ORIGINAL ARTICLE

Association between air pollution and preterm birth among neonates born in Isfahan, Iran

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Background: Although several studies have investigated the association between maternal exposure to air pollution and preterm birth, the results are inconsistent. The aim of this study was to further investigate the relation between maternal exposure to ambient air pollution during pregnancy and the risk of preterm birth and low birth weight (LBW) in an Iranian pregnant population. **Materials and Methods:** In this study, we identified 4758 consecutive singleton birth records from one large referral hospital (2010-2012) in Isfahan, Iran. We identified cases of preterm birth and LBW, which were combined with meteorological and air pollution monitoring data. We estimated the effect of air pollution exposure during the entire pregnancy, each trimester, and last month, and preterm birth (gestational age <37 weeks) and LBW (<2500 g) by Pollutant Standard Index (PSI) using logistic regression adjusted for gestational age, neonate gender, birth order, and mother's age. **Results:** The PSI for entire pregnancy was significantly associated with preterm birth [Odds Ratio (95% CI) = 1.26 (1.20, 1.33)]. There was no association between maternal exposure to ambient air pollution and each trimester and the last month of pregnancy, and preterm birth or LBW. **Conclusion:** Maternal exposure to ambient air pollution during the entire pregnancy was associated with preterm birth in Isfahani women.

Key words: Air pollution, low birth weight, Pollutant Standard Index, pregnancy outcome, premature birth, preterm delivery

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INTRODUCTION

Preterm birth (before 37 gestational weeks) and low birth weight (LBW) are leading causes of neonatal morbidity and mortality as well as possible increased morbidity in adulthood,[1,2] and its rate is increasing worldwide,[3] affecting 13-15% of births.[4] Families of preterm neonates also bear a substantial economic burden, including inpatient hospital costs[5,6] and long-term health care costs during the first year[6,7] and through early childhood.[7-9] The etiology of the majority of preterm births remains unknown. Thus, it is necessary to identify the risk factors for preterm delivery and work toward their prevention. Although over the last two decades or so, several studies mainly performed in North America and Australia have investigated the possible adverse effects of exposure to ambient air pollution during different periods of pregnancy on preterm birth/LBW, the role of air pollution as a risk factor for preterm birth/LBW is small and not always consistent.[10-27] In most studies, the risk of preterm delivery was slightly increased,[12-15,19-21,24] whereas others reported no association.[11,16,22,23,25-28] The risk of preterm delivery was stronger than LBW[19] or the opposite was observed[20] or inconclusive results were obtained,[17,18] making the results of these studies difficult to interpret. The inconsistency noted between studies may be related to many factors, including chance, sample size, design, risk factors, and variation across the population, differing analytic methods, and issues related to data quality and measurement error and other characteristics.

While there have been abundant epidemiological studies in Western countries, no study has been undertaken in Iranian pregnant women, where the ambient air pollution patterns and ethnicity are different. However, from clinical and public health point of view, it is important to clarify the role of ambient air pollution in association with preterm birth/LBW because the growing fetus may be particularly susceptible to the toxic effects of air pollution. Our study contributes to this issue by examining the association between ambient air pollution, measured by Pollutant Standard Index (PSI) during entire pregnancy, 1st, 2nd, 3rd trimesters, and the last month of pregnancy, and preterm birth/LBW in Isfahan, Iran. Our hypothesis is that exposure to air pollution contributes to the etiology of preterm birth/LBW.

MATERIALS AND METHODS

Study area

This study was conducted in Isfahan, a very large area where the pollutant levels are high. This place is

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situated in central Iran, located at a height of 1590 m above the sea level, between latitudes 30° and 34° north of the equator and longitude 49°-55° east, with a population of approximately 1.8 million [1,799,180 in 2004 (men 926,134, women 873,046)]. The total area is 15,263 km^2. The climate is dry and temperate, with quite wide temperature differences between the summer and the winter with a mean daily temperature of 2.8ºC in January and February, 29.5ºC in July and August, and 19.1ºC in September and October. The mean annual precipitation is 146.0 mm (reference period 2004). Major pollutant sources include vehicles and stationary combustion sources.

Subjects

The birth records of 4758 healthy pregnant women without major structural birth defects were identified from Beheshti Obstetrics and Gynecology Hospital (largest women's hospital in Isfahan) affiliated to the Isfahan University of Medical Sciences, Iran between January 2010 and June 2012. Pregnant women were eligible if they were living in those urban areas of Isfahan city with air pollution monitoring stations. Entry criteria included healthy pregnant women of 18-35 years, with no complicated pregnancy, carrying a singleton fetus, and living in Isfahan. Tenets of current version of the Declaration of Helsinki were followed; study protocol was reviewed and approved by the institutional ethical committee of Isfahan University of Medical Sciences.

Definitions

Preterm birth was the main outcome evaluated, which was defined as a singleton live-birth delivery before 37 completed weeks of gestation. Gestational age was computed on the basis of the date of a woman's last menstrual period (LMP) supported by an ultrasound scan. For women whose LMP date was missing, the clinical estimate of gestational age was substituted. No individual information is available about whether or not the gestational age was based on an ultrasound examination or the date of the LMP. We used the estimate of gestation in completed weeks to back-calculate the date of conception. LBW was defined as weight at birth less than 2500 g.

Air pollution data

Data of the four existing fixed-site air-monitoring stations in the Isfahan city were used to represent the exposure of participants to air pollutants. For categorizing the air quality measurement, we used the PSI for five major pollutants routinely monitored in many parts of the world [CO, O_3, NO_2, SO_2, and particulate matter less than 10 μm (PM_{10})]. The PSI converts air pollution concentrations to a simple number between zero and 500 and assigns descriptive terms such as "good" or "moderate" to that value. PSI values of 0-50 and 51-100 indicate good and moderate air quality, respectively. A PSI value of 100 indicates that at least one pollutant reached its ambient air quality standard on that day. PSI values of 101-150 show that the air quality is unhealthy for sensitive groups, and values of 151-200 indicate unhealthy air. A PSI of 200 corresponds to a first-stage alert during which time elderly persons with existing heart or lung disease are advised to stay indoors and reduce their physical activity; and PSI values of 201-300 indicate very unhealthy air. A second-stage alert is called when the PSI reaches 300, at which point the general public is advised to avoid outdoor activity, i.e., PSI values of 301-500 indicate hazardous air quality. Pollution data on the entire pregnancy period, at the 1st (defined as gestational weeks 1-13), 2nd (defined as gestational weeks 14-26), and 3rd (defined as from 27 weeks to birth) trimesters, and at the last 4, 6, and 8 weeks before birth day and at birth day were collected and the citywide daily average levels was matched for each woman. PSI data were matched with the time of pregnancy for each woman to estimate pollution effects on preterm/LBW. To estimate pollution effects on preterm/LBW, we calculated for every participant, the average PSI concentration during the entire pregnancy, at the 1st, 2nd, 3rd trimesters, and at the last month and last week of pregnancy from the daily average concentration.

Statistical analysis

Statistical methods used included the Student's *t*-test, one-way analysis of variance (ANOVA), chi-squared test, and binary logistic regression. Comparisons between quartile of PSI were calculated by ANOVA followed by Tukey–Kramer *post-hoc* comparison. Univariate and multivariate binary logistic regressions were fitted to identify predictors of preterm birth/LBW using the SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). Two models were used to assess the relationship between PSI for the entire pregnancy, the 1st, 2nd, and 3rd trimesters, and the last 4, 6, and 8 weeks before birth day and at birth day, and preterm birth/LBW; the first model was unadjusted and the second model was adjusted for maternal age, neonatal gender, and birth order. Age-adjusted means were calculated and compared using general linear models. All tests for statistical significance were two-tailed and performed assuming a type I error probability of <0.05.

RESULTS

Characteristics of the 1069 (22.5%) neonates with preterm birth and 3689 (77.5%) neonates with term birth, as well as of 837 (17.6%) neonates with birth weight <2500 g and 3921 (82.4%) neonates with birth weight ≥2500 g are shown in Table 1. Women with preterm birth/LBW were older and had lower maternal age-adjusted mean gestational age and PSI for 2nd and 3rd trimesters, and those with LBW had lower proportion of boys and higher proportion of 1st birth order. The gender of the neonate was not associated with preterm

Table 1: Age, age-adjusted means (SE), and proportions of selected characteristics between 1067 preterm births and 3685 term births and 837 neonates with birth weight <2500 g and 3921 neonates with birth weight ≥2500 g

Variables	Mean (SE)			
	Preterm birth	Term birth	Weight <2500 g	Weight ≥2500 g
Maternal age (years)	27.7 (0.17)	26.9 (0.09)***	27.5 (0.19)	27.0 (0.09)*
Gestational age (weeks)	33.8 (90.05)	38.8 (0.03)***	34.6 (0.8)	38.3 (0.04)***
Neonatal weight (g)	2387 (15.71)	3121.4 (8.44)***	1986.2 (13.7)	3162.5 (6.31)***
PSI for entire pregnancy	103.4 (0.21)	103.2 (0.21)	103.3 (0.24)	103.3 (0.11)
PSI for 1st trimester	107.0 (0.45)	107.3 (0.25)	107.8 (0.52)	107.1 (0.24)
PSI for 2nd trimester	104.1 (0.43)	105.3 (0.23)*	103.9 (0.49)	105.3 (0.23)*
PSI for 3rd trimester	99.5 (0.46)	102.5 (0.25)***	99.3 90.52)	102.4 (0.24)***
PSI for last 4 weeks before birth	99.7 (0.52)	100.6 (0.28)	99.7 (0.59)	100.5 (0.27)
PSI for last 6 weeks before birth	99.9 (0.49)	100.8 (0.27)	99.9 (0.55)	100.7 (0.26)
PSI for last 8 weeks before birth	100.2 (0.45)	101.2 (0.24)*	100.2 (0.51)	101.2 (0.24)
PSI for 1 week before birth	97.7 (0.77)	98.2 (0.41)	97.9 (0.67)	98.2 (0.40)
PSI at birth	98.5 (0.84)	100.3 (0.45)	99.2 90.95)	100.0 (0.44)
Male neonate, %	53.9	51.4	47.7	52.9**
Birth order, %				
First	48.5	49.9	54.0	48.6*
Second	33.0	33.0	30.1	33.6
Third	12.5	12.2	10.5	12.6
≥4	6.1	4.9	5.4	5.2
Season of birth, %				
Spring (March-May)	25.3	21.0*	25.6	21.9*
Summer (June-August)	24.1	26.3	24.3	25.9
Fall (September-November)	27.4	27.6	26.9	27.5
Winter (December-February	23.2	25.1	23.3	24.7
Year of birth, %				
2009	27.3	29.5***	29.0	29.0*
2010	46.7	50.6	46.4	50.4
2011	26.0	19.9	24.6	20.6

Age-adjusted means were calculated using general linear models. The difference in the mean or percentage of the variables between preterm births and term births and between weight <2500 g and weight ≥2500 g. *P < 0.05, **P < 0.01; ***P < 0.001. CI = Confidence interval

birth. The mean (SD) maternal age was 27.7 (7.0) years for those with preterm birth and 26.9 (6.5) years for those with term birth. The mean (SD) PSI for the entire pregnancy was 103.4 (3.2) for those with preterm birth and 103.2 (4.1) for those with term birth. The total PSI for the entire pregnancy ranged from 85.6 to 128.3.

The characteristics of the study participants by PSI for the entire pregnancy quartile are shown in Table 2. In age-adjusted comparisons of variables, all PSI variables were more likely to slightly increase and gestational age was more likely to slightly decrease across the four subject groups.

To determine the independent predictors of factors associated with preterm birth/LBW, stepwise binary logistic regression was used to test 12 predictor variables [mother's age, birth order, infant gender (male and female), PSI for the entire pregnancy, 1st, 2nd, and 3rd trimesters, and the last 1, 4, 6, and 8 weeks before birth day and at birth day]. The dependent variable was birth under 37 weeks of gestation or birth weight <2500 g.

In crude and adjusted analyses, there was a significant positive association between PSI levels and preterm birth during the entire pregnancy [Odds Ratio (OR) (95% CI) = 1.26 (1.20, 1.33)]. No association was found between PSI and preterm birth/LBW in all exposure periods. Controlling for mother's age, neonate's gender and birth order did not appreciably alter the OR compared to the unadjusted model [Table 3]. There was no indication for an adverse effect of air pollution on LBW from these analyses.

DISCUSSION

We studied the association between ambient air pollution, measured by PSI during entire pregnancy and eight gestational windows, and preterm birth/LBW in Isfahan, Iran. Our analysis suggests that ambient air pollution during the entire pregnancy may have an impact on preterm birth, but not on LBW. There was no association between air pollution at particular gestational windows and preterm birth/LBW. There could be several explanations to these null effects. One possible explanation is that there is no effect. The other

Table 2: Age, age-adjusted mean (SD) and proportion characteristics of mothers and neonates by pollutant standard Index (PSI) quartile for the entire pregnancy

Characteristic	Total	Pollutant standard Index quartile for entire pregnancy mean (SEM)			
		1st quartile (<97.4)	2nd quartile (97.5-102.5)	3rd quartile (102.6-109.2)	4th quartile (≥109.3)
Number (%)	4029 (100)	1008 (25.0)	1008 (25.0)	1008 (25.0)	1005 (24.9)
Maternal age (years)	27.1 (0.09)	27.2 (0.17)	27.2 (0.17)	27.2 (0.17)	26.9 (0.17)
Gestational age (weeks)	37.5 (0.04)	37.2 (0.09)	37.8 (0.09)*[a]	37.6 (0.09)*[a]	37.4 (0.09)*[a]
Neonatal weight (g)	2946.0 (9.40)	2916.0 (19.15)	2973 (19.14)	2962.8 (19.14)	2932.1 (19.17)
PSI for entire pregnancy	103.3 (0.10)	95.2 (0.06)	100.1 (0.06)*[a]	105.9 (0.06)*[a]	111.8 (0.06)*[a]
PSI for 1st trimester	107.2 (0.21)	94.3 (0.37)	112.0 (0.37)*[a]	111.6 (0.37)*[a]	111.1 (0.37)*[a]
PSI for 2nd trimester	102.7 (0.20)	91.9 (0.25)	93.9 (0.254)*[a]	108.2 (0.25)*[ab]	116.8 (0.26)*[ab]
PSI for 3rd trimester	98.9 (0.21)	100.3 (0.40)	94.0 (0.40)*[a]	95.8 (0.40)*[ab]	105.8 (0.40)*[ab]
PSI for last 4 weeks before birth	97.9 (0.25)	102.7 (0.51)	95.9 (0.51)*[a]	96.3 (0.51)*[a]	96.7 (0.51)*[a]
PSI for last 6 weeks before birth	97.8 (0.23)	102.3 (0.46)	95.4 (0.46)*[a]	93.2 (0.46)*[ab]	100.4 (0.46)*[ab]
PSI for last 8 weeks before birth	98.1 (0.21)	102.0 (0.40)	95.1 (0.40)*[a]	91.8 (0.40)*[ab]	103.6 (0.40)*[ab]
PSI for 1 week before birth	98.3 (0.32)	103.0 (0.65)	97.9 (0.65)*[a]	98.6 (0.65)*[a]	93.7 (0.65)*[ab]
PSI at birth	96.4 (0.40)	103.6 (0.81)	99.7 (0.81)*[a]	99.6 (0.81)*[a]	91.7 (0.81)*[ab]
Male neonate, no. (%)	2108 (52.3)	519 (51.5)	509 (50.5)	535 (53.1)	545 (54.2)
Birth order, no. (%)					
First	1980 (49.1)	495 (49.1)	513 (50.9)	469 (46.5)	503 (50.0)
Second	1348 (33.5)	343 (34.0)	308 (30.6)	353 (35.0)	344 (34.2)
Third	488 (12.1)	117 (11.6)	128 (12.7)	132 (13.1)	111 (11.0)
≥4	213 (5.3)	53 (5.3)	59 (5.9)	54 (5.4)	47 (4.7)

Age-adjusted means were calculated using general linear models with Bonferroni correction for multiple comparisons. Data are expressed as mean (SE) or number (%).*$P < 0.001$ comparison across all four groups. The difference in the mean of the variables compared with the [a]1st quartile and [b]2nd quartile

Table 3: Association between Pollutant Standard Index (PSI) levels in the entire pregnancy, 1st, 2nd, 3rd trimesters, 1st, 4th, 6th, 8th weeks before birth, and on birth day, and preterm birth and low birth weight

	Odds ratio (95% CI)[†]	
	Preterm birth	Low birth weight
PSI for entire pregnancy	1.26 (1.20, 1.33)*	1.001 (0.99, 1.01)
PSI for 1st trimester	1.00 (0.99, 1.00)	1.004 (0.99, 1.01)
PSI for 2nd trimester	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
PSI for 3rd trimester	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
PSI for last 4 weeks before birth	1.01 (0.99, 1.02)	1.00 (0.99, 1.001)
PSI for last 6 weeks before birth	1.01 (0.98, 1.04)	1.00 (0.99, 1.001)
PSI for last 8 weeks before birth	1.00 (0.96, 1.01)	1.00 (0.99, 1.00)
PSI for 1 week before birth	1.00 (0.99, 1.00)	1.00 (0.99, 1.002)
PSI at birth	1.00 (0.99, 1.002)	1.00 (0.99, 1.002)

[†]Odds Ratio (with 95% CI) calculated by binary logistic regression. Adjusted for maternal age, neonatal gender, and birth order; CI = Confidence interval

possible explanation for these null results could be an underestimation of effect due to the use of ambient measurements instead of personal exposure. Extrapolation from citywide measurements to individual exposures can be problematic. In addition to exposure measurement error, gestational age is known to be measured with error on birth records.[29] Finally, as in previous studies, we could identify only conceptions resulting in a live birth; association between early pregnancy air pollution exposure and preterm birth would be underestimated if air pollution increased the risk of fetal loss in addition to preterm birth. Limited variability in air pollution levels may be another explanation for the absence of an effect in the present study. Despite differences in the pollutants and study design, several epidemiologic studies have reported weak evidence of an association between ambient air pollution level and preterm birth/LBW, beyond individual level characteristics. For example, maternal exposure to carbon monoxide or motor vehicle exhaust late in the pregnancy was associated with preterm birth/LBW in Canada and the United States.[12,25,30-34] Other studies have linked preterm birth/LBW to late pregnancy exposure to $PM_{2.5}$ and PM_{10} in the Unites States and Brazil.[12,30,34,35] Early pregnancy exposure to ozone and PM_{10} increased the risk of preterm delivery in Australia.[16] Increased concentrations of several pollutants during the 1st and 3rd trimesters were linked with preterm birth in the Republic of Korea.[36] A study from the Czech Republic found SO_2 to be associated with preterm birth regardless of period of exposure.[37] Another study from China reported that exposure to elevated level of SO_2 during the last trimester shortened gestational length[38] and contributed to LBW.[39] Additionally, exposure to particles during early gestation as well as to nitrogen oxides and nitrogen dioxide during early or late gestation was associated with preterm birth/LBW.[23,34,40] However, several studies have found no consistent association. In the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort, there was no significant association between preterm birth and NO_2 during the 1st trimester, last month,

or the entire pregnancy.[22] Neither was there any significant association between NO_2 and preterm birth in a study from the United States.[11] From Australia, an unexplained protective effect of NO_2 has been reported.[23] Several studies have found no association between exposure to CO, SO_2, nitrogen dioxide, petrochemical pollutant, and the risk of LBW or small for gestational age.[41-44] The few studies conducted on ozone have not found robust associations.[11,16,23,25] Our estimated effect sizes for preterm birth/LBW may not be directly comparable to those from other air pollution studies because we estimated air pollution based on PSI. PSI may be a more appropriate metric than gas or particle mass concentration when evaluating health risk from air pollution. Ambient air pollution comprises a complex mixture of pollutants, and it is very difficult, if not impossible, to separate the effects of individual pollutants from those of others. The limitations of single pollutant models in explaining health consequences are increasingly recognized.[45,46] Expanding the number of pollutants measured in a study design is thus desirable.[46,47] However, we believe that it is likely that the linkage between preterm birth and temporal variations in ambient air pollution that we observed in this study was due to the mixture of air pollutants rather than just one component. It will be of significant interest to examine the impact of the interaction between these various measures and functional outcomes in pregnancy.

Although the exact mechanisms whereby air pollution is associated with higher risk of preterm birth/LBW are not entirely clear yet, several mechanisms, some of which may be specific to particular time windows in gestation, can be proposed. The weak association of air pollution with higher risk of preterm birth/LBW may be attributed to implantation errors in early pregnancy, oxidative stress, placental dysfunction, and inflammation,[48,49] which may increase the risk of preterm birth/LBW. There is evidence that in late pregnancy, maternal exposure to air pollution triggers inflammation that could increase maternal susceptibility to infections, which have been linked to uterine contractions and the initiation of preterm birth.[49,50] The component chemicals of air pollution can lead to systemic oxidative stress, resulting in DNA damage that has been linked to restricted fetal growth and lower birth weights.[49,50] Air pollution may also restrict fetal growth by causing placental dysfunction and subsequent nutrient and oxygen delivery to the fetus.[31] Reduced placental perfusion may result from inflammation[36,49] and increased blood viscosity[50] associated with maternal exposure to air pollution. Likewise, the crucial windows of exposure are not clear yet. The 1st trimester exposure and the exposures during the 3rd trimester and the last weeks preceding birth have been implicated as the most relevant.[11] Air pollution levels in the weeks following conception could disrupt implantation and placentation and increase the risk of preterm birth through suboptimal placental function. Maternal exposure to air pollution in a later stage of gestation may cause disturbances in cord blood flow or increased susceptibility for maternal infections, which may cause premature rupture of membranes leading to an earlier birth.[30] While a number of plausible pathways related to these mechanisms, particularly inflammation and implantation error, have been proposed, the mechanisms underlying the observed associations remain unclear, both because of the complex nature of preterm birth/LBW etiology as well as the heterogeneous composition of air pollution.

This study had several limitations. One potential source of bias is residual confounding due to the risk factors that we were unable to account for in our analysis (socio-economic status, educational level, air conditioning use, proximity to roadways, geographic location, level of physical activity, smoking, stress, nutrition, work environment, and maternal weight gain). Moreover, unknown confounders cannot be adjusted for. Thus, the observed minimal increased risk of preterm birth associated with air pollution may reflect confounding by these risk factors.

Furthermore, we assumed that ambient air pollution, measured by PSI, was spatially homogeneous within a geographic area around each monitor site. We also assumed that the mothers did not move during pregnancy. Finally, ambient air pollution levels were used as a surrogate measure for actual personal air pollution exposure. Our exposure estimates were based only on residential addresses, ignoring other microenvironments that might be important for personal exposure. Ritz *et al*.[11] reported the associations between monitor-based estimates of air pollution exposure during pregnancy and preterm birth to be greater for women who did not work (and for whom a residence-based measure of exposure presumably is more accurate) than for women who worked outside their homes.

In conclusion, the results from this study support a weak positive association between maternal exposure to ambient air pollution during the entire pregnancy and preterm birth. These associations are probably due to confounding factors, because of the observational design of our study. Further studies are warranted to find out more about these associations and possible mechanisms.

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Authors' contributions

Janghorbani M. conceived the study aims and design, contributed to the discussion and revision of the manuscript, and drafted the manuscript. Piraei E. contributed to data collection, performed the analysis, and revised the manuscript. All authors discussed the results and reviewed and edited the manuscript.

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