birth outcomes with air pollution is complex. Integrating spatial data mining, epidemiology, and geography can accelerate future research on the association between air pollutant mixtures and adverse birth outcomes [48]. Guo et al. debated on the relationship between air pollution and adverse birth outcomes that may be relatively stable. However, relations can be affected by key factors of importance. It is recognized as the toxicity and effects of pollutants that may vary geographically. A significant effect of exposure to NO_2 or PM_{10} was observed only for non-Asian studies, which may be due to the fact that fewer studies were conducted in Asian countries [49]. It suggests that more studies are required to be conducted, especially in developing countries that generally have higher environmental pollution. Lavigne et al. findings suggest that intercity differences in glutathione (GSH) oxidative potential related to $PM_{2.5}$ may modify the association between exposure to ambient $PM_{2.5}$ mass concentrations during pregnancy and adverse birth outcomes [50].

The results of the study and review of similar studies showed that the exact mechanism(s) that link ambient air pollution and adverse birth outcomes could not be clearly defined. Evidence suggests that oxidative stress may have an important effect. The effects of oxidative stress on enzymatic antioxidants may contribute to adverse birth outcomes such as infertility, miscarriage, preeclampsia, intrauterine growth restriction, and preterm delivery [51].

Strengths and limitations

In this study, the relationship between adverse birth outcomes and five air pollutants (CO, NO_2, O_3, SO_2, and PM_{10}) and the AQI in Yazd city was reported. The study was conducted as a time series and data analysis was done using ARMA model to identify possible exposure relationships.

This study also had several limitations. The researchers could not conclude the relationship based on individual exposure to air pollutants. Some uncontrollable factors, such as economic status, medical history, job, and place of residence may effect on person's level of exposure to air pollutants. Prospective studies may benefit from a prospective cohort research design that allows researchers to use biomarkers and if possible, use a collection of detailed information about the characteristics of people being studied. The second limitation is that the residential address is unique to the address at the time of birth. However, many women may have lived in other cities during pregnancy. Therefore, the researchers were unable to adjust their analysis for mothers' residential mobility during pregnancy.

Also, it could be said that to compare and combine the estimation of air pollutants, the results were scaled according to the concentration ratios of different averaging times, which only reflected the scale differences, not the actual difference related to the peak and average exposure.

Conclusions

In this study, the effect of exposure to various air pollutants on the adverse outcomes of birth and pregnancy was investigated, using ARMA model. A total of 2131 singleton live births, 193 premature births, and 237 spontaneous abortions were studied. The results showed that an increase in NO_2 concentration and AQI were associated with an increase in the ratio of a girl born to total births (Coef:7.943, 95%CI:2.797,13.089 and Coef:0.001, 95%CI:0.000,0.001, respectively) and the risk of premature birth (Coef:2.915, 95%CI:0.224, 5.606 and Coef:0.001, 95%CI:0.000,0.001, respectively).,There was also a significant relationship between the mean concentration of NO_2 (Coef: 44.751, 95%CI: 26.872, 62.629) and O_3 (Coef: -4.124, 95%CI: -8.031, -0.218) pollutants in the air with spontaneous abortion. The results of the present study cannot show a definitive relationship between air pollution and other adverse

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birth outcomes. The lack of association between air pollutants and pregnancy outcomes in present study may be due to low levels of pollutants, limitations of individual exposure assessment, or lack of association. Therefore, more studies are required to be conducted.

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Conflict of interest

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