

Maternal Exposure to Air Pollution and Fetal Abnormalities

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ABSTRACT

BACKGROUND AND OBJECTIVE: Congenital anomalies are the main causes of neonatal mortality and morbidity. Since identification of the cause of anomalies is one of the important factors in the prevention of abnormalities, the present study aimed to investigate the relationship between the exposure of mothers with air pollution and embryonic anomalies through systematic review.

METHODS: In this systematic review, the effects of air pollution on congenital anomalies was investigated by searching articles using the keywords air pollution, congenital malformations and their English equivalent in Persian and English journals indexed in Iranmedx, SID, Scopus, Pubmed, Google scholar between 2000 and 2018 was carried out.

FINDINGS: A total of 28 articles from 245 articles were lastly included. The results of studies showed significant association between first trimester exposures to air pollution with congenital abnormalities. The relationship between air pollution and abnormalities of the heart and jaw-mouth was confirmed. Increased level of Carbon monoxide (CO), Particulate matter <10 microns (PM10), PM2.5, Ozone (O3), sulfur dioxide(SO2), nitrogen oxide (NO2) are associated with increased risk of specific congenital heart defects , particularly ventricular septal defect (VSD) , tetralogy of fallot (TF), atrial septal defects (ASD), and patent ductus arteriosus (PDA). Also, SO2, NO2, CO and PM10 were significantly associated with cleft palate (CP) with or without cleft palate (CL ± CP). Some studies show that Air Pollution exposure was associated with neural tube defects, Omphalocele, and Urogenital defects.

CONCLUSION: The results of present study indicated that exposure to air pollutants during pregnancy resulted in increased risk of congenital anomalies such as congenital heart defects and cleft palate with or without cleft.

KEY WORDS: *Congenital Abnormality, Congenital Defect, Air Pollutions, Maternal Exposures.*

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Introduction

Today, air pollution is one of the main concerns of public health. Due to the increase in urbanization, the consumption of industrial gases and transport by vehicles, the rate of air pollution is also increasing and the impact of air pollution on human health has become a global problem (1).

The most common air pollutants include nitrous oxide (NO₂), sulfur dioxide (SO₂), solid particles (PM), carbon monoxide (CO), and ozone (O₃). The results of various studies indicate that these air pollutants are associated with respiratory diseases such as asthma and chronic obstructive pulmonary disease (2-4), lung cancer (5), heart disease (6), and infertility (7,8). Although air pollution affects all age groups, the developing embryo, pregnant women and infants are more vulnerable to exposure to air pollution.

The results of the studies indicate that exposure of pregnant mothers with air pollution is associated with limited intrauterine growth, low birth weight, preterm labor, and preeclampsia (9-11). According to studies, the prevalence of congenital anomalies was reported to be 6.2%. The prevalence of abnormalities in boys (63%) is higher than girls (36%) (13,12). Congenital anomalies account for 20% of the deaths in children under one year and 25% of cases of hospitalization (14). On the other hand, diagnosis of abnormalities is associated with a wide range of psychological and emotional responses in the family (15,16). The etiology of congenital abnormalities is unknown in 40 to 60% of cases. It is estimated that multifactorial factors, such as contact with environmental factors are the causative agents of congenital anomalies (17).

Investigations have shown that there is a correlation between maternal placement in polluted air and the risk of fetal abnormalities, so that with increased air pollution, the risk of fetal abnormalities also increases (18). The study by Agay-Shay et al. indicates that airborne dust increases the cardiovascular abnormalities (19). The results of other studies also indicate an increase in the incidence of fetal anomalies such as cardiac abnormalities, cleft palate, cleft lip, abnormalities of the nervous system, amphotericin, and abnormalities of the urogenital system in the case of

mother contact with air pollutants (20-46). Earlier studies have been conducted on the prevalence of anomalies in Iran and the region. However, due to changes in health and the increase of environmental degradation factors in recent years, the necessity of conducting studies in this field is more than ever. On the other hand, the treatment and rehabilitation of congenital anomalies causes a great deal of cost to society.

Therefore, it is more cost effective to recognize and prevent the occurrence of congenital anomalies. Also, considering that Iran is one of the areas exposed to pollution and dust, there is no study conducted in Farsi to study the systematic compilation of air pollution and embryonic anomalies. Therefore, the present study was conducted with the aim of systematically reviewing the studies on exposure of mothers to air pollution and embryonic anomalies through systematic review.

Methods

This review study was carried out after approval by the Ethics Committee of the Mashhad University of Medical Sciences with the code IR.MUMS.NURSE.REC.1397.050. In this systematic review, the effects of air pollution on embryonic anomalies were investigated. Using the Persian key words of dust, air pollution, human health and fetal abnormalities, articles from 2000 to 2018 were searched. The reason for choosing this period is the availability of all the papers in this area, and since the first study on air pollution and abnormalities was conducted in 2002, studies from this time scale (2000) were investigated.

To obtain English articles, the keywords of Air Pollutants, Congenital Abnormality, Human Health, Birth Defect were used, and all related articles in Iranian Medx, SID, Scopus, Pubmed, Google Scholar, IranDoc, and Magiran databases were used. The researcher initially collected all articles related to air pollution and fetal abnormalities and, after completing the search, provided a list of abstracts. At this stage, all the articles mentioned in their title "Air Pollution" and "Fetal Abnormalities" were listed (Table 1).

Table 1. Specifications of the articles reviewed in this study

Author (year) (reference)	Country	type of study (No. of samples)	Data collection time	Exposure assessment	Pregnancy period	Controlled variables	Main findings
Ritz (2002) (20)	America (California)	Case-control (754030 births) 3121 cases and 9357 controls	1987- 1993	Average 24-hour air pollution including NO ₂ PM ₁₀ , CO, O ₃ at 16 km from the nearest meteorological stations	First trimester, second, third trimester and three months before pregnancy	Age, race and mother's education; infant sex; fertilization season; prenatal care; marital status; other airborne contaminants	There was a significant relationship between exposure in the second month of pregnancy with CO and O ₃ and ventricle wall, valvular defects, vascular defects in the aorta and pulmonary arteries.
Gilboa (2005) (21)	America (Texas)	Case- control (607500 births) 1719 cases and 3667 controls	1997- 2000	The average daily and hourly concentrations of NO ₂ , SO ₂ PM ₁₀ , CO, O ₃ pollutants in the range of 8 to 54 kilometers from meteorological stations	From 8 weeks pregnancy	Age, race, and mother's education; newborn sex; fertilization season; prenatal care; marital status; smoking; parietal status; marital status; illness	There was a significant relationship between exposure to SO ₂ and ventricular and atrial wall defects; CO with phallot tetralogy; and PM ₁₀ with atrial wall defect
Kim (2007) (22)	Korea (Seoul)	Cohort (1514births) 14 structural abnormalities in 1514 births	2001- 2004	Mean concentration of PM ₁₀ from the nearest meteorological stations	First , second, third trimesters of pregnancy	Age and education of the mother; gender; birthday; BMI; birth rank; smoking	There was a significant relationship between PM ₁₀ and congenital anomalies.
Hwang (2008) (23)	Taiwan	Case - control (721289 births) 653 cases-6530 controls	2001- 2003	Mean monthly exposure to NO ₂ , SO ₂ PM ₁₀ , CO, O ₃ in 72 meteorological stations	First trimester of pregnancy	Age of mother; infant gender; population density; parity; fertilization season; gestational age	There was a significant correlation between O ₃ and cleft lip.
Rankin (2009) (24)	England	Case - control (242268 births) 2779 cases-1500 controls	1985- 1990	Mean daily exposure to SO ₂ and black smoke from all meteorological stations within 10 km of mothers' place of residence	First trimester of pregnancy	Infant weight; infant gender	There was a significant relationship between black smoke and abnormalities of the nervous system
Strickland (2009) (25)	America	Cohort (715,500 births) of 3338 cases with cardiovascular anomalies	1986- 2003	The average daily concentrations of NO ₂ , SO ₂ PM ₁₀ , CO, O ₃ in one of the central meteorological stations	From 7 weeks of pregnancy	-	There was a significant relationship between PM ₁₀ and patent ductus arteriosus.
Hansen (2009) (26)	Australia	Case - control (150308 births) for each case of cardiac and cleft palate abnormalities there was five control	1997- 2004	The average concentration of exposure to NO ₂ , SO ₂ PM ₁₀ , CO, O ₃ in 18 meteorological centers with a maximum radius of 30 km from the city	From 8 weeks pregnancy	Age of mother; Infant sex; marital status; history of the first day of the last menstruation; socioeconomic status; distance from meteorological centers; fertilization season; marital status; smoking	There was no significant relationship between air pollution and embryonic anomalies
Dolk (2010) (27)	England	Cohort (759993 birthday) 9085 cases of chromosomal and non-chromosomal anomalies	1991- 1999	Average annual concentrations of NO ₂ , PM ₁₀ , SO ₂	The average annual exposure in 1996	Maternal age, socioeconomic status	There was a significant relationship between SO ₂ and phallot tetralogy and PM ₁₀ with omphalocell.

Marshall (2010) (28)	America (New Jersey)	Case-control (690000 births) 770 cleft lip cases with or without cleft palate	1998- 2003	Mean concentrations of exposure to SO ₂ , NO ₂ , CO, PM ₁₀ , PM _{2.5} , O ₃ in meteorological stations at a distance of 13 to 20 kilometers	3 to 7 weeks of pregnancy	Maternal age, race, fertilization season, smoking and alcohol	There was no significant relationship between air pollution and embryonic anomalies
Dadvand (2011) (29)	England	Case - control (449355 births) 2713 cases with cardiac abnormalities and 9975 controls	1985- 1996	The average weekly black smoke and SO ₂ concentrations from 56 meteorological centers	3 to 8 weeks pregnancy	Year of birth; Infant sex; Socioeconomic status; Urban level; Fertilization season	There was a significant relationship between maternal exposure to black smoke and cardiac anomalies.
Dadvand (2011) (30)	England	Case - control (356767 births) 2140 cases with cardiac abnormalities and 14256 controls	1993- 2003	The average weekly concentrations of SO ₂ , NO ₂ , CO, PM ₁₀ , NO, O ₃ from the nearest meteorological stations at an average distance of 8 to 12 kilometers	3 to 8 weeks pregnancy	Year of birth; Infant sex; Socioeconomic status; Urban level; Fertilization season	There was a significant relationship between NO ₂ with ventricular wall defects, cardiac valvular abnormalities and phallot tetralogy, and CO with ventricular septal defects, cardiac valvular abnormalities, and pulmonary valve stenosis.
Shay (2013) (19)	Israel (Tel aviv)	Case - control (135527 birth) 1860 cases with cardiac anomalies - 130402 controls	2000- 2006	Average weekly concentration of maternal exposure to SO ₂ , NO ₂ , CO, PM ₁₀ , PM _{2.5} , O ₃ based on maternal address	3 to 8 weeks pregnancy	Religion; infant sex; marital status of parents; parental age; fertilization season	There was only a significant relationship between PM ₁₀ and heart abnormalities.
Schembari (2013) (31)	Italy (Brindisi)	Case - control (5246 birth) 2247 cases- 2999 controls	1994- 2006	The average daily exposure of mothers to NO ₂ , NO _x PM ₁₀ , PM _{2.5} , PM _{coarse}	3 to 8 weeks pregnancy	Age of mother; Year of birth; Economic-social status; Fertilization season	There was a significant relationship between NO ₂ with coarctation of the aorta and gastrointestinal defects; and PM coarse with abdominal wall defects.
Padula (2013) (32)	America (California)	Case - control (1651 birth) 839 cases with neurological abnormalities and 853 controls	1997- 2006	The average daily exposure of mothers to NO ₂ , NO, PM ₁₀ , PM _{2.5} , CO, O ₃ at a maximum distance of 50 km from the meteorological stations	The first two months of pregnancy	Mother's race; education; multi-vitamin use	There was a correlation between the increase in exposure to NO and CO with neurodegenerative abnormalities.
Padula (2013) (33)	America (California)	Case - control (1675 birth) 822 cases with neurological abnormalities and 849 controls	1997- 2006	The average daily exposure of mothers to NO ₂ , NO, PM ₁₀ , PM _{2.5} , CO, O ₃ at a maximum distance of 50 km from the meteorological stations	The first two months of pregnancy	Mother's race; education; multi-vitamin use	There was a significant relationship between PM ₁₀ with valvular stenosis and ventricular septal defects; and PM _{2.5} with transposition of great arteries.
Padula (2013) (34)	America (California)	Case - control (1723 births)- 874 cases with gastrointestinal malformations, urogenital and abdominal wall	1997- 2006	The average daily exposure of mothers to NO ₂ , NO, PM ₁₀ , PM _{2.5} , CO, O ₃ at a maximum distance of 50 km	The first two months of pregnancy	Mother's race; education; multi-vitamin use	There was no significant relationship between air pollutants and abnormalities

Study		Study design		Exposure		Outcome	
		defects and 849 controls		from the meteorological stations			
Gianicolo (2014) (35)	Italy (Brindisi)	Case - control (674 births) 194 cases with cardiac abnormalities and 480 controls	2002-2010	The average daily exposure of mothers to total suspended solids (TSP)	upto 8 weeks pregnancy	Gender; socioeconomic status; gestational age	There was a significant relationship between SO ₂ and ventricular septal defects and congenital heart disease.
Farhi (2014) (36)	Israel	Cohort (21670 births) 4058 cases of abnormalities	1997-2005	The average daily exposure of mothers to SO ₂ , PM ₁₀ NO _x , O ₃	First, second and third trimester of pregnancy	Age and education of mother ; country origin of mother; infant gender; gestational age; birth date; birth weight; spontaneous pregnancy or fertility; birth season; single or multiple pregnancy.	There was a significant relationship between PM ₁₀ and NO _x with circulatory and genital system abnormalities
Lin (2014) (37)	Taiwan	Case-control (1510064 births) 1687 cases with cleft palate and 1 to 10 people for each case as controls)	2001-2007	The mean daily exposure of mothers to SO ₂ , PM ₁₀ CO, NO ₂ , O ₃ in weeks 1 to 4, 5 to 8, and 9 to 12 gestational age	The first trimester of pregnancy	Mother's age; Newborn sex; Social-economic status; Gestational age	Mother's exposure with so ₂ at 9-12 weeks of pregnancy was associated with an increase in the incidence of cleft lip.
Stingone (2014) (38)	America	Case - control (7960 births) 3328 cases with cardiac abnormalities and 4632 controls)	1997-2006	The average daily exposure of mothers to NO ₂ , NO, PM ₁₀ , PM _{2.5} , CO, O ₃ at a maximum distance of 50 km from the meteorological stations	upto 8 weeks pregnancy	Demographic characteristics of the mother; alcohol and tobacco use	Significant relationship was observed between NO ₂ with coarctation of aorta and pulmonary valve stenosis; PM with left hypoplastic heart
Jin (2015) (39)	China (lanzu)	Cohort (8969 births)	2009-2012	The average daily exposure of mothers to SO ₂ , PM ₁₀ , NO ₂	First and second trimester and the entire period of pregnancy	Age and education of mother; Disease; Fertilization season; Body mass index; Income; Smoking; Folic acid and drug therapy; Use of fuel for cooking; Temperature.	There was a significant relationship between PM ₁₀ and NO ₂ with patent ductus arteriosus in the second trimesters and the entire period of pregnancy
Hwang (2015) (40)	Taiwan	Case-control (1533748 births)1087 cases-10870 controls	2001-2007	The average daily exposure of mothers to SO ₂ , PM ₁₀ ,NO ₂ , O ₃	The first trimester of pregnancy	Mother's age; disease; infant's gender; number of nodes; gestational age; smoking and alcohol; mother's disease.	There was a significant relationship between O ₃ with patent ductus arteriosus, ventricular septal defects, and atrial septal defects; and PM ₁₀ with atrial septal defects.
Girguis (2016) (41)	America (Massachusetts)	Case-control (611854 births)-3713 cases of cardiac abnormalities, nervous system and face anomalies	2001-2008	The average daily exposure of mothers to PM _{2.5}	The first trimester of pregnancy	Age, race, education and language of mother; infant birth year; fertilization season; prenatal care; marital status; tobacco and alcohol use; number of feathery; parity	Exposure to PM _{2.5} during pregnancy was accompanied by an increase in abnormalities of the ventricular septal defect, the patent ductus arteriosus and the open foramen oval

Yao (2016) (42)	china	Cohort (16332 births) 398 cases of abnormalities	2010-2012	The average daily exposure of mothers to NO ₂ , PM ₁₀ , and SO ₂	Three months before fertilization, the first, second and third trimesters of pregnancies	Age of mother; infant gender; gestational age; number of pregnancies; other airborne contaminants	Exposure of mothers before fertilization and in the second trimester with SO ₂ was associated with an increase in fetal anomalies.
Padula (2017) (43)	America (California)	Case - control (605 births) 139 cases with neurological abnormality - 466 controls	1997-2006	The average daily exposure of mothers to NO ₂ , NO, PM ₁₀ , PM _{2.5} , CO, O ₃ at five kilometers distance from the meteorological stations	The first two months of pregnancy	Education; multi-vitamin use	There was a correlation between the increase in exposure to NO ₂ , NO, and CO with neurodegenerative abnormalities in areas close to high pollutant meteorological stations.
Pedersen (2017) (44)	Denmark	Cohort (84218 births) 4018 cases with anomalies	1997-2002	The average daily exposure of mothers to NO ₂	6 to 22 weeks of gestation	Age of parents; Maternal education; Fertilization season; Income; Pre-pregnancy BMI; Smoking and alcohol; parity.	There was no significant relationship between air pollutants and abnormalities
Ren (2017) (45)	America (Ohio)	Cohort (747849 births) 782 cases of abnormalities	2006-2010	The average maternal exposure to PM _{2.5} at 5.7 and 10 kilometers distance from the meteorological stations	One, two and three months before fertilization and fertilization	Age, race, education; infant sex; fertilization season; diabetes; marital status; smoking and alcohol	Exposure to PM _{2.5} before fertilization was associated with an increase in abdominal wall abnormalities and hypospadias.
Zhao (2018) (46)	china	Cohort (105927 births) 133 infants with cleft palate	2011-2013	The mean daily concentration of mothers exposure to PM _{2.5} , PM ₁₀ , O ₃ , CO, SO ₂ at an average distance of 5 km from Meteorological	First trimester of pregnancy	Age and mother's education; infant sex; fertilization season; parity; location temperature, humidity and air pressure	There was a relationship between the increase in exposure to PM _{2.5} PM ₁₀ , CO with cleft lip with or without cleft palate; and, O ₃ PM _{2.5} , with the cleft palate alone.

Results

In the initial search using keywords, 246 abstracts became available. After re-reviewing, articles were selected in English and Persian, and all duplicate articles and articles without free access to their full text were deleted. Finally, 28 articles were reviewed over the years 2000 to 2018 (Fig. 1). The profile of the reviewed articles is shown in Table 1. Based on available studies, 28 investigated articles were cohort studies (22,25,27,36,39,42-4,46) and 18 article were case-control studies (19-23). 11 article were conducted in the United States (California, Ohio, Mass., Texas) (20,21,25,28,32-34,38,41,43,45); four studies in the UK (24,27,29,30); three studies in China (39,42,46); three studies in Taiwan (23,37,40); two studies in Italy (3, 35); two studies in Israel (19,36); and three other studies in North Korea 22), Australia (26) and Denmark (44). The studied pollutants include: PM₁₀ (22 studies); NO₂

(19 studies); SO₂ (17 studies); O₃ (16 studies); CO (16 studies); PM_{2.5} (10 studies); NO (five studies). Few studies were conducted on black smoke (20, 25), NO_x (27,32), and PM coarse (27). Most studies have been performed on cardiovascular and maxillofacial anomalies, but a number of studies have also examined a wide range of structural abnormalities.

Cardiac abnormalities: For the first time, there was a significant relationship between maternal exposure in the second month of pregnancy with CO and O₃ and ventricular wall defect (VSD), valve defects, vascular defects in the aorta and pulmonary artery in the study of Ritz et al. (20). In the study of Gilboa et al. in Texas, there was a significant relationship between exposure to SO₂ and atrial/ventricular wall defect; CO with tetralogy of fallot; and PM₁₀ with atrial septal defect (ASD) (21). The study of Strickland et al showed a significant relationship between maternal exposure to

PM10 and patent ductus arteriosus (PDA) (25). There was a significant relationship between PM10 and cardiac abnormalities in study of Agay-Shay et al. (19). The study of Dolk et al. in the United Kingdom was found the correlation between exposure of mothers with SO₂ and tetralogy of fallot (TF) (27). The study of Dadvand et al. reported a significant relationship between NO₂ with VSD, valvular malformations of the heart and TF, and CO with VSD, valvular abnormalities of the heart and pulmonary valve stenosis (30). In the study of Schembari et al., a significant correlation was found between NO₂ and aortic coarctation (31). A study of Padula et al. reported a significant relationship between PM10 with valvular stenosis and VSD; and PM2.5 with transposition of great arteries (33).

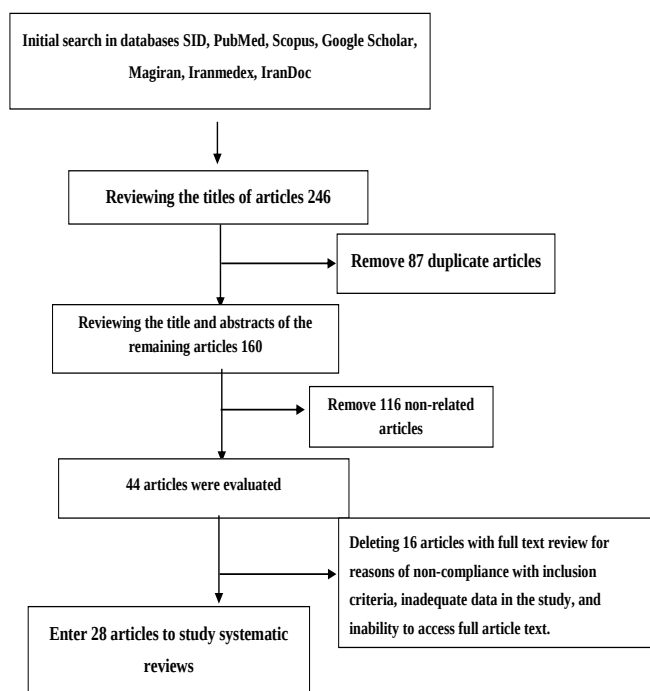


Figure 1. Flowcharts for the introduction of studies in systematic review

In the study of Gianicolo et al in Italy, there was a significant relationship between SO₂ and VSD and congenital heart disease (35). A significant correlation was found between NO₂ and aortic coarctation and pulmonary valvular stenosis; 10 PM with the left side hypoplastic heart in the study of Stingone et al. in the United States (38). The study of Jin et al., in China also shows a significant relationship between PM10 and NO₂ with patent ductus arteriosus before the second trimester and the total pregnancy period (39). The results of Hwang et al. demonstrated a significant

relationship between O₃ with PDA, VSD and ASD; and PM10 with ASD (40). In the study of Girguis et al., the exposure of mothers with PM2.5 during the first trimester of pregnancy was accompanied by an increase in VSD, PDA and patent foramen oval (41). In spite of the above results, only two studies by Hansen et al in Australia and Pedersen et al. in Denmark did not show a meaningful relationship between air pollution and cardiac abnormalities(26, 44).

maxillofacial abnormalities: In association with maxillofacial abnormalities, for the first time study of Hwang et al in Taiwan demonstrated a significant relationship between O₃ and cleft lip (23). Another study conducted in Taiwan by Lin et al. also indicated that mother's contact with SO₂ resulted in increased rate of cleft lip at 9-12 weeks of pregnancy (37). In China, the results of the study by Zhao et al. showed that there is an association between the increase in exposure to PM2.5, PM10 and CO with cleft lip with or without cleft palate, and O₃ and PM2.5 with a single cleft palate (46). In contrast, in investigations conducted by Marshall et al. in the United States and Hansen et al. in Australia, there was no significant relationship between air pollution and cleft lip with or without cleft palate(26,28)

Other Abnormalities: In the study of Kim et al. (18), there was a significant correlation between PM10 and congenital structural abnormalities (22). There was a significant relationship between black smoke and abnormalities of the nervous system (NTD) in study of Rankin et al. (24). In addition, investigation of Padula et al. in the United States indicated that there is a correlation between exposure to NO and CO with NTD (32). Four years later, Padula et al showed that there was a correlation between exposure to NO₂, NO and CO with NTD in areas close to pollutant adsorption stations (43). The results of a study conducted by Dolk et al. indicated relation between increased maternal exposure to PM10 with an increase in amphotocell abnormalities in neonates (27). In Israel, according to study of Farhi et al., there was a significant relationship between PM10 and NO_x with circulation system and genital system abnormalities (36). Other studies in Italy show a significant relationship between NO₂ with gastrointestinal defects and PM coarse with abdominal wall defects (31). The results of Ren and colleagues in the United States show that maternal exposure to PM2.5 before fertilization is associated with an increase in

abdominal wall abnormalities and hypospadias (45). Contrary to the above results, the results of two studies in Denmark and the United States did not show a significant correlation between air pollutants in gastrointestinal tract, urogenital and abdominal wall defects (34,44).

Discussion

The results of this study showed that air pollution causes an increase in fetal abnormalities. Most studies have confirmed the effects of various airborne pollutants such as SO₂, NO₂, CO, PM₁₀, PM_{2.5}, O₃ on cardiac abnormalities such as tetralogy of fallot, Ventricular septal defect, atrial septal defect, patent ductus arteriosus and pulmonary valve stenosis and only two studies did not confirm this relationship (26, 44). In regard with abnormalities maxillofacial anomalies, some studies have confirmed the association between O₃, SO₂, CO, PM₁₀, PM_{2.5} with cleft lip with or without cleft palate(23.37.46), but another study has not confirmed this relationship (28).

Although most of the studies examined cardiovascular abnormalities and maxillofacial anomalies, a number of studies have also investigated the relation of air pollution with other abnormalities, and these studies have confirmed the relationship between black smoke, PM₁₀, NO_x, NO, NO₂, CO, PM Coarse with the abnormalities of the nervous system, amphalocele, and abnormalities of the urogenital system (45, 43, 36, 32, 31, 27, 24), while two other studies did not confirm the association between air pollution and gastrointestinal abnormalities, urogenital defects and abdominal wall defects (34, 44).

Perhaps the contradiction between the results of studies is due to the concentration of pollutants, the time of exposure to pollutants, the use of air purifying systems and the distance between mothers' living place and meteorological stations, so that different studies vary from five to 50 kilometers from the site of the meteorological stations (21,30,34,45), and most of the studies considered the residential address of mothers' homes for exposure to air pollution, while mothers could be exposed to air pollution in other places, such as the workplace and the community, and this variable as a confounding factor has not been considered. Most

of the studies (19-44,46) investigated the exposure of pregnant mothers with the pollutants in the first trimester of pregnancy, which also include an organogenesis period, and the number of two (42, 45) studies considered the contact with air pollution in the pre-fertilization period and some others investigated the exposed to pollutants throughout the pregnancy (20.22.36.39.42). The main difference in investigations was in the diagnosis of abnormalities, the classification of abnormalities, and definitions in the study. Hansen et al. and Gilboa (2005) performed the classification of cardiac and maxiofacial abnormalities based on the anatomical classification used in the Ritz study, but Strickland et al. and Jin et al. used a more categorized classification system(20,21,25,26). Some studies (24,27,29,30) also used the International Classification of Diseases (WHO Edition 9) system for classifying abnormalities (47).

Although the main mechanism causing abnormalities in the fetus is unknown due to air pollutants, some studies have suggested that air pollutants can directly bond to lipid and protein compounds and produce oxidative stress and radicals, which are destructive for cells and tissues and also subsequently leads to defects in the fetus (48). Oxidative stress due to air pollution during pregnancy has been reported in a number of studies (49, 50). Additionally, evidence suggests that air pollution can lead to epigenetic changes, including alteration of the methylation of RNA and DNA (51, 52), and these epigenetic changes during pregnancy can lead to normal growth disturbances and abnormalities in the fetus. In general, the results of the study show that exposure to air pollution during pregnancy increases the level of anomalies (cardiovascular, lips and cleft palate and other structural abnormalities) in the fetus. Therefore, further studies are needed to understand this problem and to make a proper plan for the prevention of congenital anomaly.

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