Environmental Research 135 (2014) 173–180

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

The possible association between exposure to air pollution and the risk for congenital malformations

Adel Farhi [a,*], Valentina Boyko [a], Jonatan Almagor [b], Itzhak Benenson [b], Enrico Segre [c], Yinon Rudich [c], Eli Stern [d], Liat Lerner-Geva [a,e]

[a]Women and children's Health Research Unit, Gertner Institute for Epidemiology and Health Policy Research Ltd., Israel
[b]Department of Geography and Human Environment, Tel Aviv University, Israel
[c]Department of Earth and Planetary Sciences, Weizmann Institute of Science, Israel
[d]Center for Risk Analysis, Gertner Institute for Epidemiology and Health Policy Research Ltd., Israel
[e]School of public health, Sackler Faculty of Medicine, Tel Aviv University, Israel

ARTICLE INFO

Article history:
Received 4 May 2014
Received in revised form
21 July 2014
Accepted 11 August 2014

Keywords:
Congenital malformations
Air pollution
Particulate matter $<10\ \mu m$
Nitrogen oxides
Ozone
Assisted reproductive technology

ABSTRACT

Background: Over the last decade, there is growing evidence that exposure to air pollution may be associated with increased risk for congenital malformations.
Objectives: To evaluate the possible association between exposures to air pollution during pregnancy and congenital malformations among infants born following spontaneously conceived (SC) pregnancies and assisted reproductive technology (ART) pregnancies.
Methods: This is an historical cohort study comprising 216,730 infants: 207,825 SC infants and 8905 ART conceived infants, during the periods 1997–2004. Air pollution data including sulfur dioxide (SO_2), particulate matter $<10\ \mu m$ (PM_{10}), nitrogen oxides (NO_x) and ozone (O_3) were obtained from air monitoring stations database for the study period. Using a geographic information system (GIS) and the Kriging procedure, exposure to air pollution during the first trimester and the entire pregnancy was assessed for each woman according to her residential location. Logistic regression models with generalized estimating equation (GEE) approach were used to evaluate the adjusted risk for congenital malformations.
Results: In the study cohort increased concentrations of PM_{10} and NO_x pollutants in the entire pregnancy were associated with slightly increased risk for congenital malformations: OR 1.06(95% CI, 1.01–1.11) for $10\ \mu g/m^3$ increase in PM_{10} and OR 1.03(95% CI, 1.01–1.04) for 10 ppb increase in NO_x. Specific malformations were evident in the circulatory system (for PM_{10} and NO_x exposure) and genital organs (for NO_x exposure). SO_2 and O_3 pollutants were not significantly associated with increased risk for congenital malformations. In the ART group higher concentrations of SO_2 and O_3 in entire pregnancy were associated (although not significantly) with an increased risk for congenital malformations: OR 1.06 (95% CI, 0.96–1.17) for 1 ppb increase in SO_2 and OR 1.15(95% CI, 0.69–1.91) for 10 ppb increase in O_3.
Conclusions: Exposure to higher levels of PM_{10} and NO_x during pregnancy was associated with an increased risk for congenital malformations. Specific malformations were evident in the circulatory system and genital organs. Among ART pregnancies possible adverse association of SO_2 and O_3 exposure was also observed. Further studies are warranted, including more accurate exposure assessment and a larger sample size for ART pregnancies, in order to confirm these findings.

1. Introduction

Over the last decade, there is growing evidence that exposure to air pollution may be associated with adverse health outcomes and some populations appear to be more vulnerable. Moreover, the possibility that exposure to air pollution may be associated with adverse birth outcomes such as low birth weight, intrauterine growth restriction and preterm birth has been raised (Glinianaia et al., 2004; Maisonet et al., 2004; Shah et al., 2011; Sram et al., 2005; Stieb et al., 2012). Kannan et al. (2006) provide a biological plausible mechanistic pathway of air pollution's influence on fetal development through the cardiovascular mechanisms of oxidative stress, inflammation, coagulation, endothelial function and hemodynamic response. In recent years, several studies (Dolk et al., 2010; Gilboa et al., 2005; Rankin et al., 2009; Ritz et al., 2002; Schembari et al., 2014) reported possible

* Correspondence to: Sheba Medical center, Tel – Hashomer 5261, Israel.
E-mail address: dollyf@gertner.health.gov.il (A. Farhi).

http://dx.doi.org/10.1016/j.envres.2014.08.024
0013-9351/

association between air pollution and specific cardiac malformations. In contrast, Rankin et al. (2009) found a significant negative association between sulfur dioxide (SO_2) levels and cardiac defects. Other studies reported an increased risk for cleft palate in relation to ozone (O_3) levels (Hansen et al., 2009) and neural tube defects in relation to CO and nitrogen oxides (NO_x) (Padula et al., 2013). Although reports on the association between exposure to air pollution and congenital malformations (CMs) have been accumulating, the results are still controversial. Furthermore, special attention should be devoted to specific sub-populations that may be more susceptible. Assisted reproductive technology (ART) pregnancies may represent such a susceptible sub-population. The study of Perin et al. (2010) evaluated the effect of exposure to PM_{10} during ART treatment and found an increased risk for pregnancy loss. Another study (Legro et al., 2010) observed a significant adverse effect of air quality on the rate of conception and live birth following ART treatments.

The current historical cohort study evaluates the possible association between exposure to air pollution (SO_2, PM_{10} (particulate matter $< 10\ \mu m$), NO_x and O_3) during first trimester and entire pregnancy and congenital malformations. In addition, this study attempts to assess these associations by mode of conception (ART and SC pregnancies).

2. Methods

The study cohort was comprised of all women with a positive pregnancy laboratory test from one of the largest Health Maintenance Organizations (HMO) in Israel (Clalit Health Services) who spontaneously conceived (SC) during the period 2000–2004. In addition, all women with positive pregnancy laboratory tests that underwent ART treatments in 8 in vitro fertilization (IVF) units during the years 1997–2004 were included (Farhi et al., 2013). The cohort comprised of 209,630 women and 216,730 infants: 207,825 infants who were born following SC pregnancies and 8905 infants born following ART conceived pregnancies. The database was linked to the National Live Birth Registry at the Ministry of Health using mother's unique personal identification number and pregnancy laboratory test date in order to determine the maternal characteristics including residency during pregnancy, age, ethnicity, education, country of birth and pregnancy outcomes including infant date of birth, gender, plurality, gestational age, birth weight and whether the infants were diagnosed with CM. Under Israeli law, reports on CM are required to the Ministry of Health. The reports are limited to CM that are evident at birth or are detected prior to release from the hospital. CMs are stated according to a predetermined list by the Ministry of Health and coded according to the International Classification of Disease 10th Revision (Q00–Q99) (Appendix A).

2.1. Exposure data

Air pollution concentrations were measured at 117 air quality monitoring stations across Israel during the years 1997–2005. The major pollutant includes sulfur oxides (SO_2), particulate matter $< 10\ \mu m$ (PM_{10}), nitrogen oxides (NO_x) and ozone (O_3). The raw measurements were available as half-hourly averages in most of the cases, and as 5 min averages in some minority. Monthly averages were computed for each station, whenever at least 50% of the measurements of the month were valid.

2.2. Spatial prediction of pollutants

A spatial prediction for the pollutants was assessed by using the Ordinary Kriging method (Chils and Delfiner, 2012) that is a part of the Geostatistical Analyst extension of the ArcGIS 10.1. Based on pollutants' measurements, continuous raster layers of pollutants' concentrations at resolution of 500 m were calculated.

2.3. Linkage of the maternal residency and pollutants exposure estimates

Using a GIS, the women's residency addresses were geo-coded, located spatially as a point layer and were overlaid with the surfaces of each pollutant to estimate values of the pollutant concentrations during the research period. For each woman, exposure to air pollutants during the first trimester and the entire pregnancy was calculated by using the relative number of exposure days and the average pollutant level per month.

2.4. Statistical analysis

CM represents the dependent variable in the analysis and was defined as a dichotomous category. The following maternal and infants' characteristics represent the independent variables: mother's age, ethnicity (Jewish/others), country of birth (Israel/others), education (≤ 12 years/13+ years/unknown), mode of conception (SC/ART conceived), plurality (singleton/multiple births), season of birth and infant gender. The air pollutants exposures (SO_2, PM_{10}, NO_x and O_3) during first trimester, second trimester and the entire pregnancy represent independent variables that were analyzed as continuous variables as well as categorical variables according to tertiles of distributions in the entire dataset. To compare rate of CM between population's subgroups, a chi-square test was used. All tests were two tailed and p-Values below 0.05 were considered statistically significant. First a logistic regression analysis was used to assess the independent effect of maternal and infants characteristic on CM. Further, in order to assess the independent effect of air pollution on CM a logistic regression analysis was used with adjustment for maternal and infants' characteristics. Generalized estimating equation (GEE) approach was used to estimate the effects of independent variable on CM outcome. The GEE method takes into account the correlation between siblings from the same delivery. The structure of working correlation matrix, that reflects the assumption regarding the correlation between observations from the same cluster, was defined as exchangeable. Thus the same correlation exists between any two infants of the mother.

Interactions between mode of conceptions and air pollution exposure were calculated. In addition, pollutant effect on CM was calculated in separate regression models for each sub-population (ART and SC). The results of all multivariable regression models are presented as adjusted odds ratio (OR) with 95% confidence interval (CI). Statistical analyses were performed with SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC).

3. Results

The study population comprised 216,730 infants (207,825 SC infants and 8905 ART infants). Table 1 presents maternal and infant's characteristics by mode of conception. Women in the ART group were older and with higher education level than the SC

Table 1
Population characteristics by mode of conception (N=216,730 infants).

	Spontaneous	**ART**	p-Value
	n (%)	n (%)	
Total	207,825	8905	
Maternal age, Mean ± SD	28.8 ± 5.5	31.6 ± 4.8	< 0.0001
Maternal age, years			< 0.0001
17–19	4938 (2.4)	1 (0)	
20–24	45,996 (22.1)	448 (5.0)	
25–29	70,001 (33.7)	2739 (30.80	
30–34	52,250 (25.1)	3371 (37.9)	
35–39	27,238 (13.1)	1700 (19.1)	
40–44	7367 (3.6)	646 (7.2)	
Maternal ethnicity			< 0.0001
Jewish	125,77 (60.5)	8002 (89.9)	
Others	82,052 (39.5)	903 (10.1)	
Maternal country of birth			< 0.0001
Israel	177,188 (85.3)	7021 (78.8)	
Other	30,637 (14.7)	1884 (21.2)	
Maternal education, years			< 0.0001
≤ 12	77,168 (37.1)	3325 (37.3)	
13+	51,044 (24.6)	3518 (39.5)	
Unknown	79,613 (38.3)	2062 (23.2)	
Plurality			< 0.0001
Singleton	198,334 (95.4)	4294 (48.2)	
Multiple	9491 (4.6)	4611 (51.8)	
Season of birth			< 0.0001
Winter	49,783 (24.0)	2099 (23.6)	
Spring	52,215 (25.1)	2165 (24.3)	
Summer	55,156 (26.5)	2259 (25.4)	
Fall	50,671 (24.4)	2382 (26.7)	
Infant gender			0.08
Male	106,670 (51.3)	4486 (50.4)	
Female	101,155 (48.7)	4419 (49.6)	