Environmental Science and Pollution Research (2021) 28:50696–50706
https://doi.org/10.1007/s11356-021-14182-0

RESEARCH ARTICLE

Association between prenatal phthalate exposure and anthropometric measures of newborns in a sample of Iranian population

Mohammad Darvishmotevalli[1,2] · Maryam Moradnia[1,3] · Reza Hosseini[4] · Bijan Bina[1,3] · Awat Feizi[5] · Karim Ebrahimpour[3,1] · Hamidreza Pourzamani[1,3] · Ghasem Kiani Feizabadi[1,3] · Roya Kelishadi[6]

Received: 1 March 2021 / Accepted: 26 April 2021 / Published online: 9 May 2021

Abstract
Phthalates or phthalic acid esters (PAEs) are a group of compounds which they can be entered into the human body through the various pathways. The aim of this study was to examine associations between prenatal phthalates exposure with anthropometric measures of neonates. Urine samples were obtained from 121 Iranian pregnant women at their first trimester of pregnancy, and the levels of monobutyl phthalate (MBP), mono-benzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), and mono (2-ethyl-5hydroxyhexyl) phthalate (MEHHP) metabolites were determined by gas chromatography mass spectrometry (GC/MS). The correlations between the maternal urinary concentrations of phthalate metabolites with anthropometric measures of neonates as well as with the socio-demographic factors of participants (maternal education, age, family income, pre-pregnancy body mass index), their lifestyle variables (smoking habit, food pattern, and physical activity), and use of cleaning products (cosmetic and household cleaning products) were investigated. MBzP, MBP, MEHP, and MEHHP were detected in 100% of the participants with the concentration ranged 120 to 860 μg/g creatinine. Significant correlations were observed between the urinary levels of maternal MBzP (adjusted $\beta = 0.3$ (0.001), $p = 0.03$) and MEHHP (adjusted $\beta = 0.3$ (0.001), $p = 0.04$) with the birth weight of female neonates. MBP (adjusted $\beta = -0.3$ (0.02), $p = 0.04$) and MBzP (adjusted $\beta = -0.3$ (0.001), $p = 0.02$) had negative associations with the head circumference in male and female newborns, respectively. Furthermore, plastic packaging for pickle and passive smoking during pregnancy were identified to be significantly associated with low birth weight (p value < 0.05). Iranian pregnant women had higher concentrations of urinary phthalates compared to the other countries. Based on the findings, the higher prenatal exposure to phthalates could adversely impact the health status of newborns.

Responsible Editor: Lotfi Aleya

✉ Maryam Moradnia
moradnia.mui@gmail.com

Mohammad Darvishmotevalli
mohamad.darvish68@gmail.com

Reza Hosseini
reza.hosseini6970@yahoo.com

Bijan Bina
bbina123@yahoo.com

Awat Feizi
awat.feizi@gmail.com

Karim Ebrahimpour
k.ebrahiim@gmail.com

Hamidreza Pourzamani
hamidpkh6@gmail.com

Ghasem Kiani Feizabadi
ghasem_kiani@yahoo.com

Roya Kelishadi
roya.kelishadi@gmail.com

1 Department of Environmental Health Engineering, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

2 Research Center for Health, Safety and Environment (RCHSE), Alborz University of Medical Sciences, Karaj, Iran

3 Environment Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

4 Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

5 Department of Biostatistics and Epidemiology, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

6 Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

Keywords Phthalate · Pregnancy · Urinary metabolites · Neonatal weight · Iran

Introduction

Phthalates are a group of compounds widely used in the production of industrial goods. The low molecular weight phthalates such as diethyl phthalate (DEP) and dibutyl phthalate (DBP) are commonly used as additives/stabilizing agents in cosmetics, perfumes, lotions, and pesticides, whereas high molecular weight phthalates (with ≥ 8 carbons in the alkyl chain) including di-2-ethyl hexyl phthalate (DEHP) and butyl benzyl phthalate (BBzP) are mainly applied as plasticizers in the manufacture of packaging materials, polyvinylchloride (PVC), and blood transfusion devices and catheters (Amin et al. 2018c, 2019a; Gao and Wen 2016). Phthalates can easily be released from materials containing these hazardous compounds; therefore, they can be entered into the body through inhalation, ingestion, or dermal adsorption (Amin et al. 2019a, b; Bui et al. 2016). However, dietary intake has been regarded to contribute as the main route of human exposure to phthalates (Bui et al. 2016; Moridzadeh et al. 2020). Upon the absorption, the diester phthalates are quickly hydrolyzed into the respective monoesters (mono-2-ethylhexyl phthalate, MEHP), which in turn are oxidized into the more simple products such as MEHHP (mono2-ethyl-5-hydroxyhexyl), and can be excreted into the urine and feces (Lee et al. 2017; Rafiee et al. 2018).

Previous studies have detected substantial amounts of phthalates in the cord blood and amniotic fluid, indicating that these compounds can cross the placenta and may harmfully affect the growing fetus. In this regard, several epidemiological studies have shown a potential relationship between maternal exposure to phthalates and the risk of poor birth outcomes (Li et al. 2018; Rafiee et al. 2019; Shahsavani et al. 2017). Due to these potential adverse effects, many developed countries have prohibited the use of di-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBzP) in industrial products (Becker et al. 2009). However, no strict regulation has been set up yet regarding the use of these chemicals in most of the developing countries, including Iran. So, pregnant women and their fetus are exposed to more negative health effects by the exposure to environmental chemicals (Amin et al. 2018b, 2019a, b; Mohammadi et al. 2019; Wenzel et al. 2018). To the best of our knowledge, no previous publication has investigated the association between exposure to phthalates during pregnancy and birth outcomes among Iranian pregnant women. Therefore, in the present study, we aimed to evaluate the urinary concentrations of phthalate metabolites in a sample of Iranian pregnant women at their first trimester, as an indicator of exposure to phthalates, and examine associations between prenatal phthalate exposures with the anthropometric measures of neonates. The findings of this study may also provide an insight into common sources of exposure to phthalates among Iranian pregnant women which can help decision-makers to take the appropriate measures.

Materials and methods

Study population

This cross-sectional study was a part of PERSIAN birth cohort survey conducted between the years 2018 and 2019 on 121 pairs (mother-newborn) who lived in Isfahan city, Iran. The participants were selected randomly among those pregnant women at their first trimester who attended at the healthcare centers in Isfahan city. The purpose of the study was completely explained to the participants so that people were voluntarily involved in the study. The distributions of participants' location are given in Fig. 1. All the participants were informed about the objectives, methodology, as well as the voluntary nature of the survey, and a signed consent letter was taken from them. It should be mentioned that the protocols and ethical issues related to this study were approved and observed by the Ethics Committees of Isfahan university of Medical sciences.

Urine sampling

The early morning urine samples were taken from the participants who visited the healthcare center, collected in borosilicate containers, and transferred to the laboratory to be kept at -20 °C for the future experiments. During the sample collection, the PERSIAN Birth Cohort questionnaires were used to gather the data on socio-demographic variables (maternal education, age, family income), lifestyle factors (pre-pregnancy BMI, smoking habit, and physical activity (PA)), and food habits and household cleaning products use (Kelishadi et al. 2012). The total physical activity (MET-minutes/week) score were computed by IPAQ (International Physical Activity Questionnaire) (Cleland et al. 2018). To obtain the data regarding food habits of the participants, food frequency questionnaire (FFQ) was applied. The questionnaire included the questions asking about the frequency of consuming fried foods (as daily, 1–2 per week, 1–3 per month, seldom, and never) and the use of plastics for packaging certain foods including bread, lemon juice, pickle, leftover, and water.

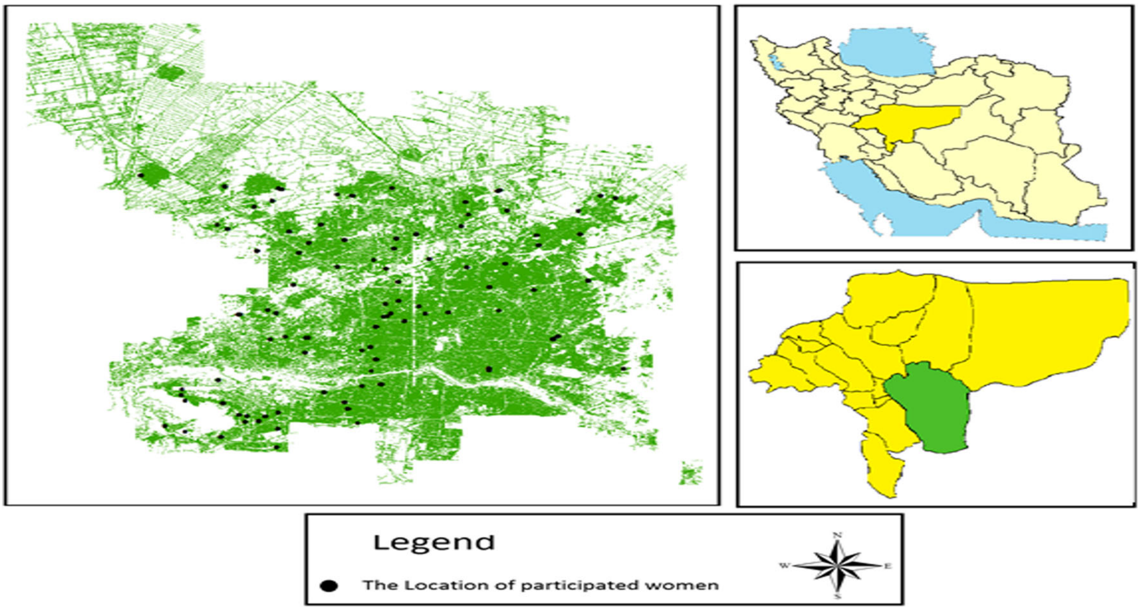

Fig. 1 The distribution of participants' location in Isfahan city

Measuring urinary metabolites of phthalate

All the measurements were done along with the standard solutions of MBP, MBzP, MEHP, and MEHHP. To measure the phthalate content of urine samples, the following steps were taken. At first, in order to extract MBP, MBzP, MEHP, and MEHHP metabolites, 10 ml of the urine samples were defrizzed and digested by 20 μl of β-glucuronidase enzyme for 18 h incubation at 37 °C. Then, 0.2 g of sodium chloride was added to the preparation and shaked for 24 h at 37 °C. Afterwards, 5 ml of the obtained mixture was diluted with the same volume of distilled water, and the solution pH was adjusted to 2 using 10% sulfuric acid solution. In the next step, 1 ml of acetone and 20 μl of chlorobenzene were added to the previously obtained mixture and centrifuged for 5 min at 5000 rpm. Then, the sediments were withdrawn from the bottom of the tubes using a micro-syringe and collected in different microtubes and dried under nitrogen gas stream. Thereafter, 10 μl of MSTFA was mixed with the sediment and centrifuged. At the final, 10 μl of the prepared solution was injected into the GC/MS (Model A 7890 of Agilent Technologies, USA) to measure the concentration of investigated phthalate metabolites (Amin et al. 2018a). To minimize the bias of the dilution difference between the samples, the phthalate concentrations were adjusted using creatinine levels. The limits of detection (LOD) were 0.017, 0.0126, 0.018, and 0.019 μg/L for MBP, MBzP, MEHP, and MEHHP, respectively. For the metabolite concentrations below the LOD, LODs divided by 2 were considered in the statistical analysis (Schuhmacher et al. 2009).

Anthropometric measures of neonates

Data on the anthropometric indices (weight, length, and head circumference) and other related information of neonates of corresponding mothers who participated in this study were retrieved from the hospital records which had been measured by experienced obstetric nurses using standardized procedures.

Quality assurance and quality control (QA/QC)

To confirm the reliability of the analytical data and to increase confidence in the relevance of obtained responses, the quality assurance and quality control (QA/QC) assessments were performed. Accordingly, the linear regression gave a good fit (R2 ≥ 0.98) with high precision (≤ 13.2 % RSD). The limit of detection (LOD) and limit of quantification (LOQ) were based on the signal-to-noise ratio of 3 and 10, respectively. For the metabolite concentrations below the LOD, LODs divided by 2 were considered in the statistical analyzes (Schuhmacher et al. 2009). Furthermore, to minimize the bias of the dilution difference between the samples, the phthalate concentrations were adjusted using creatinine levels. The R2, precision (% RSD), LOD, LOQ, and mean recovery are summarized in Table 1.

Data analysis

Continuous variables have been presented as mean ± SD and median (minimum-maximum), while categorical variables were expressed as percentages. Normality of continuous data was evaluated by using Kolmogorov-Smirnov test and Q-Q

Table 1 QA/QC parameters of phthalate metabolites

	MBP	MBzP	MEHP	MEHHP
R^2	0.99	0.99	0.99	0.98
RSD (%)	7	6.9	13.2	6.2
LOD (μg/L)	0.017	0.013	0.018	0.019
LOQ (μg/L)	0.06	0.04	0.06	0.07
Recovery (%)	83	94	90	69

plot. Independent sample *t*-test was used to compare the mean values of birth outcomes across categories of possible demographic and lifestyle determinants, while Pearson or non-parametric correlation coefficients were used for the evaluation of bivariate associations between the maternal urinary phthalate concentrations with infants' anthropometric measures and continuous determinants. Multiple linear regressions were used for evaluating the association of metabolites with infants' anthropometric measures, and adjustment was done for mothers' basic demographic and clinical characteristics. All statistical analyses were done using SPSS software version 23 (IBM SPSS Inc., Chicago, IL). A p value < 0.05 was considered statistically significant.

Results and discussion

The characteristics of the participants are summarized in Table 2. Descriptively, 59% (n = 71) of participants were ≥ 30 years old, and 41% (n = 50) were ≤ 30 years old. The majority of the participants (69%, n = 83) were categorized into overweight, while 29% of them (n = 35) had normal weight, and only 2 % (n = 3) were classified as underweight. Most of the participants were academically educated (n = 105, 86.8%). The majority of the participants had family income of 100–300 $ per month and grouped into the middle income category (n = 69, 57%). Household cleaning products and cosmetic products were found as the most common products used by 92.6% (112) and 100% (121) of the participants, respectively. Moreover, more than half (51.26%) of the pregnant women have reported the use of plastics for packaging of bread (n = 76, 62.8%), lemon juice (n = 67, 55.4%), pickle (n = 55, 45.5%), leftover (n = 52, 43%), and water (n = 60, 49.6%). The data showed that 31.4% (n = 38) of the subjects have used fried foods more than 1 time per week (1–2 times/week); however, 4.1% (n = 5) of them had never used fried food items. The majority of the participants did not have enough physical activity, where 53.7% of study population (n = 65) were grouped into the low physical activity category. Among the studied pregnant women, only 6.6% of them (n = 8) had high physical activity.

The mean (± SD) of birth weight, birth length, and head circumference of infants of the corresponding mothers who participated in this survey was 3204.04 ± 480.94 g, 50.35 ± 3.16 cm, and 34.5 ± 1.71 cm, respectively.

Table 3 shows the mean, minimum, and maximum concentration of phthalate metabolites adjusted by creatinine. All the urine samples (100%, n = 121) were positive for phthalate metabolites. MEHHP had the highest concentration (866.5 ± 307.6 μg/g creatinine), while MEHP was detected in the all samples with the lowest level (126.5 ± 118.3 μg/g creatinine). The mean concentration of MBP, MBzP, MEHP, and MEHHP found in this study were 13, 30, 20, and 44 times greater than those levels that have been reported by the studies in US and European countries (Berman et al. 2009; Valvi et al. 2015; Wenzel et al. 2018). These results are in accordance with the findings of Amin et al. who previously reported higher levels of exposure to phthalates in Iranian population (Amin et al. 2018a). Several factors including the socio-demographic, environmental and regional variables, as well as the size of study population, can be attributed to the different levels of exposure obtained in this survey and those that have been reported by other countries.

The results of correlation analysis between the creatinine-adjusted urinary levels of phthalate metabolites and birth outcome measures are presented in Table 4. None of the phthalate metabolites exhibited significant correlation with the birth outcomes, and only the correlation between MBzP with birth weight was of borderline significance (β = 0.2 (0.16), p = 0.06). Based on the results, it is obvious that the concentration of phthalates in the first trimester maternal urine was positively correlated to the birth weight of neonates; however, negative correlation was observed between urinary phthalate levels with birth length and head circumference of newborns.

In line with the results found in this study, Suzuki et al. (2010) and Philippat et al. (2011) have also found no statistically significant associations between prenatal phthalate exposure and birth outcomes. Furthermore, Huang et al. have reported negative association between the maternal urinary phthalate concentration with the head circumference of their newborns; however, the significant correlations were only noted in female neonates (Huang et al. 2014). In line with the results obtained in this study, no significant relationship was found between maternal urinary phthalates and birth by Zhu et al. (2018).

On the contrast, Shoaff et al. have shown that a tenfold increase in the maternal urinary MEP levels is associated with a 0.23 standard deviation reduction (95% CI: −0.46, −0.01) in birth weight z-score; however, after adjustment for confounding factors, this relationship was attenuated towards the null (Shoaff et al. 2016). Casas Sanahuja et al. (2016) have assessed the effect of prenatal exposure to eight phthalates on fetal growth but found no significant association between the maternal

Table 2 Maternal characteristics of 121 pregnant women enrolled in the study

Variables	Mean, *n* (%)	Variables			Mean, *n* (%)
Maternal age (years)		Cosmetic usage		No	9 (7.4)
				Yes	112 (92.6)
< 25	8 (6)	Smoking during pregnancy		No	121 (100)
				Yes	0 (0)
25–29	42 (35)	Passive smoking during pregnancy		No	56 (46.3)
				Yes	65 (53.7)
30–34	47 (39)	Using household cleaning products		No	0 (0)
				Yes	121 (100)
> 34	24 (20)	Plastic packaging usage	Bread	No	45 (37.2)
Pre-pregnancy BMI (kg/m^2)				Yes	76 (62.8)
Underweight (< 18.5)	3 (2)		Lemon juice	No	54 (44.6)
				Yes	67 (55.4)
Normal weight (18.5–23.9)	35 (29)		Pickle	No	66 (54.5)
				Yes	55 (45.5)
Overweight (≥ 24)	83 (69)		Leftover	No	69 (57)
				Yes	52 (43)
Education			Water	No	61 (50.4)
				Yes	60 (49.6)
Less than high school	7 (5.8)		Total	No	(48.74)
				Yes	(51.26)
High school	9 (7.4)	Physical activity			
College	105 (86.8)	High			8 (6.6)
Family income ($/month)		Moderate			48 (39.7)
High (> 300)	12 (9.9)	Low			65 (53.7)
Middle (100–300)	69 (57)	Eating fried foods			
Low (< 100)	40 (33.1)	Daily			30 (24.8)
Birth weight (g)	3204.04 (480.94)	1–2 per week			38 (31.4)
Head circumference(cm)	34.5 (1.71)	1–3 per month			35 (28.9)
Birth length (cm)	50.35 (3.16)	Seldom (< once a month)			13 (10.7)
		Never			5 (4.1)

urinary ∑DEHP concentration and any of the neonatal growth outcome measures. In another study conducted by Wolff et al., they investigated the association between maternal urinary phthalates concentration at third trimester with the body size measures of infants at birth. They found that low molecular weight phthalates had a positive, but not statistically significant association with the head circumference of newborns (Wolff et al. 2008).

Table 3 Mean concentration of phthalate metabolites (μg/g creatinine) in pregnant women urine

Creatinine-adjusted phthalate metabolites(μg/g)	MBP	MBzP	MEHP	MEHHP
LOD (μg/L)	0.017	0.013	0.018	0.019
%> LOD*	100	100	100	100
Min	8.5	15.6	4.2	37.8
Max	602.2	705.4	455.9	1285.9
Mean (SD)	342.5 (193.8)	308.5 (229.4)	126.5 (118.3)	866.5 (307.6)

*Counts of detectable sample] / [Total sample counts] × 100(%)

Table 4 Correlation between urinary phthalate concentrations and anthropometric measures of neonates

Phthalate metabolites	Birth weight				Birth length				Head circumference			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	β* (SE**)	p	β* (SE**)	p	β* (SE*)	p	β* (SE**)	p	β* (SE**)	p	β* (SE**)	p
MBP	-0.2 (0.2)	0.02	0.1 (0.001)	0.9	-0.08 (0.001)	0.4	-0.03 (0.001)	0.8	-0.13 (0.2)	0.2	-0.06 (0.001)	0.6
MBzP	-0.3 (0.2)	0.006	0.2 (0.16)	0.06	-0.1 (0.001)	0.1	-0.11 (0.001)	0.3	-0.07 (0.001)	0.4	-0.15 (0.001)	0.2
MEHP	-0.2 (0.3)	0.02	0.01 (0.0004)	0.9	-0.2 (0.002)	0.07	-0.14 (0.002)	0.2	-0.07 (0.001)	0.4	-0.2 (0.001)	0.09
MEHHP	-0.2 (0.1)	0.06	0.1 (0.001)	0.8	-0.2 (0.001)	0.04	-0.16 (0.001)	0.1	-0.14 (0.3)	0.2	-0.07 (0.001)	0.5

Adjusted for maternal age, pre-pregnancy BMI, gestational age, educational level, family annual income, total exposure to chemical products, and plastic packaging

* *β* Regression coefficient

** *SE* standard error

Despite the mentioned studies, there are several other reports that have shown inverse (Lenters et al. 2015; Zhang et al. 2009) or negative associations (Botton et al. 2016; Ferguson et al. 2016) between maternal urinary levels of phthalate metabolites and birth outcomes. In this regard, Lenters et al. (2015) and Zhang et al. (2009) have shown that maternal urinary levels of some DEHP metabolites during pregnancy are associated with low birth weight or increased risk of low birth weight. The discrepancy between the results might be explained by the potential contamination with phthalate diesters or the differences in the levels of exposure to these compounds among different populations (Kato et al. 2003).

The results of crude and adjusted associations between maternal urinary phthalate concentration with the birth outcomes in boys and girl neonates are presented in Table 5. According to these findings, MBP (adjusted β = -0.3(0. 2), $p = 0.04$) and MBzP (adjusted β = -0.3 (0.001), $p = 0.02$) were negatively associated with the head circumference in boys and girls, respectively. Furthermore, positive associations were observed between maternal urinary levels of MBzP (adjusted β =0.3 (0.001), $p = 0.03$) and MEHHP (adjusted β =0.3 (0.001), $p = 0.04$) with birth weight in girls after adjusting for potential confounding factors.

The correlation between prenatal exposure to MBzP and MEHHP with higher birth weight in female neonates may suggest that exposure to these chemicals during pregnancy can influence the function of feminine hormones and thus increase fetal growth or induce fat accumulation. Consistently, it has been demonstrated that phthalates have weak estrogenic activities (Ghisari and Bonefeld-Jorgensen 2009; Kiyama and Wada-Kiyama 2015) and can promote adipocyte differentiation by activation of peroxisome proliferator-activated receptor gamma (PPARs) (Hao et al. 2012). Furthermore, due to their estrogenic activities, phthalates may engage nuclear receptors and induce the expression of several other genes involved in obesity. Additionally, it is possible that prenatal phthalate exposure may affect thyroid axis function, disrupt energy balance and metabolism, and thus result in the fat accumulation (Boas et al. 2012). These compounds may also affect the pituitary-adrenal axis, which is crucial for fetal growth (Liu et al. 2014). Since we observed a sex difference in the associations of maternal urinary phthalate metabolite levels with birth weight of infants, hence it can be concluded that the most potential mechanism by which these compounds have resulted in higher birth weight might be related to their influence on sexual hormones or sex-related biological variables (Grün and Blumberg 2009). However, further studies are warranted to shed light on this claim.

We also examined the effects of some potential factors which may be associated with the prenatal exposure to phthalates including maternal education level, family income per month, and plastic packaging (bread, lemon juice, pickle, leftover, water) and might influence the neonatal birth outcomes (Table 6).

According to the results, maternal education level, family income per month, and physical activity had no significant influences on the investigated birth outcome measures (p value > 0.05). However, birth weight of infants was significantly different (p value < 0.05) among those participants who used plastic packaging for pickle and passively exposed to smoke. This can be explained by the fact that phthalates are still widely used as plasticizers in materials used for food and water packaging for many years; therefore, the plastic packaging of food items can be associated with higher exposure to these chemicals (European Food Safety Authority).

Although the main part of the participants in the present work were non-smokers, more than half of them (n = 65, 53.7%) were passively exposed to smoking. Likewise, previous studies have also linked smoking habits to higher exposure levels to phthalates (Arbuckle et al. 2014; Valvi et al. 2015). In this regard, Casas et al. observed that smoking has

Table 5 The crude and adjusted associations of phthalate metabolite concentrations in first trimester maternal urines with anthropometric measures of neonates

Phthalate metabolites			Birth weight		Birth length		head circumference	
			Girl	Boy	Girl	Boy	Girl	Boy
MBP	Crude	β (SE)	-0.2 (0.2)	-02 (0.3)	-0.1 (0.001)	-0.05 (0.002)	-0.07 (0.001)	-0.1 (0.001)
		p	0.1	0.1	0.4	0.7	0.6	0.4
	Adjusted	β (SE)	0.1 (0.2)	-0.1 (0.4)	-0.1 (0.002)	0.06 (0.002)	-0.2 (0.001)	-0.3 (0.2)
		p	0.2	0.6	0.2	0.7	0.1	0.04
MBzP	Crude	β (SE)	-0.3 (0.2)	-0.2 (0.2)	-0.16 (0.001)	-0.1 (0.001)	-0.2 (0.001)	0.08 (0.001)
		p	0.007	0.2	0.2	0.4	0.1	0.6
	Adjusted	β (SE)	0.3 (0.001)	-0.1 (0.3)	-0.1 (0.001)	-0.1 (0.002)	-0.3 (0.001)	0.08 (0.001)
		p	0.03	0.6	0.3	0.5	0.02	0.7
MEHP	Crude	β (SE)	-0.3 (0.3)	-0.1 (0.5)	-0.1 (0.003)	-0.2 (0.003)	-0.1 (0.002)	-0.02 (0.001)
		p	0.02	0.3	0.4	0.1	0.3	0.9
	Adjusted	β (SE)	0.1 (0.1)	0.04 (0.6)	-0.1 (0.003)	-0.2 (0.004)	-0.2 (0.002)	-0.09 (0.002)
		p	0.3	0.8	0.5	0.2	0.08	0.6
MEHHP	Crude	β (SE)	-0.2 (0.1)	-0.2 (0.2)	-0.2 (0.001)	-0.1 (0.001)	0.03 (0.001)	-0.04 (0.001)
		p	0.2	0.2	0.06	0.4	0.8	0.8
	Adjusted	β (SE)	0.3 (0.001)	-0.2 (0.2)	-0.2 (0.001)	-0.1 (0.002)	-0.2 (0.001)	-0.1 (0.001)
		p	0.04	0.2	0.1	0.4	0.2	0.6

Adjusted for maternal age, pre-pregnancy BMI, gestational age, educational level, family annual income, total exposure to chemical products, and plastic packaging

[*] *β* Regression coefficient

[**] *SE* standard error

a direct association with the elevated urinary phthalates (Casas et al. 2011; Darvishmotevalli et al. 2019b). It has been demonstrated that cigarette smoke and filters contain phthalates in the form of di-2-methoxyethyl phthalate (Jackson Jr and Darnell 1985). Furthermore, it has been assumed that low-quality cigarettes may also further increase the urinary concentration of phthalates metabolites both in first- and second-hand smokers. Table 7 presents the results of correlations between quantitative determinants and birth outcome measures.

Here, we found positive significant correlations between prenatal BMI and the use of cosmetics and household cleaning products with the neonatal birth weight (p value < 0.05 and r = 0.18, r = 0.21, and r = 0.24, respectively). However, there were no significant relationships observed between maternal age, consumption of fried foods, and physical activity with the birth measures (p value > 0.05).

There are a large body of evidences indicating that urinary phthalate metabolites in pregnant women are positively associated with the amount and frequency of cosmetics and household cleaning products they use (Darvishmotevalli et al. 2019a, c). On contrast with our findings, Valvi et al. (2015) showed no association between the use of cosmetics and urinary levels of phthalates. The legislative actions regarding the production of cosmetics and care products in various countries are thoroughly different. For instance, the use of some phthalates including DEHP, di-n-butyl phthalate, di-iso-butyl phthalate, and BBP in the production of cosmetics have been prohibited by the EU (European Union) (Wittassek et al. 2011); however, there is no strict regulation regarding the use of these chemicals in the production of various industrial goods in developing countries, including Iran. Besides, Iran has been ranked as the second country in the Middle East with the highest use of personal care products (Volpe et al. 2012). This is in line with our observation that a large proportion of the participants in this study have reported higher amounts of cosmetics use. On the other hand, since the majority of the women participated in this survey were of low or middle income families, therefore it can be assumed that the main part of this population may use inexpensive with low-quality cosmetic products containing higher grades of phthalates.

Household cleaning products have also been regarded as another important source of phthalate exposure, especially among pregnant women (Harley et al. 2016). Accordingly, Valvi et al. (2015) have shown that the use of household chemical products is associated with the higher urinary concentrations of MEHHP, MEHP, and MBzP. In countries like Iran, females are mainly involved in household works; thus, they may expose to higher levels of phthalates through the use of

Table 6 Association of some maternal factors with possible influence on prenatal exposure to phthalates with the neonatal anthropometric measures

Variables			Birth weight		Birth length		Head circumference	
			Mean ± SD	*p* Value	Mean ± SD	*p* Value	Mean ± SD	*p* Value
Education		College	3120 ± 315	0.8	49.5 ± 2.5	0.9	33.9 ± 2	0.4
		High school	3160 ± 252		49.9 ± 1.6		33.7 ± 1	
		< High school	3271 ± 305		50.6 ± 2.5		33.4 ± 1	
Family income per month ($)		< 100	3161 ± 429	0.5	49.6 ± 2.6	0.9	33.9 ± 1	0.7
		100–300	3124 ± 322		49.5 ± 1.9		33.7 ± 1.5	
		> 300	3014 ± 388		49.9 ± 4		33.8 ± 1	
Plastic packaging	Bread	Yes	3115 ± 378	0.7	49.3 ± 2.2	0.1	33.8 ± 1.3	0.8
		No	3142 ± 348		50 ± 2.6		33.8 ± 1.4	
	Lemon juice	Yes	3103 ± 412	0.5	49.4 ± 2.4	0.3	33.8 ± 1.4	0.9
		No	3153 ± 302		49.8 ± 2.4		33.8 ± 1.3	
	Pickle	Yes	3051 ± 401	0.04*	49.3 ± 2.4	0.3	33.7 ± 1.4	0.6
		No	3188 ± 324		49.8 ± 2.4		33.8 ± 1.3	
	Leftover	Yes	3096 ± 306	0.4	49.7 ± 2.7	0.7	34 ± 1.6	0.3
		No	3148 ± 406		49.5 ± 2.1		33.7 ± 1.1	
	Water	Yes	3065 ± 337	0.07	49.3 ± 2.1	0.3	33.9 ± 1.4	0.5
		No	3185 ± 386		49.8 ± 2.6		33.7 ± 1.3	
Passive smoking during pregnancy		Yes	3050 ± 326	0.01*	49.3 ± 2.2	0.2	34 ± 1.2	0.1
		No	3213 ± 393		50 ± 2.6		33.6 ± 1.5	
Physical activity		Low	3109 ± 322	0.08	49.5 ± 1.9	0.07	33.7 ± 1	0.8
		Moderate	3188 ± 368		50 ± 2.8		33.9 ± 1.7	
		High	2885 ± 586		47.9 ± 2.9		33.8 ± 1.3	

chemical cleaning products. Furthermore, exposure to chemicals occurs with more adverse effects for pregnant women and their growing fetus due to the physiological changes (Philips et al. 2017).

In this study, higher levels of MBzP, MEHHP, and MBP were found in urinary samples of obese individuals compared to women with normal body weight.

Prenatal maternal BMI is considered one of the most important determinants of fetal weight, growth, and body composition (Hajizadeh et al. 2020; Sewell et al. 2006). It is clear that the maternal BMI is not playing as a biological effector and the mechanism by which prenatal maternal BMI affects the fetal growth remains largely unknown (Hajizadeh et al. 2021; Roland et al. 2012). Several studies have demonstrated that fetal growth is largely influenced by placental capacity in transferring nutrients to fetus, the genetics of parents, as well as by maternal supply of nutrients. Since maternal BMI may influence nutrients supply and the capacity of placenta in transporting nutrients from mother to fetus, thus it can affect the fetal growth measures. Previous studies have also positively linked maternal BMI to the levels of circulating glucose. Additionally, higher maternal BMI and plasma glucose levels have been associated with the longer gestational age and greater body fat in newborns (Nathanielsz et al. 2007). In spite of influencing adipogenesis, phthalates

Table 7 The effect of some maternal determinates on the neonatal anthropometric measures

Variables	Birth weight		Birth length		Head circumference	
	r	*p* Value	*r*	*p* Value	*r*	*p* Value
Age	0.09	0.3	0.01	0.9	0.04	0.6
BMI	0.18	0.04	0.03	0.7	0.1	0.1
Cosmetic	0.21	0.02	0.03	0.7	0.04	0.6
Household cleaning	0.24	0.007	0.05	0.6	0.12	0.2
Fried foods	0.01	0.9	0.04	0.6	0.07	0.4
Physical activity	0.12	0.2	0.06	0.5	0.09	0.3

r Correlation coefficient

have lipophilic properties enable these chemicals to be stored in adipose tissue. Therefore, it would be expected that obese mothers may exhibit higher urinary levels of phthalates and potentially have more affected newborns (Philips et al. 2017).

Limitations and strengths

One of the important limitations of the present study was its cross-sectional nature. Additionally, this study has assessed the maternal urinary phthalate concentration only at first trimester period as spot sampling. However, we tried to adjust the mean concentration of phthalate by creatine adjusting. To the best of our knowledge, no or only a limited number of studies have been conducted in Iran to address this issue; thus, these findings can provide a basis for the future studies and help decision-makers to implement proper actions. Taken together, higher exposure to neglected chemicals such as phthalates, especially during pregnancy, could threaten the health of both mothers and newborns. We recommend further investigations to evaluate the prenatal exposure to phthalates during second and third trimesters as well. Such data on the whole period of pregnancy can be more meaningful.

Conclusion

This study was conducted to determine the possible relationship between prenatal phthalate exposure and neonatal anthropometric measures in association with maternal lifestyle variables and characteristics of pregnant women. According to the findings, the following conclusions can be made:

- MBzP, MBP, MEHP, and MEHHP were detected in 100% of urines obtained from pregnant women at their first trimester.
- Investigated metabolites had higher concentration in the Iranian pregnant women urines compared to the other countries.
- Our findings revealed a positive association between the maternal concentrations of MBzP and MEHHP with increased birth weight in girl neonates.
- Urinary concentration of phthalates were significantly higher among those pregnant women who had higher pre-pregnancy BMI, as well as among the users of cosmetics and household cleaning products, and those subjects who routinely used plastic packaging for pickle storage.
- Pregnant women who passively exposed to smoking had significantly higher levels of urinary phthalates.

Acknowledgements The authors are grateful to the staff at the laboratory of the Department of Environmental Health Engineering, Isfahan University of Medical Sciences (IUMS).

Data Availability and material The material and raw data are available upon request.

Code availability Not.

Authors' contributions M. Darvishmotevalli , M. Moradnia, and R. Hosseini surveyed the studies for data extraction, inclusion, and assessing the study quality and wrote the first draft of the manuscript. B. Bina supervised this study. A Feizi performed the data analysis. K Ebrahimpour, H Pourzamani, G Kiani Feizabadi provided the critical input for the manuscript. R Kelishadi did critical revision of the manuscript. All authors have contributed considerably, and all authors are in agreement with respect to the manuscript content. The authors read and confirmed the final manuscript.

Funding This research was supported by the Isfahan University of Medical Sciences. The main cohort study is funded by the Ministry of Health with the project number IR.MUI.REC.1394.1.354.

Declarations

Ethics approval This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Code: IR.MUI.RESEARCH.REC.1397.441) with project number #397573.

Consent to participate All participants voluntarily agree to participate in this research study.

Consent for publication The studied participant consent for publication of their identifiable details.

Competing interests The authors declare no competing interests.

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