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

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ARTICLE INFO

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

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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 $\pm$ SD	28.8 $\pm$ 5.5	31.6 $\pm$ 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)	

group. Higher rate of multiple births was observed in the ART group. CM was observed in 4508 infants (1.9%) of the study cohort.

Table 2 presents maternal and infants' characteristics and the prevalence of CM in each category. A multivariable logistic regression model demonstrated increased risk for CM in older women, non-Jewish mothers, multiple births, spring and winter seasons and male gender. Infants born following ART were at statistically increased risk for CM compared to SC infants (OR 1.20 95% CI 1.02–1.40).

For each pollutant a specific study population was defined according to availability of the exposure data (Table 3). For SO_2 and NO_x exposure, 97% of the infants had available data; PM_{10} and O_3 data were available only from year 2000 and therefore presented for 84% of the infants. No bias was found after excluding infants lacking exposure data: the rate of CM was similar for each specific

pollutant population (Table 3). Air pollution concentrations for each pollutant are presented in Table 4.

The adjusted risks for CM in the first trimester second trimester and in the entire pregnancy are presented in Table 5. Higher concentrations of SO_2 or O_3 exposures were not associated with increased risk of CM; moreover, an inverse association was observed for SO_2 exposure.

Higher levels of PM_{10} and NO_x exposures in 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). These associations were also evident in the analysis of high vs. low tertiles of exposures. In the first and second trimesters, the association was less evident for PM10 and a significant increase risk for CM was found in NO_x exposure. In addition, separate

Table 2
Population characteristics and the risk for congenital malformations ($N=216{,}730$ infants).

	Population	Congenital malformations	p-Value	Multivariable adjusted		
	%	n (%)		OR	95% CI	p-Value
Total	100	4058 (1.9)				
Mode of conception			< 0.0001			0.04
Spontaneous	95.9	3845 (1.9)		1.00		
ART	4.1	213 (2.4)		1.20	1.02–1.40	
Maternal age, years			< 0.0001			< 0.0001
17–19	2.3	102 (2.1)		1.10	0.90–1.35	
20–24	21.8	841 (1.8)		1.01	0.93–1.11	
25–29	33.5	1271 (1.7)		1.00		
30–34	25.7	1017 (1.8)		1.05	0.97–1.14	
35–39	13.4	603 (2.1)		1.21	1.09–1.33	
40–44	3.7	224 (2.8)		1.65	1.43–1.91	
Maternal ethnicity			< 0.0001			< 0.0001
Jewish	61.7	2280 (1.7)		1.00		
Others	38.3	1778 (2.1)		1.30	1.22–1.39	
Maternal country of birth			0.84			0.72
Israel	85.0	3457 (1.9)		1.00		
Other	15.0	601 (1.9)		0.98	0.90–1.07	
Maternal education, years			0.07			0.39
≤ 12	37.1	1521 (1.9)		1.05	0.97–1.15	
13+	25.2	952 (1.7)		1.00		
Unknown	37.7	1585 (1.9)		1.05	0.97–1.15	
Plurality			< 0.0001			< 0.0001
Singleton	93.5	3703 (1.8)		1.00		
Multiple	6.5	355 (2.5)		1.36	1.19–1.55	
Season of birth			0.03			0.01
Winter	23.9	992 (1.9)		1.10	1.01–1.20	
Spring	25.1	1083 (2.0)		1.15	1.05–1.25	
Summer	26.5	1004 (1.7)		1.00		
Fall	24.5	979 (1.8)		1.05	0.96–1.15	
Infant gender			< 0.0001			< 0.0001
Male	51.3	2467 (2.2)		1.00		
Female	48.7	1591 (1.5)		0.67	0.63–0.72	

Table 3
Study populations and the rate of congenital malformations.

Pollutant	Exposure data		All infants		Spontaneous		ART	
	Number of stations	% infants with exposure data[a]	Congenital malformations		Congenital malformations		Congenital malformation	
			N	%	N	%	N	%
SO_2 (ppb)	96	97	210,832	(1.9)	202,470	(1.8)	8362	(2.4)
PM_{10} ($\mu g/m^3$)	32	84	182,435	(1.9)	177,097	(1.8)	5338	(2.3)
NO_x (ppb)	82	97	210,955	(1.9)	202,571	(1.8)	8384	(2.4)
O_3 (ppb)	53	84	182,538	(1.9)	177,189	(1.8)	5349	(2.3)

[a] % of infants with available exposure data was calculated from total cohort of 216,730 infants.

Table 4
Pollutants exposure concentrations in the first trimester, second trimester and in the entire pregnancy period.

Pollutant	Exposure data								
	Mean ± SD	Min	25th percentile	Median	75th percentile	Max	Tertile 1	Tertile 2	Tertile 3
SO_2 (ppb)									
First trimester	2.81 ± 0.96	0.51	2.10	2.63	3.35	12.84	< 2.25	2.25–3.05	> 3.05
Second trimester	2.74 ± 0.92	0.51	2.08	2.58	3.24	12.90	< 2.22	2.22–2.97	> 2.97
Entire pregnancy	2.74 ± 0.75	1.16	2.21	2.57	4.22	9.22	< 2.33	2.33–2.85	> 2.85
PM_{10} ($\mu g/m^3$)									
First trimester	53.5 ± 13.6	15.0	43.9	50.1	60.3	118.0	< 45.9	45.9–56.1	> 56.1
Second trimester	52.7 ± 13.0	15.0	43.8	49.5	58.8	118.2	< 45.6	45.6–55.1	> 55.1
Entire pregnancy	52.0 ± 8.3	16.0	45.8	50.9	58.0	88.9	< 47.4	47.4–55.5	> 55.5
NO_x (ppb)									
First trimester	27.8 ± 22.6	4.8	14.8	19.5	32.4	274.6	< 16.2	16.2–26.5	> 26.5
Second trimester	26.8 ± 20.4	4.9	14.6	19.3	31.7	274.9	< 16.2	16.0–25.4	> 25.4
Entire pregnancy	26.3 ± 16.6	7.8	14.3	19.0	34.7	235.6	< 15.8	15.8–27.0	> 27.0
O_3 (ppb)									
First trimester	32.4 ± 6.2	16.9	28.0	32.3	36.1	54.4	< 29.5	29.6–34.6	> 34.6
Second trimester	32.7 ± 6.3	17.0	28.3	32.6	36.5	54.9	< 29.9	29.9–34.9	> 34.9
Entire pregnancy	32.1 ± 4.5	6.9	28.8	31.3	34.6	50.0	< 29.7	29.7–33.4	> 33.4

Table 5
Adjusted risk for congenital malformations using continuous and high vs. low levels of air pollution exposures.

Pollutant	First trimester			Second trimester			Entire pregnancy		
	OR[a]	95% CI	*p*-Value	OR[a]	95% CI	*p*-Value	OR[1]	95% CI	*p*-Value
SO_2									
1 ppb increase	0.96	0.92–0.99	0.01	0.97	0.93–1.00	0.08	0.96	0.92–1.00	0.04
High vs. low tertile	0.91	0.84–0.99	0.03	0.93	0.86–1.01	0.10	0.93	0.86–1.01	0.08
PM_{10}									
10 $\mu g/m^3$ increase	1.01	0.98–1.05	0.34	1.03	0.99–1.06	0.11	1.06	1.01–1.11	0.01
High vs. low tertile	0.99	0.90–1.10	0.92	1.06	0.96–1.17	0.2	1.10	1.01–1.20	0.03
NO_x									
10 ppb increase	1.01	0.99–1.03	0.08	1.02	1.00–1.03	0.01	1.03	1.01–1.04	0.006
High vs. low tertile	1.12	1.02–1.21	0.01	1.14	1.05–1.24	0.002	1.14	1.05–1.23	0.003
O_3									
10 ppb increase	1.05	0.98–1.12	0.18	0.94	0.88–1.01	0.18	0.97	0.89–1.05	0.41
High vs. low tertile	1.06	0.95–1.19	0.26	0.96	0.86–1.06	0.40	0.99	0.91–1.08	0.86

[a] OR – odds ratio adjusted for maternal age, maternal ethnicity, maternal country of birth, maternal education, mode of conception, plurality, season of birth, infant gender.

models were calculated for singleton and multiple births yielding similar results (data not shown).

Table 6 demonstrates adjusted risk for CM in ART conceived infants and SC infants with first, second trimester and entire pregnancy exposure.

Opposed to the inverse association that was observed in the SC infants, in the ART group SO_2 exposure was associated, although not significantly, with slightly increased risk for CM: OR 1.06 (95% CI 0.96–1.17) in the entire pregnancy. A statistically significant interaction was observed between mode of conception and SO_2 exposure in first trimester ($p=0.04$) and in the entire pregnancy ($p=0.02$). Ozone exposure during entire pregnancy was also positively associated (although without statistically significant interaction) with an increased risk for CM in the ART group OR 1.15 (95% CI 0.69–1.91) per 10 ppb increase and OR 1.31 (95% CI 0.82–2.09) in high vs. low tertiles. No differences in the effects of PM_{10} or NO_x exposures were found on the risk for CM between ART and SC groups.

Table 7 displays the results for specific malformations for each exposure. Congenital malformations in the circulatory system were observed in 0.8% infants of the cohort.

Increased risk for malformations in the circulatory system was found for PM_{10} exposure during the entire pregnancy OR 1.07 (95% CI 1.00–1.14) for 10 $\mu g/m^3$ increase and for NO_x pollutant OR 1.03 (95%

CI 1.01–1.06) for 10 ppb increase. No positive association was found between SO_2 and O_3 exposures and circulatory malformations.

Ventricular septal defect (VSD) was the most prevalent circulatory defect (1200 infants; 70% of all circulatory CM). Increased risk for VSD was observed with PM_{10} and NO_x exposures in entire pregnancy, and also in the first and second trimesters of NO_x exposure.

Higher exposure with NO_x was associated with genital organ malformations in first trimester, second trimester and entire pregnancy exposure. This association was not evident with other pollutants. No association was observed between exposure to any of the pollutants with cleft lip and cleft palate. Higher levels of O_3 exposure were associated with chromosomal defects, however with no statistically significant increase in the first trimester. Regarding others specific congenital malformations and the difference between SC and ART, the numbers in each separate group were too small for analyzing no prominent differences which were observed in the univariate analysis.

4. Discussion

The current study extends the knowledge regarding the possible association between air pollution exposure during pregnancy

Table 6
Adjusted risk for congenital malformations in first trimester, second trimester and the entire pregnancy using continuous and high vs. low levels of air pollution exposures by mode of conception.

Pollutant	Mode of conception					
	Spontaneous			ART		
	OR[a]	95% CI	p-Value	OR[a]	95% CI	p-Value
First trimester						
SO$_2$						
1 ppb increase	0.94	0.91–0.98	0.002	1.03	0.95–1.12	0.49
High vs. low tertile	0.90	0.82–0.98	0.01	1.34	0.89–2.02	0.16
PM$_{10}$						
10 µg/m^3 increase	1.02	0.99–1.05	0.30	0.97	0.82–1.16	0.77
High vs. low tertile	1.00	0.91–1.11	0.97	0.80	0.47–1.38	0.42
NO$_x$						
10 ppb increase	1.01	1.00–1.03	0.04	0.99	0.94–1.04	0.75
High vs. low tertile	1.12	1.03–1.22	0.01	1.19	0.73–1.93	0.49
O$_3$						
10 ppb increase	1.05	0.98–1.12	0.19	1.05	0.70–1.58	0.80
High vs. low tertile	1.06	0.95–1.19	0.27	1.10	0.64–1.89	0.74
Second trimester						
SO$_2$						
1 ppb increase	0.96	0.92–1.00	0.03	1.02	0.94–1.12	0.58
High vs. low tertile	0.94	0.86–1.02	0.16	0.85	0.59–1.23	0.40
PM$_{10}$						
10 µg/m^3 increase	1.03	0.99–1.06	0.09	0.98	0.83–1.17	0.86
High vs. low tertile	1.06	0.96–1.17	0.23	1.12	0.63–1.96	0.70
NO$_x$						
10 ppb increase	1.02	1.01–1.04	0.003	0.98	0.92–1.04	0.44
High vs. low tertile	1.16	1.07–1.27	0.001	0.76	0.48–1.18	0.22
O$_3$						
10 ppb increase	0.94	0.87–1.01	0.08	1.14	0.76–1.78	0.53
High vs. low tertile	0.94	0.84–1.05	0.25	1.59	0.84–2.98	0.15
Entire pregnancy						
SO$_2$						
1 ppb increase	0.94	0.89–0.98	0.01	1.06	0.96–1.17	0.25
High vs. low tertile	0.92	0.85–1.00	0.06	1.08	0.74–1.57	0.70
PM$_{10}$						
10 µg/m^3 increase	1.06	1.01–1.11	0.01	0.96	0.74–1.25	0.75
High vs. low tertile	1.10	1.01–1.21	0.03	1.07	0.63–1.83	0.80
NO$_x$						
10 ppb increase	1.03	1.01–1.05	0.001	0.97	0.91–1.04	0.36
High vs. low tertile	1.15	1.05–1.25	0.001	0.93	0.56–1.53	0.77
O$_3$						
10 ppb increase	0.96	0.89–1.05	0.37	1.15	0.69–1.91	0.59
High vs. low tertile	0.98	0.90–1.08	0.72	1.31	0.82–2.09	0.25

[a] OR – odds ratio adjusted for maternal age, maternal ethnicity, maternal country of birth, maternal education plurality, season of birth, infant gender.

and congenital malformations. Moreover, this study explores a specific population of women that underwent ART treatments with fetuses that might be even more susceptible. The analysis was performed for entire pregnancy and for first and second trimesters exposure to investigate whether the exposure timing may be critical in the development of the fetus and whether a specific organ may be more vulnerable in a critical time window (Perera et al., 1999). The critical period for the development of some CM may occur after the first trimester (Czeizel, 2008); therefore analyses were conducted for the first trimester, second trimester and the entire pregnancy.

In the current study, **PM$_{10}$** exposure during pregnancy was associated with an increased risk for overall CM and for circulatory systems defects, in particular VSD. This observation is consistent with the results of a meta-analysis published in 2011 (Vrijheid et al., 2011) which included 10 studies, most of them focused on heart defect anomalies. PM$_{10}$ exposure was significantly associated with combined odds ratio of 1.14 for atrial septal defect (ASD). Increased risk for VSD and coarctation of aorta was also reported,

although not statistically significant. A more recent study (Agay-Shay et al., 2013), found a significant increased risk for multiple congenital heart defects (defined in the presence of two or more cardiac malformations). Only two studies in the above mentioned meta-analysis included the full spectrum of major structural CM: Dolk et al. (2010) did not find an association between PM$_{10}$ and non-chromosomal defects and Kim et al. (2007) found an association between PM$_{10}$ and total CM in the second trimester.

In our study, exposure to PM$_{10}$ was associated with chromosomal malformations; a small excess risk for chromosomal defect was found also by Dolk et al. (2010).

In contrast to others studies associated with non-significant increased risk for cleft lip/cleft palate (Gilboa et al., 2005; Marshall et al., 2010), in the current study, no association between PM$_{10}$ exposure and cleft lip/cleft palate was observed.

Regarding **NO$_x$** exposure, in the current study NO$_x$ exposure was associated with an increased risk for total CM. An association of NO$_x$ and specific malformations was found in circulatory system especially VSD and genital organs malformations. The association of NO$_x$ exposure with specific heart malformations was also evident in the meta-analysis (Vrijheid et al., 2011). On the other hand, no association was found by others (Agay-Shay et al., 2013; Dolk et al., 2010). No association was observed between NO$_x$ and cleft lip and palate in contrast to the study by Marshall et al. (2010).

In our study, **SO$_2$** was inversely associated with CM. Such an inverse association was also reported by others (Dadvand et al., 2011; Agay-Shay et al., 2013). However few studies observed an increased risk for CM associated with SO$_2$ exposure (Gilboa et al., 2005; Marshall et al., 2010). Inverse association between air pollution exposure and congenital malformations may be the result of competing outcomes such as spontaneous early abortions (Ritz, 2010).

In the current study, non-consistent and non-significant association was evident with **O$_3$** exposure (inverse association during second trimester and entire pregnancy, contrary to a non-significant positive association in the first trimester). However, in specific malformations, positive association was found between O$_3$ exposures and chromosomal defects. Non-significant association between O$_3$ and specific heart defect was found by others (Agay-Shay et al., 2013; Gilboa et al., 2005; Ritz et al., 2002; Strickland et al., 2009).

Legro et al. (2010) hypothesized that an embryo may be more vulnerable especially outside the uterine environment as occurring in ART treatments. They found (Legro et al., 2010) that increase in NO$_2$ concentration both at the patient's address and at the IVF lab was significantly associated with lower pregnancy and live birth rates. Perin et al. (2010) found an association between PM$_{10}$ exposure and early pregnancy loss among women undergoing IVF treatments.

The number of ART treatments has been steadily increasing worldwide and it is important to look at this unique subpopulation. In Israel, ART is funded by the Ministry of Health for the first two children, with no limit on the number of treatment cycles for women up to 45 years-of-age, and for oocyte donation up to age 54. Currently, 4.2% of all live births in Israel are conceived with ART thus becoming a large subpopulation that cannot be overlooked. To the best of our knowledge, this is the first study that assessed the effect of air pollution in relation to congenital malformations among children born following ART treatments. The current results show that higher level of SO$_2$ and O$_3$ exposures were associated with slightly increased risk for CM even though not statistically significant in the ART group, as opposed to an inverse association in the SC group. However, interpreting these results need to be taken with caution and larger sample size needed to confirm these preliminary findings. Regarding specific congenital malformations in the ART group, the numbers were too small to draw definite conclusions.

Table 7
Adjusted risk for congenital malformations in first trimester, second trimester and the entire pregnancy using continuous and high vs. low levels of air pollution exposures ($N=216,730$).

	n	%	First trimester			Second trimester			Entire pregnancy		
			OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Total infants with CM	**4058**	**1.87**									
SO_2 Exposure											
Circulatory system	1641	0.78									
1 ppb increase			0.93	0.89–0.99	0.01	0.97	0.92–1.02	0.24	0.95	0.89–1.01	0.09
High vs. low tertile			0.88	0.77–0.99	0.04	0.95	0.84–1.08	0.46	0.92	0.82–1.04	0.20
VSD	1160	0.55									
1 ppb increase			0.94	0.89–1.00	0.07	0.98	0.92–1.04	0.44	0.95	0.88–1.02	0.17
High vs. low tertile			0.94	0.81–1.10	0.45	0.96	0.83–1.13	0.64	0.94	0.81–1.08	0.37
Genital organ	646	0.31									
1 ppb increase			1.02	0.95–1.11	0.54	1.07	0.98–1.16	0.14	1.06	0.96–1.17	0.27
High vs. low tertile			1.11	0.91–1.36	0.28	1.05	0.87–1.27	0.62	1.07	0.89–1.30	0.47
Cleft lip and palate	166	0.08									
1 ppb increase			1.03	0.88–1.21	0.71	0.99	0.82–1.19	0.90	1.02	0.83–1.26	0.82
High vs. low tertile			1.24	0.84–1.82	0.28	0.83	0.57–1.22	0.34	0.96	0.66–1.41	
Chromosomal	162	0.08									
1 ppb increase			1.04	0.88–1.22	0.67	0.90	0.75–1.08	0.26	0.94	0.76–1.16	0.56
High vs. low tertile			1.07	0.74–1.57	0.71	0.71	0.46–1.08	0.11	0.92	0.62–1.37	0.69
PM_{10} exposure											
Circulatory system	1445	0.79									
10 µg/m³ increase			1.03	0.99–1.08	0.16	1.03	0.98–1.08	0.19	1.07	1.00–1.14	0.05
High vs. low tertile			1.00	0.86–1.16	0.99	1.12	0.96–1.30	0.15	1.16	1.01–1.33	0.03
VSD	1022	0.56									
10 µg/m³ increase			1.03	0.97–1.09	0.31	1.05	0.99–1.11	0.10	1.07	0.99–1.16	0.08
High vs. low tertile			1.00	0.83–1.19	0.96	1.18	0.99–1.42	0.06	1.18	1.01–1.39	0.04
Genital organ	541	0.30									
10 µg/m³ increase			0.96	0.89–1.03	0.27	0.99	0.92–1.07	0.89	0.99	0.88–1.12	0.86
High vs. low tertile			0.93	0.72–1.18	0.54	1.13	0.88–1.44	0.35	1.00	0.80–1.24	0.97
Cleft lip and palate	145	0.08									
10 µg/m³ increase			0.99	0.86–1.16	0.94	1.03	0.91–1.16	0.68	1.06	0.87–1.29	0.55
High vs. low tertile			0.74	0.45–1.19	0.21	1.23	0.78–1.95	0.36	1.21	0.77–1.89	0.41
Chromosomal	142	0.08									
10 µg/m³ increase			1.14	1.01–1,28	0.04	1.04	0.88–1.21	0.67	1.20	0.97–1.49	0.09
High vs. low tertile			1.54	0.93–2.57	0.10	1.33	0.81–2.18	0.26	1.55	1.01–2.36	0.04
NO_x exposure											
Circulatory system	1643	0.78									
10 ppb increase			1.01	0.99–1.03	0.39	1.03	1.01–1.05	0.01	1.03	1.01–1.06	0.01
High vs. low tertile			1.10	0.96–1.25	0.17	1.13	1.00–1.29	0.06	1.11	0.98–1.26	0.11
VSD	1161	0.55									
10 ppb increase			1.02	0.99–1.04	0.13	1.03	1.00–1.05	0.03	1.04	1.01–1.07	0.007
High vs. low tertile			1.18	1.02–1.38	0.03	1.18	1.01–1.38	0.04	1.16	1.00–1.34	0.05
Genital organ	646	0.31									
10 ppb increase			1.03	1.00–1.06	0.04	1.05	1.02–1.08	0.002	1.06	1.02–1.10	0.001
High vs. low tertile			1.72	1.38–2.14	< 0.001	1.53	1.24–1.88	< 0.001	1.57	1.27–1.93	< 0.001
Cleft lip and palate	166	0.08									
10 ppb increase			1.03	0.95–1.11	0.48	1.05	0.96–1.14	0.31	1.05	0.95–1.17	0.34
High vs. low tertile			0.88	0.60–1.30	0.53	1.09	0.73–1.62	0.67	1.01	0.69–1.50	0.95
Chromosomal	162	0.08									
10 ppb increase			1.01	0.93–1.09	0.81	0.93	0.83–1.04	0.18	0.94	0.83–1.06	0.29
High vs. low tertile			0.98	0.65–1.49	0.94	0.77	0.50–1.17	0.22	0.98	0.65–1.48	0.94
O_3 exposure											
Circulatory system	1447	0.79									
10 ppb increase			0.98	0.89–1.09	0.77	0.83	0.75–0.93	0.01	0.84	0.74–0.95	0.01
High vs. low tertile			1.01	0.86–1.19	0.92	0.88	0.74–1.03	0.11	0.90	0.79–1.03	0.14
VSD	1023	0.56									
1 ppb increase			0.95	0.84–1.08	0.43	0.84	0.74–0.95	0.006	0.83	0.71–0.96	0.01
High vs. low tertile			0.98	0.81–1.20	0.87	0.90	0.74–1.10	0.31	0.89	0.76–1.04	0.16
Genital organ	541	0.30									
10 ppb increase			0.99	0.83–1.18	0.89	0.95	0.80–1.13	0.56	0.96	0.79–1.18	0.71
High vs. low tertile			0.94	0.71–1.23	0.64	1.01	0.78–1.30	0.96	0.90	0.73–1.11	0.33
Cleft lip and palate	145	0.08									
10 ppb increase			0.90	0.63–1.29	0.57	0.94	0.68–1.29	0.69	0.87	0.60–1.27	0.46
High vs. low tertile			0.90	0.53–1.52	0.69	0.76	0.47–1.25	0.28	0.87	0.57–1.35	0.54
Chromosomal	142	0.08									
10 ppb increase			1.26	0.93–1.70	0.14	1.40	1.04–1.89	0.02	1.42	1.02–1.98	0.04
High vs. low tertile			1.26	0.74–2.13	0.40	1.50	0.86–2.64	0.15	2.13	1.25–3.64	0.006

OR – odds ratio adjusted for maternal age, maternal ethnicity, maternal country of birth, maternal education plurality, season of birth, infant gender.
CM – congenital malformations; VSD – ventricular septal defect.

This study benefits from unselective nationwide study populations from both the spontaneously conceived pregnancies (from the largest HMO in Israel) as well as for the ART pregnancies (ART treatments are covered by health insurance law). In addition, the current study used a long standing register of CM which ensures a high case ascertainment. However, the current study has several limitations. For one third of the women in the cohort educational level data was not available. However, no differences were observed between educational subgroup regarding maternal age, infant gender and season of birth. Although adjustments for several confounders such as maternal age, ethnicity, and infant gender were conducted, several others potential risk factors for congenital malformations such as maternal occupational exposures, smoking and use of vitamin supplements were not taken into account. These factors are known to be correlated with socioeconomic status (Parker et al., 2011) and were indirectly taken into consideration by adjusting for educational level. In a prospective study, conducted by our group (Farhi et al., 2013), only 8% of the pregnant women reported smoking during pregnancy. This rate is relatively low compared to Smedberg et al. (2014) that found wide variation of smoking rate during pregnancy among 15 European countries ranging from 4.2% to 18.9%.

The exposure assessment relies on air monitoring stations that are scattered through the state of Israel. Although the larger metropolitan and coastal areas are highly-represented, the rural and more remote areas are less covered by the monitoring network. The maternal exposure assessment was according to residential status at delivery, assuming that women did not change their residence during pregnancy which may lead to exposure misclassification. Fell et al. (2004) found that 12% of women moved at least once during pregnancy and among them the majority (62%) moved within the same municipality. In Israel, according to the central bureau of statistics data, only 3.5–6.7% of women at the ages 20–44 migrated between localities (Central Bureau of Statistic, 2008); therefore, misclassification assumes to be small. Our study, as most other studies published thus far, did not account for women with chronic conditions such as asthma and cardio-respiratory condition that may be more vulnerable to air pollution exposure.

5. Conclusion

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 air pollution was observed particularly for SO_2 and O_3 exposures. Further studies are warranted, with more accurate exposure assessment and a larger sample size for ART pregnancies, in order to confirm these findings.

Funding

Review board

This study was approved by the Israel Ministry of Health Review Board (#3303 20/5/2007).

Appendix A

See Table A1.

Table A1
Congenital malformations requiring notification according to Israeli law.

Code (according to ICD-10)	Malformation
CONGENITAL MALFORMATION OF THE NERVOUS SYSTEM	
Q00[a]	Anencephaly and similar malformations
Q01[a]	Encephalocele
Q02	Microcephaly
Q03[a]	Congenital hydrocephalus
Q04.0	Congenital malformations of corpus callosum
Q04.1	Arhinencephaly
Q04.2	Holoprosencephaly
Q04.3	Other reduction deformities of brain
Q04.4	Septo-optic dysplasia
Q04.5	Megalencephaly
Q04.6	Congenital cerebral cysts
Q04.8	Other specified congenital malformations of brain
Q04.9	Congenital malformations of brain, unspecified
Q05[a]	Spina bifida with hydrocephalus and/or without hydrocephalus
Q06[a]	Malformations of spinal cord
Q07.0	Arnold–Chiari syndrome
Q07.8	Other specified congenital malformations of nervous system
Q07.9	Congenital malformation of nervous system, unspecified
CONGENITAL MALFORMATION OF EYE, EAR, FACE AND NECK	
Q11.0–Q11.1	Anophthalmos
Q11.2	Microphtalmos
Q12.0	Congenital cataract
Q12.1–9[a]	Other congenital lens malformation
Q13.0	Coloboma of iris
Q13.1	Absence of iris
Q13.2	Other congenital malformation of iris
Q15.0	Congenital glaucoma
Q16.0	Congenital absence of (ear) auricle
Q16.1	Congenital absence, atresia and stricture of auditory canal (external)
Q16.2	Absence of Eustachian tube
Q16.3	Congenital malformation of ear ossicles
Q16.4	Other congenital malformation of middle ear
Q16.5	Congenital malformation of inner ear
Q16.9	Congenital malformation of ear causing impairment of hearing, unspecified
Q17.2	Microtia
CONGENITAL MALFORMATION OF THE CIRCULATORY SYSTEM	
Q20.1–Q20.5, Q20.8–Q20.9	Congenital malformation of cardiac chambers and connections
Q21.0, Q21.2–Q21.8	Aortopulmonary septal defectCongenital malformations of cardiac septum
Q22[a]	Congenital malformations of pulmonary valve or tricuspid valve
Q23.0	Congenital stenosis of aortic valve
Q23.1	Congenital insufficiency of aortic valve
Q23.2	Congenital mitral stenosis
Q23.3	Congenital mitral insufficiency
Q23.4	Hypoplastic left heart syndrome
Q24.0	Dextrocardia
Q24.1	Laevocardia
Q24.2	Cor triatum
Q24.3	Pulmonary infundibular stenosis
Q24.4	Congenital subaortic stenosis
Q24.5	Malformation of coronary vessels
Q25.1–Q25.4	Malformation of aorta
Q25.5–Q25.7	Malformation of pulmonary artery
Q26.2	Total anomalous pulmonary venous connection
CONGENITAL MALFORMATION OF THE RESPIRATORY SYSTEM	
Q30.0	Choanal atresia
Q32.1	Malformation of trachea
Q33.0	Congenital cystic lung
Q33.3	Agenesis of lung
Q33.6	Hypoplasia and dysplasia of lung
CONGENITAL MALFORMATION OF THE DIGESTIVE SYSTEM	
Q35.0-Q35.6, Q35.8-Q35.9	Cleft palate
Q36[a]	Cleft lip
Q37[a]	Cleft palate with cleft lip

Table A1 (continued)

Code (according to ICD-10)	Malformation
Q39.0	Atresia of esophagus without fistula
Q39.1	Atresia of esophagus with tracheo-oesophageal fistula
Q39.2	Congenital tracheo-oesophageal fistula without atresia
Q41[a]	Congenital absence, atresia and stenosis of small intestine
Q42[a]	Congenital absence, atresia and stenosis of large intestine
Q43.1	Hirschsprung's disease
Q43.7	Persistent cloaca
Q44.0-Q44.5	Malformations of gallbladder or bile ducts
Q45.0	Agenesis, aplasia and hypoplasia of pancreas

CONGENITAL MALFORMATIONS OF GENITAL ORGANS AND URINARY SYSTEM

Q54[a]	Hypospadias
Q55.0	Absence and aplasia of testis
Q55.5	Congenital absence and aplasia of penis
Q56.0	Hermaphroditism, not elsewhere classified
Q56.1-Q56.4	Pseudohermaphroditism
Q60[a]	Renal agenesis/hypoplasia
Q61[a]	Cystic kidney diseases
Q62.1	Atresia and stenosis of ureter
Q62.4	Agenesis of ureter
Q62.7	Congenital vesico-uretero-renal reflux
Q64.0	Epispadias
Q64.1	Exstrophy of urinary bladder
Q64.2	Congenital posterior urethral valves
Q64.5	Congenital absence of bladder and urethra

CONGENITAL MALFORMATIONS OF THE MUSCULOSKELETAL SYSTEM

Q66.0	Talipes equinovarus
Q69[a]	Polydactyly
Q70[a]	Syndactyly
Q71[a]	Reduction defects of upper limb(s)
Q72[a]	Reduction defects of lower limb
Q73[a]	Reduction defects of unspecified limb(s)
Q74.3	Arthrogryposis multiplex congenital
Q75.0-Q75.10	Craniosynostosis
Q76.3	Congenital scoliosis due to congenital bony malformation
Q76.4	Other congenital malformations of spine, not associated with scoliosis
Q77[a]	Osteochondrodysplasia with defects of growth of tubular bones and spine
Q78.0	Osteogenesis imperfecta
Q78.9	Osteochondrodysplasia, unspecified
Q79.0	Congenital diaphragmatic hernia
Q79.1	Other congenital malformations of diaphragm
Q79.2	Omphalocele
Q79.3	Gastroschisis
Q79.4	Prune belly syndrome

OTHER CONGENITAL MALFORMATIONS

Q81[a]	Epidermolysis bullosa[a]
Q84.0	Congenital alopecia
Q84.8	Aplasia cutis congenital
Q87[a]	Congenital malformation syndromes
Q89.3	Situs inversus
Q89.4	Conjoined twins

CHROMOSOMAL ABNORMALITIES

Q90[a]	Down's syndrome
Q91.0-Q91.3	Trisomy 18
Q91.4-Q91.7	Trisomy 13, meiotic nondisjunction

[a] Including all congenital malformations in the section.

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