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The relationship of exposure to air pollutants in pregnancy with surrogate markers of endothelial dysfunction in umbilical cord

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ABSTRACT

Background: This study aims to investigate the association of exposure to ambient air pollution during pregnancy with cord blood concentrations of surrogate markers of endothelial dysfunction.
Methods: This population-based cohort was conducted from March 2014 to March 2015 among 250 mother-neonate pairs in urban areas of Isfahan, the second large and air-polluted city in Iran. We analyzed the association between the ambient carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particular matter 10 (PM_{10}), and air quality index (AQI) with cord blood levels of endothelin-1, vascular adhesion molecule (VCAM), and intercellular adhesion molecule (ICAM). Multiple regression analysis was conducted after adjustment for potential confounding factors and covariates. The regression coefficient (beta), standard error of the estimate (SE), and 95% confidence intervals for each regression coefficient (95% CI) are reported.
Results: Data of 233 mother-neonate pairs were complete, and included in the analysis. Multiple regression analyses showed that AQI, CO and O_3 had significant correlation with cord blood ICAM-1 [Beta (SE), 95%CI: 2.93 (0.72), 1.33,5.54; 2.28(1.44), 1.56,5.12; and 2.02(0.01), 1.03,2.04, respectively] as well as with VCAM-1 [2.78(0.91), 1.69,4.57; 2.47(1.47), 1.43,5.37; and 2.01(0.01),1.07,2.04, respectively]. AQI, PM_{10}, and SO_2 were significantly associated with Endothelin-1 concentrations [Beta (SE), 95%CI: 10.16 (5.08),7.61,14.28; 9.70(3.46), 2.88,16.52; and 1.07(0.02), 1.03,2.11, respectively].
Conclusions: The significant associations of air pollutants with markers of endothelial dysfunction during fetal period may provide another evidence on the adverse health effects of air pollutants on early stages of atherosclerosis from fetal period. Our findings underscore the importance of considering environmental factors in primordial prevention of chronic diseases.

1. Introduction

Nowadays, air pollution is found to cause many adverse health effects in different periods of life (1). Particulate matter (PM), ground-level ozone (O_3), carbon monoxide (CO), sulfur oxides (SO_2) and nitrogen oxides (NO_2) are five common and harmful ambient air pollutants with well-known health problems especially in pregnancy and early childhood, which can have long term effects on chronic diseases in adulthood (F A., 2001; Kelishadi and

Abbreviations: AQI;, Air quality index; PM;, Particular matter; SO_2;, Sulfur dioxide; O_3;, Ozone; NO_2;, Nitrogen dioxide; CO;, Carbon monoxide; ELISA;, Enzyme-linked immunosorbent assay; SD;, Standard deviation; Beta;, the regression coefficient; SE;, standard error of the estimate; 95%CI;, 95%confidence intervals for each regression coefficient; IQR;, interquartile range

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Poursafa, 2010; Buka et al., 2006; Kim, 2004).

Whilst a growing body of evidence supports the association between air pollution and cardiovascular disease (Brook et al., 2010; Danesh et al., 1998; Peters et al., 1997), the underlying mechanisms remain controversial. It is suggested that the interaction between inflammatory state and coagulation system is the main reason of endothelial dysfunction leading to cardiovascular injuries (Leroyer et al., 2010). Potential physiopathogenesis for these effects include increased cytokine mediated inflammation, increased thrombosis, endothelial dysfunction, and decreased plaque stability; however, these still need to be accurately determined (Danesh et al., 1998; Peters et al., 1997). It is documented that during inflammatory response, markers of endothelial dysfunction, namely vascular adhesion molecule-1 (VCAM-1; CD 106) and intercellular adhesion molecule (ICAM-1) (CD 54) increase in elderly population (Bind et al., 2012). ICAM-1 and VCAM-1 are trans membrane proteins that mediate the adhesion of leukocytes in to the endothelium during inflammatory processes (Calderon-Garciduenas et al., 2007). Endothelin is a potent vasoconstrictor (Thomson et al., 2007); its concentration increase after exposure to air pollution, it may cause pulmonary arterial pressure and brain injuries (Barreiro et al., 2002; Modern pharmacology with clinical applications, 2004).

The result of our previous study revealed significant relationship between Tissue factor and all air pollutants except than CO, as well as a reverse relationship between serum thrombomodulin, an anticoagulation factor, and O_3 (Poursafa et al., 2011). Moreover, some recent studies have demonstrated that blood vessel endothelium is a susceptible target for air pollution(Schneider et al., 2008; Andersson et al., 2009) so that the progress of atherosclerosis might be accelerated even from childhood (Kelishadi and Poursafa, 2010; Brook et al., 2010; Franchini and Mannucci, 2007; Peel et al., 2007).

Limited experience exists on the association of air pollutants with cord blood biomarkers. Current studies have reported the association between air pollution and cord blood vitamin D, cytokines, and lymphocyte distribution (Baiz et al., 2012; Herr et al., 2010; Latzin et al., 2011).

The current study aims to determine the association of exposure to ambient air pollutants with ICAM-1, VCAM-1 and endothelin-1 levels of cord blood among a population of mothers and neonates.

2. Methods

2.1. Ethics statement

The Research and Ethics Committee of Isfahan University of Medical Sciences approved the current study. After providing sufficient information, a written consent was obtained from all mothers before involvement in the project. Participants had the authority to leave the study whenever they wanted.

2.2. Study area

Previous geographical and aerological reports have mentioned that Isfahan is considered as second large and second air-polluted city in Iran; in recent years it has been ranked among the top 10 air-polluted cities of the world. This highest industrialized city of Iran has a population of near two millions and with an average altitude of 1500 m from the sea level. This city is surrounded by NW-SE mountain range of 3000 m. The air of Isfahan is markedly influenced by industrial emissions and traffic, we used the data provided by Isfahan environmental protection agency (http://www.isfahan-doe.ir/keyfiat/). To assess the air quality conditions, we used the air quality index (AQI) levels of health concern that are provided by the U.S. Environmental Protection Agency and the World Health Organization. AQI is categorized as follows: 0–50: Good; 51–100: Moderate; 101–150: Unhealthy for sensitive group; 151-200: Unhealthy; 201–300: Very unhealthy; 301–500: Hazardous (Environmental Protection Agency, 2014; World Health Organization, 2014).

2.3. Study population and study design

This cohort was conducted between March 2014 to March 2015 in four public and private hospitals (Al-Zahra, Shahid Beheshti, Amin, and Sina) of Isfahan city. Mothers were selected by non-probability sampling. The eligibility criteria were as follows: living in an area with air pollution measurement stations in Isfahan city, living at least for one year in the same area prior to delivery, term delivery, singleton pregnancy, without history of any chronic disease or long-term medication use. Exclusion criteria consisted of stillbirths or neonates who needed resuscitation at birth. By considering a level of significance of < 0.05 and using the data of previous study (Poursafa et al., 2011), the sample size was calculated as 200; we increased it to 250 for possible missing cases.

Mothers were recruited at their first trimester of pregnancy when referred to public and private obstetrics clinics. Trained health professionals completed the checklist provided for this study, and recorded the self-reported weight of mothers before pregnancy. Demographic information and the health indices including date of delivery, working status (housewife or employed), number of pregnancies, and self-reported weight before pregnancy were registered. They visited mothers once in each trimester of pregnancy until their delivery. During the first visit, health professionals measured maternal height and weight without shoes and heavy clothing; in further two visits, weight was measured. After admission of mothers, the pre-delivery weight was documented using calibrated scales. The total pregnancy weight gain was calculated as the pre-delivery weight minus the pre-pregnancy weight.

Immediately after delivery, trained nurses obtained the cord blood after double clamping and cutting the umbilical cord. Then the anthropometric indices of newborns were measured, they consisted of weight and length, as well as circumferences of head, abdomen, and chest. Newborn's weight was categorized into three groups. Those with a birth weight of less than 2500 g were considered as low birth weight (LBW), those between 2500 and 4000 g as appropriate birth weight, and those with birth weight of more than 4000 gr as high birth weight (HBW) (Ped, Dec2, 2015).

2.4. Laboratory measurements

Serum was isolated immediately from the obtained cord blood by centrifuge at 2800 rpm for 15 min. Markers of endothelium dysfunction including ICAM-1, VCAM-1 and endothelin1concentrations were assessed via enzyme-linked immune-sorbent assay method (Abcam, Cambridge, MA. USA) according to the manufacturer protocols.

2.5. Air pollution assessment

Data from 5 air pollution measurement stations in Isfahan city were recorded daily for the pregnancy period of mothers. Daily data pertaining to main air pollutants, i.e. SO_2, O_3, PM_{10}, NO_2, and CO, as well as AQI were recorded. Daily mean values were calculated for each mother during her pregnancy period and were considered for statistical analysis.