Relationship between air pollution and pre-eclampsia in pregnant women: a case–control study

F. Nahidi,[1] R. Gholami,[2] Y. Rashidi[3] and H. Alavi Majd[4]

العلاقة بين تلوث الهواء ومُقدِّمات الارتعاج (تسمم الحمل) في الحوامل: دراسة حالة ذات شواهد

فاطمة ناهيدي، رويا غلامي، يوسف رشيدي، حميد علوي مجد

الخلاصة: تُمثِّل مُقدِّمات الارتعاج خطراً كبيراً على الصحة العمومية في البلدان المتقدمة والنامية على حدٍ سواء، وهي السبب الرئيسي لوفاة الأمهات والأجنة وإصابتهم بالإعاقة في جميع أنحاء العالم. ويتراوح معدل حدوث مُقدِّمات الارتعاج في جمهورية إيران الإسلامية بين 5 و12٪. وهناك عوامل تُسبب مُقدِّمات الارتعاج منها تلوث الهواء، وتحدد هذه الدراسة أثر تلوث الهواء في حدوث مُقدِّمات الارتعاج بين 195 حاملاً دَخَلْنَ المستشفيات في طهران (كانت 65 سيدة منهن تعانين من مقدمات الارتعاج و130 يتمتعن بصحة جيدة). وقُسِّمت النساء إلى مجموعتين للتعرُّض إحداهما مرتفعة والأخرى منخفضة بحسب متوسط كثافة التعرُّض للمُلوِّثات أثناء فترة الحمل. ولم يكن هناك ترابُط يُعتدّ به إحصائياً بين التعرُّض لمُلوِّثات الهواء ومنها أكسيد الكربون، والمادة الجسيمية، وثاني أكسيد الكبريت، وثاني أكسيد النيتروجين، والأوزون وبين مُقدِّمات الارتعاج. كما لم يكن الأثر المشترك ذا دلالة. فتلوث الهواء إحدى المشكلات التي تعاني منها المجتمعات الحديثة ويستحيل تقريباً على الحوامل تفاديه. وهذه الدراسة من شأنها أن تقلل القلق بشأن الحوامل اللائي يعشن في مدن ملوثة.

ABSTRACT Pre-eclampsia is the main cause of maternal and fetal death and disability worldwide. Its incidence in the Islamic Republic of Iran is 5%–12%. Air pollution has been reported to be one of the causative factors, and this case–control study determined its effect on pre-eclampsia in 195 pregnant women (65 with pre-eclampsia and 130 without) admitted to hospitals in Tehran. Women were divided into high and low exposure groups according to the mean density of exposure to pollutants during pregnancy. There was no statistically significant relationship between exposure to air pollutants including CO, particulate matter, SO_2, NO_2 and O_3 and pre-eclampsia. The combined effect was also not significant. Air pollution is one of the problems of modern society and its avoidance is almost impossible for pregnant women. This study should reduce concern about pregnant women living in polluted cities.

Relation entre la pollution atmosphérique et la prééclampsie chez les femmes enceintes : étude cas-témoins

RÉSUMÉ La prééclampsie est la principale cause de décès fœtal et maternel ainsi que d'incapacité dans le monde. Son incidence en République islamique d'Iran se situe entre 5 et 12 %. Selon certaines sources, la pollution atmosphérique serait l'un des facteurs responsables de la prééclampsie. La présente étude cas-témoins a permis d'évaluer ses effets sur la prééclampsie chez 195 femmes enceintes (65 atteintes de prééclampsie et 130 en bonne santé) admises dans des hôpitaux de Téhéran. Les femmes ont été réparties en deux groupes, l'un ayant été soumis à une exposition élevée tandis que l'autre avait été moins exposé à une densité moyenne de polluants pendant la grossesse. Aucune relation statistiquement significative n'a été observée entre l'exposition aux polluants atmosphériques, notamment le CO, les particules, le SO_2, le NO_2 et le O_3 et la prééclampsie. Les effets combinés étaient non significatifs. La pollution atmosphérique est l'un des problèmes de la société moderne et il est presque impossible de l'éviter pour les femmes enceintes. La présente étude devrait permettre d'alléger les préoccupations concernant les femmes enceintes qui vivent dans des villes polluées.

[1]Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran (Correspondence to F. Nahidi: nahidifateme@yahoo.com;nahidi@sbmu.ac.ir). [2]Department of Reproductive Endocrinology, Research Institute for Endocrine Sciences, Shaheed Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran. [3]Air Quality Control Company, Tehran, Islamic Republic of Iran. [4]Departmentof Biostatistics, School of Paramedical Sciences, Shaheed Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran.

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Introduction

Pre-eclampsia is a pregnancy-specific and multisystem disorder and a significant threat to public health in both developed and developing countries. It is a major cause of maternal and fetal/neonatal mortality and morbidity worldwide [1]. Pre-eclampsia is specific to humans and is characterized by high blood pressure (≥90/140 mmHg) and proteinuria (≥300 g/24 h or ≥1+ reading on a dipstick) [2]. Pre-eclampsia affects 3%–10% of pregnancies worldwide [3,4] and its incidence has increased by 40% in the past 15 years [5]. The frequency of this disorder has been reported as 5%–12% in various regions of the Islamic Republic of Iran [6].

Vasoconstriction and endothelial activation in pre-eclampsia decrease organ perfusion, which may interfere with organ function. Pre-eclampsia may cause dysfunction in the brain, cardiovascular system, blood, and endocrine and metabolic system of the mother [7], leading to serious complications and even death [3,4,7,8]. Fetal complications include preterm birth and prematurity, intrauterine growth restriction and fetal death [3].

Given the severity of the complications of pre-eclampsia, identifying its causes and establishing preventive measures are of great importance. Risk factors consistently shown to be associated with an increased rate of pre-eclampsia include elevated early pregnancy blood pressure [9], age [10], family history [11], African–American ethnicity [12], pre-existing medical conditions such as hypertension or diabetes, obstetric characteristics such as multiple gestations [13]and hydrops fetalis, and primiparity [14].

The relationship between air pollution and incidence of pre-eclampsia has been investigated. Air pollutants activate endothelial cells and oxidative stress, which induce placental inflammation and haemodynamic reactions, eventually resulting in suboptimal placentation, adverse birth outcomes, and maternal complications such as pregnancy-induced hypertension and pre-eclampsia [15]. Hypoxia at the fetal–maternal interface secondary to impaired placentation causes dissemination of free radicals that trigger pre-eclampsia in susceptible women [16,17]. Rudra & Williams [16]and Wu et al.[17] showed a significant correlation between maternal carboxyhaemoglobin levels due to CO exposure in early pregnancy and pre-eclampsia, and between exposure to nitrogen oxides and particulate matter in early pregnancy and pre-eclampsia, respectively.

According to the Air Quality Control Company (Tehran), most pollutants in Tehran include CO, particulate matter (PM), NO_2, SO_2 and O_3 [18]. According to the United States Environmental Protection Agency (EPA) and a 6-year data collection in Tehran (1999–2004), all of the pollutants were present at higher than standard levels [19].

Considering the adverse effects of pre-eclampsia on maternal and fetal health, and increasing air pollution in Tehran, the present study was conducted to evaluate the relationship between air pollution and the incidence of pre-eclampsia in pregnant women admitted to selected hospitals in Tehran during 2010–2011.

Methods

Study population

This analytical case–control study was conducted to determine the relationship between air pollution and incidence of pre-eclampsia among 195 pregnant women aged 18–35 years (65 with and 130 without pre-eclampsia). The women were admitted to Arash, Hedayat, Milad and Shahid Akbar-Abadi Hospitals, Tehran between September 2010 and March 2011. The hospitals were selected because of their high number of deliveries and referrals for prenatal care; the hospitals were given a quota. The inclusion criteria were as follows: Iranian women; singleton pregnancy; gestational age >20 weeks [based on the valid last menstrual period (LMP) or first trimester ultrasound]; no history of hypertension and pre-eclamptic pregnancy in mother or sisters; no molar pregnancy or complicated pregnancy (hyperemesis gravidarum, placenta praevia, diabetes, high blood pressure, or heart, lung or kidney diseases during pregnancy); BMI ≥30 kg/m^2 in early pregnancy; and no smoking during pregnancy. All women were living within a 5-km radius of one of the air pollution monitoring stations and the same was true for the practitioners' offices.

Interview

The women were interviewed by a trained midwife just after initial diagnosis of pre-eclampsia and hospitalization, either before or after delivery. The control group was interviewed in hospital before or after delivery. All the interviews were conducted by the same midwife and the mean duration of the interviews was 10 minutes. There were no refusals to participate in the interviews. Data were collected using a 5-section questionnaire including: demographic characteristics, obstetrics and gynaecological history, medical history, lifestyle and mean exposure to each air pollutant during pregnancy. Content validity and test/re-test methods were used to determine the validity and reliability of the questionnaire(r = 0.95).

Air pollutant measurement

The Air Quality Control Company recorded information about the concentration of air pollutants. The pollutants considered for the study were PM10 (airborne particulate matter <10 μm in diameter), NO_2, SO_2, CO and O_3

and the relevant data were obtained by regionally located monitors. Pollutant densities were measured according to the US EPA guidelines using an air pollutant analyser (Environnement, Poissy, France), which was certified by the EPA. Devices were calibrated once daily using standard gases. The participants were divided into two groups according to exposure to pollutants. Exposure to levels less than the median was considered as low exposure and exposure to levels equal to or greater than the median was considered as high exposure.

Analysis

The following confounding factors were controlled: maternal age, previous pre-eclampsia, history of systemic disease among next of kin, parity, gravidity, consumption of dairy products and fruit and vegetables, socioeconomic level (residential type, house size, parental educational level), number of mothers referred for prenatal care, urinary tract infection during pregnancy, maternal haemoglobin level and blood group, previous abortion and preterm delivery, history of intrauterine growth restriction, pregnancy interval, exposure to sun, physical activity, vitamin consumption during pregnancy and/or fertilization, and fertilization and sampling season.

We used descriptive statistics to describe the demographic characteristics of the sample, independent t-test for quantitative variables, chi-squared test for relationships between categorical variables, and Mann–Whitney U test for ordinal variables. Normality was checked using the Kolmogorov–Smirnov test. The association between the onset of pre-eclampsia and air pollution exposure was analysed using a logistic regression model. All associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analysis was performed using *SPSS* version 17. $P<0.05$ was considered as statistically significant.

Results

The mean age in the healthy and pre-eclampsia groups was 27.55 [standard deviation (SD) 4.6] and 28.17 (SD 4.78), respectively. This difference was not significant ($P = 0.39$). Socioeconomic level (residential type, size of house, parental educational level) differed between the groups, with the incidence of pre-eclampsia being significantly lower in those with a high socioeconomic level ($P = 0.017$). Therefore, socioeconomic level was considered in the logistic regression model to investigate its effect on pre-eclampsia. The demographic characteristics and obstetrics and gynaecological history were similar between the pre-eclampsia and control groups (Table 1), with the exception of paternal occupation ($P = 0.01$) and history of preterm delivery ($P = 0.002$).The latter two variables were considered in the logistic regression model. Lifestyle and medical history were similar in the pre-eclampsia and control groups including: exposure to sun ($P = 0.16$), vitamin consumption during pregnancy and/or fertilization ($P = 0.4$), physical activity ($P = 0.57$), consumption of dairy products ($P = 0.09$), history of systemic disease among next of kin ($P = 0.47$) and maternal haemoglobin level ($P = 0.83$).However, there was a substantial difference between the groups for daily consumption of fruits and vegetables ($P = 0.01$). We considered daily consumption of ≤1 serving of fruits and vegetables as low intake and ≥2 as appropriate intake. This variable also was considered in the logistic regression model.

The level of exposure to pollutants is shown in Table 2. About half of the women were exposed to high levels of all the pollutants

The percentages of pre-eclamptic and non-pre-eclamptic pregnancies were almost equal in the low and high exposure groups, and there was no significant relationship between air pollution and pre-eclampsia in the high exposure women (Table 3).

To evaluate the predictive role of various factors such as air pollutants, paternal occupation, socioeconomic level, history of preterm delivery, and daily consumption of fruit and vegetables in onset of pre-eclampsia, a logistic regression model was used. Table 4 lists the estimated ORs for these risk factors; none of which had a predictive role in pre-eclampsia.

Discussion

This is believed to be the first study of five major air pollutants and their effect on pre-eclampsia. A considerable number of examinations were performed on mothers, to provide the required information about the relevant potentially confounding variables. We observed no relation between air pollution and the onset of pre-eclampsia, even after controlling for any potential confounding factors. Previous studies have reported that some factors increase the risk of pre-eclampsia, such as: maternal age [10],woman's occupation, history of abortion [20], gravidity, parity [3,14], interval between two pregnancies, number of mothers referred for prenatal care [20], fertilization season [3], exposure to sun [21,22], vitamin consumption during pregnancy and/or fertilization, consumption of dairy products [23], physical activity[24], history of systemic disease in first-degree relatives [3], urinary tract infection during pregnancy [25], maternal blood group [20], and maternal haemoglobin level [26]. We controlled for all of these factors through randomization.

No association was seen between air pollution and the onset of pre-eclampsia after adjustment for other possible confounding factors including: paternal occupation [27], socioeconomic level [14,28,29], previous preterm delivery [25], and daily consumption of fruit and vegetables [7]. This is contrary to the studies of Rudra and Williams [16] and Wu et al. [17] but confirms the findings

Table 1 Comparison of demographic and obstetric characteristics among women with pre-eclampsia and controls without pre-eclampsia using the chi-squared test

Variable	Pre-eclampsia (*n* = 65) No. (%)	Controls (*n* = 130) No. (%)	*P*-value
Maternal occupation			0.12
Housewife	52 (80)	109 (83.85)	
Working	13 (20)	21 (16.15)	
Paternal occupation			0.01
Office worker	22 (33.85)	39 (30)	
Manual worker	12 (18.46)	8 (6.15)	
Self-employed	31 (47.69)	83 (63.85)	
History of abortion			0.16
Yes	20 (30.77)	28 (21.54)	
No	45 (69.23)	102 (78.46)	
History of preterm delivery			0.002
Yes	11 (16.92)	5 (3.85)	
No	54 (83.08)	125 (96.15)	
Gravidity			0.53
Nulligravida	25 (38.46)	56 (43.08)	
Multigravida	40 (61.54)	74 (56.92)	
Parity			1
Nulliparous	32 (49.23)	64 (49.23)	
Multiparous	33 (50.77)	66 (50.77)	
Two pregnancies interval (years)			0.66
No pregnancy	24 (36.92)	56 (43.08)	
1	10 (15.38)	13 (10)	
2	2 (3.07)	5 (3.85)	
≥ 3	29 (44.63)	56 (43.07)	
Fertilization season			0.18
Spring	47 (72.3)	94 (72.3)	
Summer	12 (18.46)	14 (10.77)	
Winter	6 (9.24)	22 (16.93)	

of Van Den Hooven et al. [15] and Seyed Aghamiri et al. [18].

Rudra and Williams [16] showed the relationship between maternal carboxyhaemoglobin level due to CO exposure and the onset of pre-eclampsia. The difference from our study may be that we measured carboxyhaemoglobin at only one point during pregnancy (mean 15.9 weeks gestation) and CO exposure was not considered for the rest of the pregnancy. Also, accidental exposure to CO at the time of blood sampling may have affected carboxyhaemoglobin level. Some variables such

Table 2 Distribution of participants according to exposure level to the air pollutants

Air pollutant	High exposure No. (%)	Low exposure No. (%)
CO	104 (53.3)	91 (46.7)
PM	98 (50.3)	97 (49.7)
SO_2	109 (55.9)	86 (44.1)
NO_2	97 (49.7)	98 (50.3)
O_3	96 (49.2)	99 (50.8)

PM = particulate matter.

Table 3 Distribution of pre-eclampsia cases and controls without pre-eclampsia according to high exposure to various air pollutants

Air pollutant	High exposure		*P*-value (χ^2 test)
	Pre-eclampsia cases	Controls	
	No. (%)	No. (%)	
CO	30 (46.15)	74 (56.92)	0.15
PM	32 (49.23)	66 (50.77)	0.83
SO_2	39 (60.00)	70 (53.85)	0.41
NO_2	32 (49.23)	66 (50.77)	0.83
O_3	32 (49.23)	67 (51.54)	0.76

PM = particulate matter.

as previous pre-eclampsia, history of systemic disease among next of kin, diet, and socioeconomic level, which affect the incidence of pre-eclampsia, were uncontrolled in the study [16]. Our study did not show any significant effect of CO on pre-eclampsia. This might be due to the dual effect of CO on blood pressure. Seyed Aghamiri et al.[18] have proposed several possible mechanisms for reducing blood pressure in pregnancy caused by CO inhalation: (1) increasing trophoblastic invasion to the spiral arteries of the placenta; (2) reducing local inflammation at the decidua; (3) increasing blood flow in the uterus, placenta and fetus; (4) reducing the effects of hypoxia on apoptosis in syncytiotrophoblasts; and (5) activating haemoproteins involved in the normal activity of vascular endothelial in cooperation with NO. Also, CO can enhance protection of vascular cells against damage and prevent proliferation of vascular smooth muscle cells. In comparison with other pollutants, it seems that CO potentially affects the onset of pre-eclampsia, because its significance level was close to 0.05 and it may become significant in future studies.

Wu et al. showed a correlation between NO and PM exposure in early pregnancy and onset of pre-eclampsia [17]. The reason for this difference could be that exposure to pollutants was based on residence address at the time of delivery, so if a mother changed location during pregnancy, the exact exposure to pollutants could not be measured. Also confounding factors such as previous pre-eclampsia, history of systemic disease among next of kin, smoking, diet, and socioeconomic level, which influence the incidence of pre-eclampsia, were uncontrolled in their study.

To the best of our knowledge, no previous studies have been conducted on the direct effects of SO_2 and O_3 on the onset of pre-eclampsia. In a separate bivariate analysis, we found a significant relationship between socioeconomic level, previous preterm delivery, daily consumption of fruits and vegetables and pre-eclampsia. In the logistic regression analysis however these factors as well as the pollutants had no significant impact on the incidence of pre-eclampsia. There are several differences between the earlier and present studies that may explain the dissimilar findings.

First, previous studies primarily relied on birth records, which might have resulted in only partial information about important confounding factors. In our study, paternal occupation, socioeconomic level, previous preterm delivery, and daily consumption of fruit and vegetables were the main predictors

Table 4 Logistic regression analysis of the effect of air pollutants and some confounding factors on pre-eclampsia

Variable	OR[a] (95% CI)	*P*-value
CO	1.92 (0.92–4.02)	0.08
PM	0.98 (0.43–2.19)	0.96
SO_2	0.80 (0.40–1.60)	0.54
NO_2	0.77 (0.37–1.61)	0.49
O_3	1 (0.49–2.03)	0.98
Paternal occupation	1.29 (0.64–2.62)	0.06
Socioeconomic level	1.41 (0.99–2.01)	0.06
Previous preterm delivery	2.4 (0.64–2.88)	0.07
Daily consumption of fruit and vegetables	0.42 (0.21–1.29)	0.08

[a]*Adjusted OR after controlling for variables in regression analysis.*
PM = particulate matter; OR = odds ratio; CI = confidence interval.

in most pre-eclampsia models. Earlier studies did not have any information about these covariates [16,17], and as a result, they were probably more susceptible to residual ambiguity, which could have affected some of the observed relations. Second, the exposure metrics used in the different studies were based on different inputs, and the calculation methods varied. Third, the differences may have been related to geographic location. Tehran is the largest city in Iran and has a high population density. It is characterized by high emissions from road traffic, shipping, houses and industry. Previous studies on proximity to traffic and pregnancy outcomes were mainly performed in the United States, Canada, Netherlands and Taiwan [17,18,29]. No previous studies on these specific exposure measures and pre-eclampsia have been conducted in the Middle East, where air pollution may differ in terms of composition and density.

The present study had several limitations. The exposure estimates were based only on residential addresses, ignoring other microenvironments such as commuting that might be important for personal exposure. In addition, there may have been residual confounding due to risk factors that we were unable to account for in our analyses (e.g. type of fuel used for cooking and heating and use of kitchen ventilation). A final limitation of the current study was that the analysis was based on, to some extent, retrospective data, therefore, recall bias could have been a concern.

In conclusion, we found no relation between short-term increases in air pollution levels and onset of pre-eclampsia in Tehran. Air pollution is a serious problem in modern societies and avoiding exposure for some pregnant women is almost impossible. Pre-eclampsia is a significant threat to public health in developed and developing countries and is a major cause of maternal and fetal/neonatal morbidity and mortality. The results of our study reduce to some extent the concern about pregnant women living in polluted cities.

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