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Original Article (Pages: 18637-18648)

Associations between Prenatal Exposure to Air Pollutants and Cord-Blood Thyroid Hormones Levels: A Cross-Sectional Study in Isfahan

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Abstract

Background: Air pollution as a major health concern in the world can adversely affect pregnant women and their newborns' thyroid function. We evaluated the association between prenatal exposure to air pollutants and cord-blood thyroid hormone levels.

Method: This cross-sectional study was conducted as a sub-study of the PERSIAN birth cohort on mothers and their newborns from October 2019 to September 2021. All participants, related data, and cord blood samples were gathered from the Isfahan. The air quality index (AQI), extracted from its official website, and was used to assess overall air quality during pregnancy. The association between mean levels of AQI in the three trimesters with cord blood thyroid hormone levels was evaluated.

Results: In 195 mothers with a mean age of 29.79(5.46), the mean of TSH and free T4 was 6.96 IU/L and 1ng/dl, respectively. The total days with moderate AQI (51-100) were higher than other AQI categories over the three trimesters. This study found no significant association between the mean cord-blood TSH and AQI>100, (P>0.05). The mean cord-blood FT4 had a negative association with total unhealthy days for sensitive groups in the first trimester and total very unhealthy days in the third trimester. The mean cord-blood FT4 was positively associated with unhealthy days in the second trimester.

Conclusion: The cord-blood FT4 levels were associated with prenatal exposure to AQI higher than 100. These results highlight the need for air pollution management to minimize neonatal thyroid hormone alteration and its critical sequelae.

Key Words: Air pollution; Air quality; Maternal exposure; Thyroid stimulating hormone; TSH; Cord blood, Birth cohort.

* Please cite this article as: Golverdi E, Hashemipour M, Hovsepian S, Khoshhali M, Kelishadi R Associations between Prenatal Exposure to Air Pollutants and Cord-Blood Thyroid Hormones Levels: A Cross-Sectional Study in Isfahan. Int J Pediatr 2024; 12 (03):18637-18648. DOI: **10.22038/ijp.2024.79827.5454**

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Received date: Jan.17,2024; Accepted date: Mar.25,2024

1- INTRODUCTION

Child physical growth and neurological development have been, strongly, affected by any alteration in Thyroid Hormones (TH) which can be the result of different etiologies; the genetic defect in the regulatory pathways of TH, or maternal or neonatal endocrine disorder (1-4). The high Thyroid Stimulating Hormone (TSH) level in newborns is associated with neurodevelopmental impairment and poor growth, and maternal high free T4 in early pregnancy is related to lower birth weight (5-6).

In the first trimester of pregnancy, because of the nonfunctional thyroid glands mother supplies the embryo needs for TH. During the second trimester the fetus's thyroid glands gradually become functional; however, the fetus is partially dependent on mother TH. In the third trimester, entirely, fetus's thyroid glands are responsible for TH secretion (7). All of these indicate the importance of TH levels, not only in newborns but also in mothers during pregnancy. The key role of thyroid function in newborn neurological development leads to using TSH level as a prognostic factor of neurodevelopment and growth outcomes (8).

The recent increase in industrial pollution reduced air quality. Air pollutants like carbon monoxide (CO), sulfur dioxide (SO2), nitrogen oxides (NO), ozone (O3), heavy metals, and particulate matter (PM2.5 and PM10) had chronic and acute effects on human health (9). Air quality index (AQI) defines the overall air quality and converts the daily concentrations of different air pollutants as a number. According to AQI, air quality is divided into six descriptive categories; good, moderate, unhealthy for sensitive groups, unhealthy, very unhealthy, and hazardous (Gadekar). Exposure to air pollution is considered a critical problem for pregnant women and their embryos as a high-risk population (10). This exposure could also disrupt endocrine function (10). Based on findings of previous studies exposure to cigarette tobacco smoke (11), cadmium (12), and organochlorine compounds (13, 14) can alter TH balance. The last evidence indicated an association between maternal exposure to particulate matter and higher congenital hypothyroidism risk (15).The findings regarding their association with cord blood TH levels were controversial (16-19).

There have been few studies on the effect of maternal air pollution exposure and cord-blood TSH levels; and we found no study conducted on pregnant women who lived in Isfahan, a big industrial city with high-level air pollution in this field. The present sub-cohort study aimed to investigate the association between cord-blood TH levels and the AQI, a parameter that was used for the estimation of air pollutants exposure during pregnancy.

2- MATERIALS AND METHODS

This cross-sectional study was performed as a sub-study of the ongoing PERSIAN (Prospective Epidemiological Research Studies in IRAN) Birth cohort (20). The present study evaluated the association between maternal exposure to air pollutants during pregnancy and cord-blood TSH among 286 subjects of the PERSIAN Birth cohort from October 2019 to September 2021

2-1. Participants

Our study subjects were selected from the PERSIAN Birth Cohort participants. This ongoing cohort collected data on both health determinants and outcomes of mother-offspring pairs in five cities (Isfahan, Yazd, Semnan, Sari, and Rafsanjan). These data belong to three phases; 1- pre-pregnancy and perinatal, 2- infancy and toddlerhood (0-2), and 3- childhood (2 years old). They evaluate the population in the areas of socioeconomic, dietary, and physical activity patterns, exposure and medical history, pregnancy outcomes, and child physical, behavioral, and neurological development (20). The cord-blood samples were collected at the delivery time.

2-1.1. Inclusion and Exclusion Criteria

We enrolled all mothers with term deliveries from October 2019 to September 2021 from Isfahan center, an industrial city. The cases who had the following conditions were excluded; 1- mothers with thyroid dysfunctions (hyper- or hypothyroidism), 2- mothers with a history of medications that interfere with thyroid hormones including corticosteroids and immune-modulatory drugs, dopamine agonists and antagonists, lithium, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), anticonvulsants, rifampin, amiodarone, interferon and antineoplastic agents (21), 3- insufficient or missed cord-blood sample, 4- mother's migration, death or noncooperation.

2-2. Data collection

The trained persons from each site were responsible for collecting data through personal interviews with the participants who accepted to participate in the cohort study and sign the consent form. We extracted the following data from Isfahan birth cohort records: mothers' age and educational status, income level, living place, past medical and drug history, parity and gestational age (according to last menstrual period (LMP)), childbirth types as normal vaginal delivery (NVD)/ Cesarean Section (C/S), newborn gender and weight (were measured by calibrated equipment).

2-2-1. Cord-blood thyroid hormones levels measurement

The cord blood samples were obtained after clumping from the placental side of the umbilical vein. The TSH and free T4 (FT4) levels were measured by chemiluminescent immunoassay (CLIA) in Milad hospital laboratory.

2-2-2. Maternal exposure to air pollutants assessment during pregnancy

Air quality index (AQI) was used to assess maternal exposure to air pollution during pregnancy. AQI transforms the daily concentrations of different air pollutants as a number to report the overall quality of air. These pollutants generally include NO_2, SO_2, PM_{10}, $PM_{2.5}$, CO, and O_3. This index ranges from 0 to 500 and classifies the air quality into six categories with different colors; good (green, 0 -50), moderate (yellow, 51-100), unhealthy for sensitive groups (orang, 101-150), unhealthy (red, 151-200), very unhealthy (purple, 201-300) and hazardous (maroon, >300) (22). We extracted the daily AQI data of Isfahan air pollution monitoring stations (Bozorgmehr, Azadi, Kharazi, Parvin, Ahmad Abad, Khajoo, Roudaki, Ostandari Street, Shahin Shahr, Sejzi, and Mobarakeh) from its official website (aqms.doe.ir). After matching the participants' living places with related stations, the total days of each AQI level were recorded for all mothers during the pregnancy and over the three trimesters.

2-3. Data analysis

Continuous quantitative variables were expressed as means [standard deviations (SD)] and median (range: min-max). Categorical variables were described as numbers (percentages). The normality of the data was assessed both graphically (i.e. bell-shaped curve, normal Q-Q plot, and box plot) and statistically (Kolmogorov–Smirnov test). Thyroid hormone levels were naturally logged–transformed to improve the normality of the distributions and described by geometric mean (GM) and 10th–90th percentile (P10-P90). Univariate and multiple linear regressions were performed to determine the unadjusted and adjusted association between maternal exposure to poor air quality during the 3 trimesters of gestation and thyroid hormone levels in cord blood, respectively. The models adjusted with maternal age, educational and income levels, parity, delivery type, area living, gestational age (GA), gender, and birth weight. All statistical analyses were performed using SPSS 20.0 for Windows. P-values of less than 0.05 were considered statistically significant**.**

3- RESULT

The data from 195 mothers and their newborns were analyzed. In **Table 1**, we summarized mothers' and newborns' demographic characteristics and cord-blood thyroid hormone levels. The mean age of mothers was 29.79±5.46 years (mean ±SD) with the age range of 16-45 years. In terms of educational level, the majority of mothers had a high school diploma (44.1%). Among our subjects, the moderate-income level (71.5%) and living in the urban area (88.2%) were more frequent than others. 52.3% of newborns were female and the others were male. The mean ±SD of gestational age and newborns' birth weight were 38.74 ± 0.96 weeks and 3144.15 ± 381.12 grams, respectively. The geometric means of cord blood thyroid hormone levels were 6.96 for TSH and 1 for FT4.

Table-1: Characteristics of the mother–infant group in the study

Variables			Mean or Number	SD or %
Mothers	Age		29.79	5.460
	Type delivery	-Normal delivery -Cesarean section	89 106	45.6 54.4
	Educational levels	-Less than high school - High school - College	37 86 72	19.0 44.1 36.9
	Area living	-Rural - Urban	23 172	11.8 88.2
	Socioeconomic status	-Low -Medium -High	42 138 13	21.8 71.5 6.7
	Parity	-1 -2 ->=3	80 86 29	41.0 44.1 14.9
Infants	Birth weight	gr	3144.15	381.125
	GA	Weeks	38.74	.96
	Gender	-Girl - Boy	101 94	52.3 47.7
Thyroid hormones			GM	(P10, P90)
Thyroid hormones	TSH	(IU/L)	6.96	(3.35, 14.65)
	F.T4	(ng/dl)	1.00	(0.80,1.20)

Table 2 shows the distribution of the number of days in each AQI category during the three trimesters of pregnancy. Analyses revealed that the days with moderate AQI (51-100) were more than those with other levels over the three trimesters (in average they were more than 52 days).

Table-2: Distribution of days with different categories of Air Quality Index for mothers during pregnancy

Air Quality Index Level of Health Concern	AQI value	Trimester 1		Trimester 2		Trimester 3	
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Good	0-50	11.63(10.15)	2(11,15)	16.42(11.66)	8(14,25)	19.42(13.14)	7(23,32)
Moderate	51-100	63.52(18.83)	50(61,81)	52.41(15.30)	40(52,60)	56.89(13.53)	48(55,64)
Unhealthy for sensitive groups	101-150	8.94(7.31)	3(6,14)	12.21(7.63)	5(13,19)	9 (8.79)	1(7,13)
Unhealthy	151-200	6.65(8.37)	0(1,12)	9.97(8.46)	0(11,18)	3.24(4.46)	0(0,6)
Very unhealthy	201-300	.28(.72)	0(0,0)	.25(.67)	0(0,0)	0.46(0.82)	0(0,0)
Hazardous	301-500	0(0)	0(0,0)	0(0)	0(0,0)	0(0)	0(0,0)

SD: Standard deviation; IQR: Interquartile range

The association between the number of days with AQI level > 100 during pregnancy and cord blood thyroid hormones were presented in **Table 3**. There was no significant association between the number of days during pregnancy (in every three trimesters) with AQI level > 100 and cord blood TSH. However, there was a significant association between the number of days with unhealthy air quality (AQI: 101-150) in trimester 1; the number of days with unhealthy air quality for sensitive groups (AQI: 151-200) in trimester 2, and the number of days with very unhealthy air quality (AQI: 201-300) in trimester 3 with F. T4 ($P<0.05$) (**Table 3**). There was no significant association between the number of days with AQI level >100 and F. T4 and cord blood TSH for the whole pregnancy ($P > 0.05$) (**Table 3**).

4- DISCUSSION

The results of the present study regarding the association between maternal prenatal exposure to air pollutants and cord-blood thyroid hormone levels indicated no association between cord-blood TSH level and unhealthy levels of AQI. We found negative associations between different unhealthy levels of AQI during pregnancy and the cord blood T4 level.

Several studies have reported the importance of maternal and neonatal thyroid function for proper neonatal growth and development (1-4, 23). Accordingly, higher levels of maternal and cord blood TSH levels and lower levels of FT4 are associated with an increased risk of low birth weight and small fetus for gestational age (SGA) (6). Low thyroid hormone level in congenital hypothyroidism is the main cause of mental retardation in patients which could be properly prevented by early diagnosis and thyroid hormone replacement therapy. However, there have been few studies investigating the correlation between prenatal air pollution exposures and maternal or neonatal thyroid hormone levels; and most of the available data are related to particular matters and thyroid hormone, but not AQI. In addition, few studies have measured cord blood thyroid hormones level. In this study, we evaluate the association between AQI and cord blood thyroid hormones levels, because AQI considered the concentration of the eight pollutants, including PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, O_3, NH_3, and Pb for up to 24 hours averaging period.

Table-3: Association between the number of days, Air Quality Index > 100 during pregnancy, and cord blood thyroid hormones

log TSH	Number of days	Unadjusted	P value	Adjusted*	P value
		β (SE)		β (SE)	
Trimester 1	Unhealthy for sensitive groups	0.005(0.006)	0.468	0.006(0.007)	0.332
	Unhealthy	0.002(0.006)	0.756	0.004(0.006)	0.490
	Very unhealthy	0.030(0.065)	0.642	0.020(0.068)	0.771
Trimester 2	Unhealthy for sensitive groups	-0.004(0.006)	0.542	-0.004(0.006)	0.492
	Unhealthy	-0.007(0.006)	0.213	-0.008(0.006)	0.143
	Very unhealthy	0.064(0.071)	0.374	0.039(0.074)	0.603
Trimester 3	Unhealthy for sensitive groups	0.006(0.005)	0.280	0.007(0.005)	0.236
	Unhealthy	-0.001(0.011)	0.954	-0.005(0.011)	0.639
	Very unhealthy	0.022(0.057)	0.695	0.043(0.058)	0.464
Whole pregnancy	Unhealthy for sensitive groups	0.005(0.005)	0.294	0.005(0.005)	0.289
	Unhealthy	-0.007(0.006)	0.261	-0.010(0.007)	0.142
	Very Unhealthy	0.057(0.046)	0.220	0.047(0.046)	0.308
log F.T4					
Trimester 1	Unhealthy for sensitive groups	-0.002(0.002)	0.183	-0.003(0.002)	0.180
	Unhealthy	-0.004(0.002)	0.018	-0.004(0.002)	0.024
	Very unhealthy	0.014(0.019)	0.451	0.021(0.020)	0.278
Trimester 2	Unhealthy for sensitive groups	0.004(0.002)	0.015	0.004(0.002)	0.045
	Unhealthy	0.002(0.002)	0.324	0.001(0.002)	0.502
	Very Unhealthy	0.001(0.020)	0.965	0.003(0.021)	0.897
Trimester 3	Unhealthy for sensitive groups	0.0003(0.002)	0.871	0.001(0.002)	0.745
	Unhealthy	0.003(0.003)	0.393	0.005(0.003)	0.114
	Very unhealthy	-0.046(0.016)	0.005	-0.042(0.017)	0.012
Whole pregnancy	Unhealthy for sensitive groups	0.001(0.001)	0.305	0.001(0.001)	0.381
	Unhealthy	-0.002(0.002)	0.302	-0.001(0.002)	0.455
	Very unhealthy	-0.023(0.013)	0.086	-0.018(0.014)	0.195

Models were adjusted with maternal age, educational and income levels, socioeconomic status (low, medium, high), parity, delivery type, area living, GA, gender, and birth weight.

Though PM2.5 which is evaluated in almost all previous studies in this field is considered the main component of AQI for the estimation of overall air quality, it seems that evaluation of AQI in this study would be more practical for health care system plans. However further studies would be planned to determine the role of each mentioned component separately.

In this study, we found a negative association between unhealthy levels of AQI and cord blood T4 during the 1st and 3rd trimesters and a positive association between unhealthy levels of AQI and T4. We did not find any association between AQI and cord blood TSH.

As previously mentioned, few studies have investigated the association between particular matters and cord blood thyroid hormones. Janssen et al. in Belgium investigated the association between PM2.5 concentration during the third trimester and cord blood thyroid hormones levels. According to their findings, it was associated inversely with cord blood thyroxin level and positively with TSH level (16).

Recently, Zhang et al. in China also reported the association between PM2.5 exposure during the first trimester and decreased level of maternal serum FT4. They did not find any association with TSH (24). In another recent study from China by Zhou et al., early pregnancy exposure to PM2.5 and its inorganic constituents including Al, Si, K, Mn, and Zn, were associated with fetal growth and maternal thyroid hormone levels. They reported similar results (25).

The PM2.5 exposure during the first trimester of maternal hypothyroxinemia was confirmed in the study by Ghassabian et al. that analyzed the data obtained from five cohorts. Moreover, they mentioned that PM10 exposure didn't significantly associated with thyroid function (26).

Based on available evidence, PM 2.5 could penetrate the blood and placenta which could consequently affect placental thyroid hormones receptors and transporters.

In a recent study in Belgium, Neven et al. reported similar results. In addition, they indicated that the effect of PM2.5 exposure during pregnancy is mediated by placental iodine load (27).

Zhao et al. surveyed 8077 pregnant women. They showed a negative association between prenatal PM2.5 and NO2 exposure during the second trimester and FT4 (20). TSH had an increasing trend, but the association was not significant (19).

Findings of a cohort study by Wang et al. (18) indicated similar results to that reported by Zhao et al. (19) In addition, they studied the association between maternal PM2.5 exposure and neonatal TSH levels within the first 72 hours after birth and did not show a significant association between them (18).

Recently, Zhou et al. showed a positive association between maternal PM2.5 levels and TSH (25). The findings of Janssen et al. (16), Wang et al. (18), Ghassabian et al. (26) and Ilias et al. (27) were also similar to the results of that study.

Our findings were similar to the recent study of Zhang et al. (24) regarding the lack of association between AQI and TSH levels.

The findings of our study regarding the positive association between unhealthy level of AQI and cord blood T4 level was similar to that reported by Howe et al.(17) and Neven et al. (28). Based on their suggestion the association may be due to the increased production of maternal thyroid hormones and their transportation to the fetus.

The mechanism associated with the effects of air pollutants on maternal or fetal thyroid hormone function is not determined clearly. Some suggested mechanisms include activation of the hypothalamic-pituitary-thyroid (HPT) axis (29), oxidative and nitrosative stress, and systemic inflammatory reaction due to exposure to air pollutants specially PM2.5 (30, 31). Accordingly, oxidative stress and inflammation could cause liver dysfunction and activation of the HPA axis (32). Liver has an important role in the conversion of T4 to T3 (33).

The inconsistent findings regarding the association between trimester-specific exposure and cord blood TH levels are important and require further investigations. The negative association observed between the air quality index and T4 in the 1st and 3rd trimesters is consistent with findings of some previous studies reporting similar associations; specially, in the 1st trimesters due to the dependency of the fetus to maternal thyroid hormones. However, the positive association observed in the 2nd trimester needs more evaluations.

One possible explanation is that individual susceptibility to environmental exposures may play a role in these inconsistent findings. Another suggested explanation is related to the exposure of specific pollutants. It seems that certain pollutants may have stronger associations with cord blood TH levels than others, depending on the timing of exposure during pregnancy. In this study, we evaluate the total AQI.

Overall, further research is needed in this field. More comprehensive assessments of environmental exposures and individual susceptibility are needed to better understand the complex relationship between air pollution and thyroid hormone levels during pregnancy.

Further, it is suggested that iodine also could have potential antioxidant activity. It is proposed that during the second trimester of pregnancy, it could be conserved due to exposure to air pollution and consequent antioxidant requirements (26, 34-36).

As mentioned, fetal growth is influenced by prenatal environmental pollutants exposure which may result in fetal growth impairment and low birth weight.

Shields et al. (5), Korevaar et al. (37), and Medici et al. (6) demonstrated that in normal healthy pregnant women a lower level of cord blood FT4 is associated with low birth weight.

Further, Shang et al. in China investigated the association between AQI, PM2.5, and PM10 with CH. They reported that a higher level of PM2.5 is associated with an increased risk of CH. (15). Some evidence has indicated that in addition to low birth weight, prenatal exposure to particulate matters is correlated with cardiac birth defects including ostium secundum atrial septal defect (osASD), patent foramen ovale (PFO) and ductus arteriosus (PDA), which was meaningful only in the osASD (38).

4-1. Limitations of the study

The main limitation of our study was its selected subjects only from the Isfahan ongoing birth cohort that may not be compatible with a variety of participants. Also, unfortunately, we couldn't have access to the data of each pollutant (PM2.5, PM10, SO2, NO2, CO, and O3) concentration separately and to detailed information from different monitoring stations over different time periods. In addition, we did not measure the iodine level, daily iodine, FT3, and FT4/FT3 ratio (16, 39) which could help us gain a better understanding of the process.

Despite the limitations, our study has addressed the considerable association of prenatal air pollution exposure with neonatal thyroid function. Although additional studies should be designed in a larger population and different regions to confirm our findings, a follow-up of these newborns to evaluate the childhood thyroid function and postnatal air pollution exposure could lead to more concise findings in this field.

5- CONCLUSION

The findings of this study indicated that AQI is associated positively with cord-blood FT4 levels in the second trimester and negatively in the first and third trimesters. These findings are considered an important public health issue to prevent the possible mentioned health consequences due to impaired thyroid function during fetal life. These results also highlight the need to find ways for reducing air pollution exposure and improving air quality to minimize neonatal thyroid hormone alteration and its critical sequelae.

6- ETHICAL CONSIDERATIONS

This study was conducted as a sub-specialty thesis with the project number 3400206, funded by Isfahan University of Medical Sciences; it was a sub-study of the PERSIAN birth cohort; project 194354 (IR.MUI.MED.REC.1400.246) funded by the Ministry of Health and Medical Education.

The study was performed under the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The participants voluntarily accepted to proceed with the study, and signed the consent forms.

7- CONFLICT OF INTEREST

None.

8- AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are not publicly available due to privacy/ethical restrictions but are available from the corresponding author at reasonable request.

9- AUTHORS' CONTRIBUTION

All authors (EG, MH, SH, MKh, RK) have participated in the conception of the study as well as in the analysis and interpretation of data, elaboration, or critical reviews of the report; and they have read and approved the final version of the manuscript. The authors confirm that there are no concerns of financial involvement with organizations, entities, or individuals with an interest in the subject matter or materials discussed in the manuscript, and no conflict of interest.

10- ACKNOWLEDGMENT

We would like to acknowledge all patients and participants for their cooperation, and all laboratory staff of the Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences for their efforts in performing laboratory measurements.

The authors acknowledge resources and support from the Vice Chancellor of Research, Isfahan University of Medical Sciences.

11- ABBREVIATIONS

TH = thyroid hormones

TSH = thyroid stimulating hormone

FT4 = free T4

NO2 = nitrogen dioxide

SO2 = Sulfur dioxide

PM10 = particulate matter 10 (less or equal to 10 microns)

PM2.5 = particulate matter 2.5 (less or equal to 2.5 microns)

CO = carbon monoxide

O3 = ozone

AQI = air quality index

NVD = normal vaginal delivery

C/S = Cesarean Section

TCA = tricyclic antidepressant

SSRI = selective serotonin reuptake inhibitors

GA = gestational age

LMP = last menstrual period

CLIA = chemiluminescent immunoassay

SD = standard deviation

GM = geometric mean

gr = gram

CH = congenital hypothyroidism

PFO = patent foramen ovale

PDA = patent ductus arteriosus

osASD = ostium secundum atrial septal defect

SGA = small size for gestational age at birth

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