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RESEARCH ARTICLE

Association of maternal urinary concentration of parabens and neonatal anthropometric indices

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Abstract

Purpose Parabens are used as preservatives in a wide range of products. Although parabens are generally known as safe, but recent evidences indicate that these compounds could lead to potential adverse effects on fetal growth. Thus, this study aimed to investigate the association between maternal parabens level in a sample of Iranian pregnant women with neonatal anthropometric measures.

Methods This cross-sectional study was conducted in 2018–2019 in Isfahan city, Iran. Early morning urine samples were collected from 117 pregnant women who were in their first trimester of pregnancy. The urinary concentrations of four parabens including methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP), and butylparaben (BuP) were measured by gas chromatography-mass spectrometry. To compensate for variation in urine dilution, the paraben concentrations were adjusted by the creatinine levels. Associations between maternal parabens level and neonatal anthropometric indices were evaluated.

Results The MeP, EtP, PrP, and BuP were detected in %92, %36, %65, and %89 of the urine samples, respectively. No significant association was observed between maternal parabens level and birth length (p−value>0.05). In adjusted model, the BuP concentration in first trimester urine samples showed significantly negative association with head circumference in female neonates [$\beta = -0.013$, 95% CI: −0.024, −0.003], while positive significant association with that index in male neonates [$\beta = 0.019$, 95% CI: 0.001, 0.038]. In subgroup analysis by sex, in crude and adjusted analyses BuP was found to be only associated with higher birth weight in female neonates. PrP also showed significant positive association with head circumference and birth weight of male neonates in crude analysis.

Conclusion Findings of this study on the association of urinary parabens of pregnant mothers with birth weight and head circumference suggest that maternal exposure to parabens might impact the fetal growth, However, these findings are based on cross-sectional data, thus the results should be interpreted with caution. The current findings underscore the necessity of providing more strict regulations in industries for limiting parabens use in their products, and the importance of public education for women of reproductive age for using paraben-free compounds.

Keywords Parabens · Maternal exposure · Fetal growth · Prevention · Neonatal anthropometric indices

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Introduction

Parabens are a group of alkyl esters of para-hydroxybenzoic acid added as preservatives to cosmetics, foods, pharmaceuticals, and beverages due to their antimicrobial and antifungal properties [1–3]. The main parabens which are used as a part of a preservative system in many products are: methylparaben, ethylparaben, propylparaben, and butylparaben. Several advantageous characteristics such as low production cost, high chemical stability, neutrality, and low acute toxicity make these compounds ideal for several applications [4]. Thus, humans are widely exposed to parabens through different ways of skin adsorption, oral consumption, and inhalation due to the widespread use of these chemicals [5, 6]. Parabens have short biological half-life in body (1–7 h) [2], and are rapidly hydrolyzed or cleared by the renal system [7, 8]. *In vitro* and *in vivo* estrogenic activities have been described for parabens, and therefore these compounds have been classified as endocrine disrupting chemicals (EDCs) [9, 10]. Exposure to EDCs has been linked with several health problems, such as adverse pregnancy outcomes [3, 11], abnormal reproductive function [12, 13], neurodevelopmental delay [14], obesity [15, 16], increased risk of metabolic syndrome [17], and diabetes [18, 19].

A large body of evidences have indicated that the transport of the EDCs across the placenta from mother to the fetus is associated with detrimental effects on the growing fetus as well as effects later in life [12]. In this regard, previous investigations have also shown that paraben levels in cord blood and amniotic fluid directly correlated with the amount of these compounds in maternal blood, indicating that parabens could cross the placenta and reach the developing fetus [20, 21]. It has also been shown that unfavorable fetal growth conditions could potentially lead to lifetime health effects such as increased risk of developing hypertension and diabetes [22]. Previous evidences have revealed negative associations between prenatal urinary concentration of parabens with the hormone levels of TSH and free T4 in maternal blood during pregnancy [23]. Since maternal thyroid hormones play important roles in neuronal cell myelination, migration, and signaling, therefore exposure to parabens may result in neurological deficits during early brain development [24]. Consistently, it has been hypothesized that EDCs may increase the risk for autism spectrum disorders through dysregulation of thyroid hormones during pregnancy [25].

There are several studies have examined the associations between maternal exposure to parabens and birth outcomes including birth weight, body length and head size, and gestational age at birth, however no consensus was achieved. A study in France, has found no association between prenatal urinary parabens concentration of 191 pregnant women and their birth outcomes [26]. However, another study conducted in China revealed inverse association between parabens exposure during pregnancy and fetal and childhood growth [27]. There are also findings indicating that exposure to specific types of parabens may be associated with altered neonatal anthropometric parameters. In this regard, an increase in prenatal urinary MeP levels has been related to a slight decrease in head circumference in neonates [28]. On the contrast, a cohort study in USA has found that prenatal urinary BuP and PrP levels were negatively associated with neonatal weight and length, respectively [29].

One of the main sources of exposure to parabens is the use of cosmetic products. It has been shown that subjects who use cosmetics more frequently or in higher amounts have higher urinary parabens. Consistently, since women use higher amount of cosmetics, the urinary concentration of parabens among females has been demonstrated to be higher than males [30]. However, the patterns of the use of cosmetic products vary substantially worldwide. Accordingly, Iran has been ranked as the seventh country in the world and the second in the Middle East having the highest rate of cosmetics use [31]. It is estimated that the use of cosmetics by female population in Iran puts an annual burden of 1630 million Euros to the government [32]. In spite of the cosmetic products, other sources such as foodstuffs, pharmaceutical products, washing products and etc., may also contribute to the parabens exposure, especially among pregnant women [33]. Furthermore, the other factors including lifestyle variables, socio-economic characteristics and well as education levels of a distinct population could have impact on their exposure to different chemicals, namely parabens.

Up to now, only limited experience exist worldwide concerning the impact of maternal urinary parabens level in association with neonatal anthropometric indices, therefore further studies in different countries are warranted to provide epidemiological information and shed light on the consequences of maternal exposure to parabens. According to the mentioned notes, this study aims to investigate the association of the urinary parabens concentrations in a sample of Iranian pregnant women with neonatal anthropometric indices.

Materials and methods

Study population

This cross-sectional study was conducted between the years 2018 and 2019 on a sample of 117 pregnant women in Isfahan city, Iran. The participants were randomly selected among women who visited health centers and hospitals for pregnancy care. All the subjects were informed about the methodology and purpose of the survey and participated voluntarily. Moreover, a consent letter was completed and signed by each participant. The study protocol was approved by Research and Ethical Committee of Isfahan University of Medical Sciences, under the code of IR.MUI.REC.1394.1.354.The pregnant women who have been included in this study were those individuals (1) resided in Isfahan at least for the last one year, (2) were in their first trimester of pregnancy, (3) were willing to give urine samples, and (4) intended to give birth in hospitals and health centers in Isfahan city.

Data were collected in the face-to-face manner using validated questionnaires consisted of 482 items categorized into three sections, including general, medical and nutritional data [34]. Furthermore, the questionnaires used in this study covered socioeconomic characteristics (education, income, and occupation), lifestyle variables (dietary habits, physical activity, smoking, and body mass index), pregnancy variables (gestational age, number of deliveries, and sex of neonates), environmental exposure (cosmetics, detergents, home appliances, utensils, etc.) as well as neonatal anthropometric indices, i.e. head circumference, weight, and length, which were completed separately by the trained health providers.

Urine collection

Twenty ml of spot early morning urine was taken from each participant during their first trimester of pregnancy, poured in polypropylene containers, and transferred to the laboratory to be kept at -80 °C until the future analysis. Ten ml of the samples were used to determine the creatinine levels and 10 ml was used for measuring MeP, EtP, PrP, and BuP.

Neonatal anthropometric indices

Neonatal anthropometric measures including head circumference, weight and length were recorded at the time of delivery by nurses. Weights of the neonates were measured with the accuracy of ± 0.01 g. To measure length, the neonate lies down, with the knees fully stretched and the soles touching each other, and then the length was measured. Head circumference was measured by a non-elastic meter with the accuracy of ± 0.1 cm at the largest occipitofrontal diameter [35].

Measuring urinary parabens

MeP, EtP, PrP, and BuP with 99% purity, N-methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA), β-glucuronidase enzyme were purchased from Sigma Aldrich (Sigma-Aldrich Cooperation, St. Louis, MO, USA). Moreover, sodium chloride (NaCl), acetone and chlorobenzene used in this study were of analytical grades and obtained from Merck (Darmstadt, Germany).

In order to measure the urinary concentrations MeP, EtP, PrP and BuP, the Dispersive Liquid-Liquid Micro-Extraction (DLLME) method was applied, which was followed by GC/MS method. In summary, 10 μl of β-glucuronidase enzyme was added to 5 ml of a urine sample in 10 ml conical tube. Next, 0.1 g of sodium chloride was added to the mentioned mixture and shaked at 37 °C for 24 h. Then, 2.5 ml of the obtained preparation was mixed with the same volume of distilled water and the solution pH was adjusted to 2 using 10% sulfuric acid solution. Then, the obtained preparation was used to extract the aforementioned parabens by using DLLME method. Accordingly, the obtained preparation was mixed with 500 μl of acetone and 10 μl of chlorobenzene to form a cloudy state. The solution was centrifuged at 5000 rpm for 5 min to sediment the dispersed droplets. Afterwards, a micro-syringe was used to withdraw the sediment which was collected in a different microtube and dried under a slow stream of nitrogen gas. Then, 10 μL of MSTFA was added to the sediment and centrifuged to be mixed thoroughly. Finally, 10 μl of the solution was injected into Gas Chromatography-Mass Spectrometry (GC/MS) (Model A7890 of Agilent technologies, USA) to measure the concentration of parabens [36]. The GC-MS used in this study had a DM5-MS capillary column with 60 m length, 0.25 mm diameter and 250 μm internal film thickness. The temperature at the time of injection was set at 280 °C with the split ratio of 2:1 and injection volume of 2 μl. The flow rate of the carrier gas was set at 2 ml/min. The initial temperature of the oven was 150 °C for 4 min which was increased to 280 °C with the slope of 10 °C per minute. The total run time for each injection was 13 min. To minimize the bias of the dilution difference between the urine samples, the concentrations of parabens were adjusted using creatinine levels (Jeff method). In this regard, the creatinine levels in the urine samples were measured using a Hitachi 704 auto-analyzer and the concentration of parabens were expressed as the ratio to creatinine.

Quality assurance and quality control (QA/QC)

The GC/MS method was validated in terms of precision, accuracy and linearity according to ICH guidelines [37]. Precision of the analysis was assessed by calculation of the standard deviations of the samples analyzed in triplicate and reported as RSD% (relative standard deviation). The accuracy of the assay method was evaluated in triplicate using HPLC-grade water instead of human urine (as a blank sample). The limit of detection (LOD) and limit of quantification (LOQ) were determined by injecting dilute solutions of the standards with known concentrations. The LOD and LOQ were defined as the signal-to-noise ratio equal to 3 and 10, respectively. The results of validation procedure and QA/QC parameters of the method are presented in Table 1.

Statistical analysis

Categorical data were reported as frequency (percentage) while continuous data as mean ± standard deviation (SD). The mean ± SD, geometric mean as well as first and third quartiles for concentration values of parabens were reported. Kolmogorov- Smirnov test and Q-Q plot was used for evaluating the normality of parabens concentration. All studied parabens had non-normal distribution and were positively skewed; therefore logarithmic transformation was used to normalize their distribution. For evaluating the association between the concentrations of measured parabens and anthropometric measures of neonates, we used simple and multiple linear regressions. The regression coefficient along with 95% confidence interval (95% CI) was reported as the measure of association. All the urinary parabens concentration below the LOD were obtained LOD/√2 [38].

Crude linear regression models were performed on associations between the urinary parabens as predictor variables and the neonatal anthropometric indices as dependent variables. Based on the previous studies we evaluated and measured those variables that have confounding effects on the relation of parabens and neonatal anthropometric indices at birth [39, 40]. Adjusted linear regression models were also fitted and among many variables considered in our study, the effects of those confounders for anthropometric indices of neonates with p−value < 0.05 in univariate analysis have been adjusted. The confounding role of variables has been evaluated separately for each anthropometric index. Accordingly, for neonatal weight the effects of gestational age, mother's body mass index (BMI), educational level and kept leftover food in plastic packages have been adjusted. The multiple linear regression model for neonatal head circumference was adjusted for cosmetic use, mothers' BMI and physical activities. Also, income level and drinking water in a day were regarded as confounding factors for neonatal length and their confounding effects have been adjusted. Regression analysis was done for total sample and separately in girls and boys. Subgroup analysis by the sex of neonate was done for considering the discrepancy and differences in anthropometric indices between boys and girls [27]. In all linear regression analyses the normality of dependent variables and linear association with predictors as presumptions have been evaluated.

All statistical analyses were conducted by using SPSS version 16:00 (SPSS, Inc., Chicago IL, USA; version 16). P−value less than 0.05 was considered as statistically significant level.

Table 1 QA/QC parameters of parabens

Parabens	R^2	Precision (% RSD)	LOD (μg/L)	LOQ (μg/L)	Recovery (%)
MeP	0.995	6.4	0.014	0.049	91.2
EtP	0.989	7.11	0.015	0.051	89.3
PrP	0.995	8.4	0.016	0.055	93.3
BuP	0.995	6.3	0.046	0.154	90.5

Results

Characteristics of study populations

Maternal characteristics and neonatal demographics are presented in Table 2. The mean (± SD) age of the mothers was 30.66 years ± 4.6 (range, 20–42 years) and the mean (± SD) length of the pregnancy was 38.6 weeks ± 1.6. Based on the records, 11.1% of the pregnant women had preterm birth, 74.4% had full-term birth and 14.5% had post-term birth. According to BMI results, 36.8% of the subjects (n = 43) were overweight, whereas 60.7% (n = 71) participants had normal weights. Most of the mothers (n = 99, 84.6%) had university education. None of the participants had a history of active smoking, while 102 individuals (87.2%) have reported that they use cosmetics. Fifty-two of the neonates were boys and 65 girls. The mean (± SD) neonatal weight was 3265.4 (± 470) g (5th – 95th percentiles, 2422–3955 g), the mean (± SD) neonatal length was 50 (± 2.8) cm (5th − 95th percentiles, 43.9–54 cm), and the mean (± SD) neonatal head circumference was 34.5 (± 1.6) cm (5th − 95th percentiles, 32–37 cm).

Urinary parabens in pregnant women

The distribution of parabens concentration in the urine of pregnant women is shown in Table 3. At least one type of parabens was identified in all the samples. MeP, PrP and BuP were detected in 92, 65, and 89% of the samples, respectively. The EtP was detected only in 36% of the urine samples. Geometric means (medians) per μg/g.cre were obtained for MeP 72.8 (160.1) and for EtP 0.23 (0.04), PrP 2.2 (7.8), and BuP 4.5 (7.5). A significant positive association was observed between the measured concentrations of the four compounds studied. However, a weak association was found between MeP and EtP (R = 0.33, p−value < 0.01) and a moderate association between MeP and PrP (R = 0.59, p−value < 0.01).

Association between maternal urinary parabens and neonatal anthropometric indices

The association between parabens concentration and neonatal anthropometric indices has been evaluated using

Table 2 Characteristics of Iranian pregnant women and their offspring ($n = 117$)

Characteristic	*n* (%) or Mean, STD	Percentales		
		5th	50th	95th
Maternal				
Age (years) (mean)	30.66 ± 4.6	22	31	38
Gestational age (week) (mean)	38.6 ± 1.6	35.3	38.7	40.8
Preterm birth (< 37)	13 (11.1)			
Term birth (37–40)	87 (74.4)			
Post term birth (≥ 40)	17 (14.5)			
Pre-pregnancy BMI (kg/m^2)	25.2 ± 4.1	19.5	24.8	32.6
Underweight (< 18.5)	3 (2.5)			
Normal weight (18.5–23.9)	71 (60.7)			
Over weight (≥ 24)	43 (36.8)			
Maternal education				
Less than high school	7 (6)			
High school	11 (9.4)			
More than high school	99 (84.6)			
Active smoking during pregnancy				
Yes	0			
No	117 (100)			
Exposure to cosmetic				
Yes	102 (87.2)			
No	15 (12.8)			
Children				
Infants sex				
Male	52 (44.4)			
Female	65 (55.6)			
Birth weight (g) (mean)	3265.4 ± 470	2422	3250	3955
Birth length (cm) (mean)	50 ± 2.8	43.9	50	54
Head circumference at birth (cm) (mean)	34.5 ± 1.6	32	34.5	37

Abbreviation: BMI, body mass index

linear regression and the obtained regression coefficients (95%CI for regression coefficients) in crude and adjusted linear regression models are shown in Table 4. In this study, no statistically significant associations were observed between parabens exposure and the length of neonates (p-value > 0.05). Likewise, there was no significant association between neonatal head circumference and the maternal urine levels of parabens, however based on adjusted model and in subgroup analysis by sex negative and positive associations were observed between the BuP

Table 3 Distribution of maternal urinary concentrations of parabens (adjusted for creatinine)

Analyte (µg/g.cre)	LOD (µg/L)	% > LOD	Median	GM	Min	Measured concentrations, percentiles (µg/g.cre)			Max
						5th	25th	95th	
MeP	0.014	92	160.1	72.8	0.01	< LOD	37.54	1087.9	2496
EtP	0.015	36	0.04	0.23	0.01	< LOD	0.02	71.7	75
PrP	0.016	65	7.8	2.2	0.01	< LOD	0.04	219.1	535
BuP	0.046	89	7.5	4.5	0.04	0.08	1.66	99.6	222

LOD: Limit of Detection

GM: Geometric Mean

concentration and the head circumference in girls [β = -0.013, 95% CI: -0.024, -0.003] and boys [β = 0.019, 95% CI: 0.001, 0.038], respectively. Based on the results of crude linear regression, increased maternal PrP concentration was significantly associated with higher head circumference in boys [β = 0.006, 95% CI: 0.001, 0.011]. In all neonates, BuP levels were found to be positively associated with birth weight both in crude [β = 4.3, 95% CI: 1.6, 6.9] and adjusted models [β = 3.8, 95% CI: 1.1, 6.4]. However, in subgroup analysis by sex based on adjusted model, findings indicated that BuP concentration was significantly associated with higher birth weight in girl neonates by 3.9 g [95% CI: 0.7, 7.1]. Furthermore, the PrP concentration was observed to be positively associated with birth weight in boy neonates [β = 1.4, 95% CI: 0.04, 2.8] in crude model, however after adjusting the effects of confounders, the observed association was no more statistically significant (p−value > 0.05).

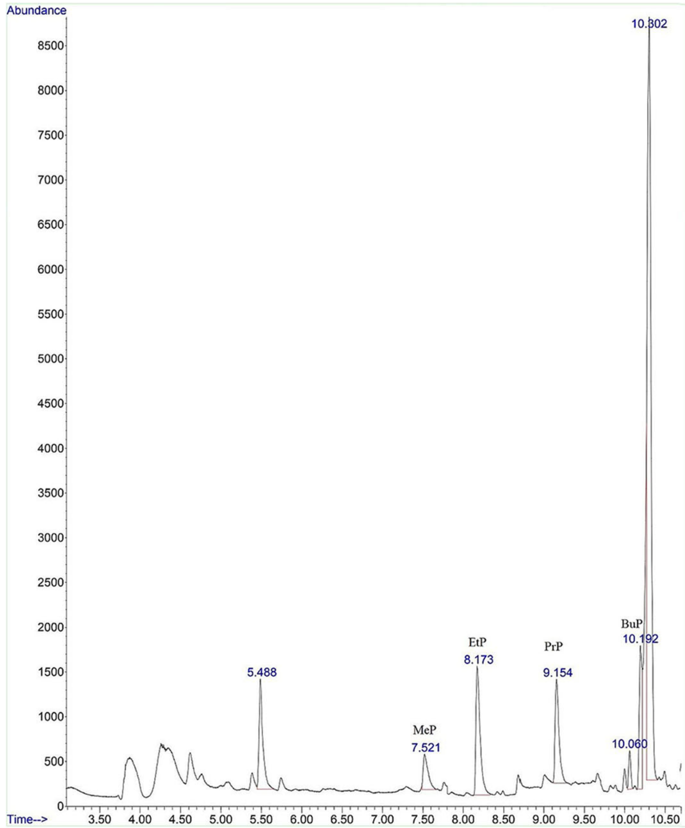
Validation procedure

The correlation coefficient of calibration curves for MeP, PrP, and BuP were above 0.995 and for EtP was 0.989. The LODs of all tested parabens were in the range of 0.014 to 0.046 μg/L and the recovery of all parabens ranged from 89.3–93.3%. The precision of methods was very good and inter and intraday variations in determinations (as RSD%) ranged from 6.3 to 8.4. Chromatograms of the first calibration point and one of the samples are presented in Fig. 1.

Table 4 The association between maternal urinary concentrations of parabens and neonatal anthropometric indices in adjusted and crude regression models

Analyte		Birth length (cm)		Head circumference at birth (cm)		Birth weight (g)	
		Beta (95% CI)	p−value	Beta (95% CI)	p−value	Beta (95% CI)	p−value
All (n = 117)							
MeP	Crude	0(−0.001 to 0.002)	0.5	0(−0.001 to 0.001)	0.9	−0.019 (−0.3 to 0.3)	0.9
	Adjusted	0.001(−0.001 to 0.002)	0.4	0(−0.001 to 0.001)	0.6	−0.009(−0.24 to 0.22)	0.9
EtP	Crude	−0.008(−0.036 to 0.020)	0.5	0.002(−0.014 to 0.017)	0.9	0.5(−6 to 7.9)	0.8
	Adjusted	−0.009(−0.038 to 0.020)	0.5	0.001(−0.015 to 0.017)	0.9	2.2(−1.9 to 6.4)	0.2
PrP	Crude	0.003(−0.003 to 0.009)	0.2	0.002(−0.001 to 0.006)	0.1	0.7(−0.19 to 1.69)	0.1
	Adjusted	0.003(−0.003 to 0.009)	0.3	0.002(−0.002 to 0.005)	0.2	0.6 (−0.3 to 1.5)	0.2
BuP	Crude	−0.01(−0.028 to 0.007)	0.2	−0.003(−0.013 to 0.006)	0.4	**4.3(1.6 to 6.9)**	**0.001***
	Adjusted	−0.008(−0.026 to 0.009)	0.3	−0.003(−0.013 to 0.006)	0.4	**3.8(1.1 to 6.4)**	**0.006***
Boys (n = 52)							
MeP	Crude	0.001(−0.001 to 0.003)	0.3	0(−0.001 to 0.001)	0.7	−0.19(−0.3 to 0.3)	0.9
	Adjusted	0.001(−0.001 to 0.003)	0.2	0.001(−0.001 to 0.002)	0.3	0.02(−0.3 to 0.38)	0.8
EtP	Crude	0.014(−0.026 to 0.054)	0.5	−0.002(−0.021 to 0.017)	0.8	0.6(−6.8 to 7.9)	0.8
	Adjusted	0.015(−0.027 to 0.058)	0.4	0.014(−0.015 to 0.043)	0.3	−0.9(−8.6 to 6.7)	0.8
PrP	Crude	0.005(−0.003 to 0.013)	0.2	**0.006(0.001 to 0.011)**	**0.02***	**1.4(0.04 to 2.8)**	**0.043***
	Adjusted	0.006(−0.002 to 0.014)	0.1	0.005(0 to 0.01)	0.05	1.1(−0.3 to 2.7)	0.1
BuP	Crude	0.001(−0.026 to 0.028)	0.9	0.016(−0.002 to 0.034)	0.07	4.7(−0.003 to 9.4)	0.05
	Adjusted	0.002(−0.025 to 0.029)	0.8	**0.019(0.001 to 0.038)**	**0.04***	3.7(−1.4 to 9)	0.1
Girls (n = 65)							
MeP	Crude	0(−0.002 to 0.002)	0.9	0(−0.002 to 0.001)	0.4	−0.06(−0.4 to 0.2)	0.7
	Adjusted	0(−0.002 to 0.002)	0.9	0(−0.002 to 0.001)	0.5	−0.05(−0.4 to 0.29)	0.7
EtP	Crude	−0.021(−0.056 to 0.013)	0.2	−0.006(−0.024 to 0.012)	0.5	4.1(−1.1 to 9.4)	0.1
	Adjusted	−0.019(−0.054 to 0.017)	0.3	−0.002(−0.021 to 0.017)	0.8	4 (−1 to 9.1)	0.1
PrP	Crude	0.002(−0.006 to 0.01)	0.6	−0.001(−0.006 to 0.003)	0.5	0.026(−1.2 to 1.3)	0.9
	Adjusted	0.002(−0.007 to 0.01)	0.6	−0.001(−0.005 to 0.004)	0.7	0.2 (−1 to 1.48)	0.7
BuP	Crude	−0.016(−0.037 to 0.005)	0.1	**−0.015(−0.025 to − 0.005)**	**0.004***	**4 (0.9 to 7.2)**	**0.012***
	Adjusted	−0.014(−0.034 to 0.007)	0.1	**−0.013(−0.024 to − 0.003)**	**0.01***	**3.9(0.7 to 7.1)**	**0.015***

*Significance level of p-value <0.05, bolded in text



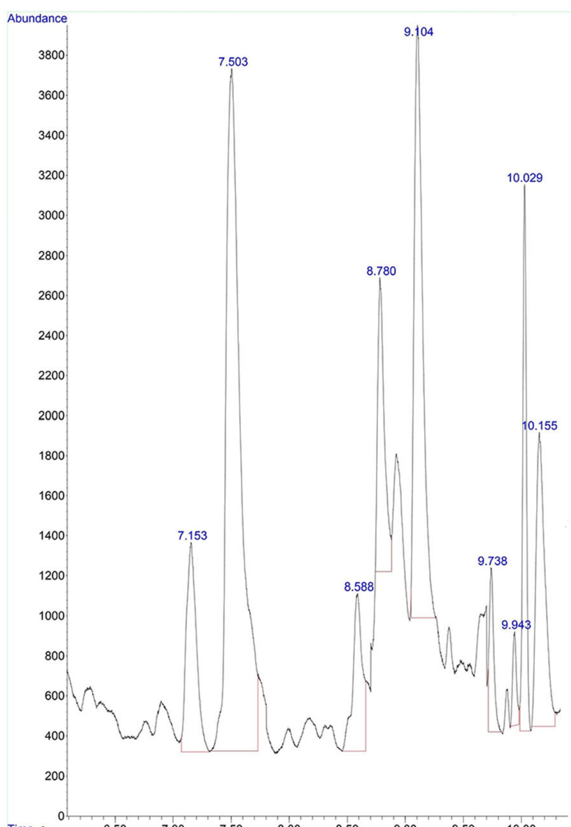


Fig. 1 The schematic presentation of the chromatogram of parabens fractions

Discussion

In the present study, the association between maternal urine parabens (as an indicator of maternal exposure to these compounds) during their first trimester of pregnancy and its association with neonatal measures including length, weight, and head circumference was investigated. To the best of our knowledge, this is the first study in the Middle East and North Africa (MENA) region that addresses the issue. In accordance with the previous studies, MeP was detected in more than 90% of the urine samples collected form pregnant women in this research. However, the detection frequency of the PrP in this study was lower than that was reported by the previous studies. On the contrast, BuP was detected with higher frequency in the present study compared to the reports from other countries [26–28, 39, 41]. The detection frequency of the EtP in China [27], Taiwan [39], Japan [41], Spain [42] and Korea [43] studies has been reported over 80%,while in studies conducted in USA [44] and Puerto Rico [45], EtP was detected in 59.5% and 57.6% of the samples, respectively. The percentage of EtP detection in this study was 36%, which was somehow within the ranges reported by Messerlian et al. in USA [28]. The geometric means of the creatinine-adjusted urinary parabens concentrations (μg/g.cr) obtained in our study were higher than that levels reported in Taiwan [39] (for MeP: 72.8 vs. 51.79, for PrP: 4.5, vs. 4.04 and for BuP: 2.2 vs. 1.12) and China [27, 46]. Furthermore, the median concentration of the parabens (for MeP: 160.1 vs. 191, for PrP: 7.8, vs. 29.8, and for EtP: 04 vs. 8.8) in this study was lower than those levels have been reported in Spain [42]. However, both the geometric and median values of BuP were higher in our study compared to all the previous studies [26–28, 39, 41, 42].

In general, various factors including exposure window, socio-demographic characteristics, economic conditions, education level, lifestyle variables, climate changes and time and methods of sampling could influence the urinary concentration of parabens [17, 27, 39]. Moreover, it has been well established so far that urinary levels of parabens strongly associate with higher use of cosmetic products. Therefore, the differences in the patterns of cosmetics use among different populations could influence the urinary levels of parabens [27, 47]. It has been shown that a combination of MeP and PrP are used in many commercial products, while EtP and BuP are applied singly [47]. The higher detection rates of the abovementioned parabens in the urine samples of pregnant women in this study, along with the previous reports ranked Iran second in the use of cosmetic products, indicted that the higher maternal urinary parabens might be attributed to the use of cosmetics [31]. Such assumptions can also be explained by the previous findings indicating that pregnant women use large amount of cosmetics during their first trimester compared to the late trimesters [27].

Association of maternal urine parabens with neonatal anthropometric indices

Previous studies have shown that Iranian women use large amount of cosmetics, which increase their exposure to phenolic compounds. During the pregnancy, exposure to these compounds can potentially influence the fetus development, and therefore may alter neonatal anthropometric measurements including length, head circumference, and birth weight [17]. Accordingly, in the present study we examined the associations between maternal urinary parabens in first trimester with the anthropometric indices of their neonates. However, there are several confounders such as maternal age, BMI, education, and etc. which should be adjusted before the data analysis. In this regard, several studies have shown that the age of mothers, work status, education levels widely associated with the delivery of underweight infants [48]. Wasunna et al. [49] have also shown that maternal education and household income are important factors affecting birth weight. Furthermore, obese mothers or those who had gestational diabetes are at higher risk of having over-weight infants, due to that the excess glucose in their serum can cross the placenta and reach the growing fetus [50, 51]. It has been shown that mother with BMI lower or higher than normal range may experience complicated pregnancy or have adverse birth outcomes [52, 53]. There are also evidences indicating that maternal age could have impact on the neonatal weight. Accordingly, women who married under the age 18 years may potentially have underweighted infants [54]. Karim et al. [55] have also found that birth weight increases with higher maternal education. In the Accordingly, in the current study we adjusted the data for the above mentioned confounders to present a more clear picture of associations between maternal urinary parabens with the neonatal anthropometric measurements.

Based on the results of linear correlation model, positive association was observed between MeP and PrP concentration with the neonatal length, while EtP and BuP had negative associations. However these associations did not reach statistical significance (p-value > 0.05). Also after subgroup analysis by sex, no statistically significant associations were observed between paraben concentrations and neonatal length. Similar in consistent results have also been reported in the previous studies. There are some studies have shown a positive but not significant association between maternal urine parabens level and the neonatal length [26, 56, 57], while some have revealed negative association between specific parabens, such as BuP, with the neonatal length [29]. Among the reasons for some non-significant associations between maternal urinary concentration of parabens and neonatal anthropometric indices, we can note the variations in the exposure profiles as well as the utilization of only one spot urine measuring for the prenatal exposure levels of parabens [27].

One of the most important, rapid and available clinical indicators for assessment of neonatal brain development is the measuring of head circumference during infancy and childhood [58]. Herein, we observed significant associations between the some parabens concentration and head circumference in neonates. In this regard, BuP concentration was observed to be negatively associated with head circumference in female neonates both in crude and adjusted analyses while positively associated with mentioned index in male neonates only in adjusted model. Accordingly, by one unit increase in BuP concentration, the head circumference was decreased 0.013 cm [95% CI: -0.024, -0.003] in girls, while was increased 0.019 cm [95% CI: 0.001, 0.038] in boys. Furthermore, positive significant associations were observed between maternal urinary PrP levels with head circumference of male neonates in crude analysis. Based on these findings, the head circumference was increased 0.006 cm [95% CI: 0.001, 0.011] by an unit increase in PrP concentration.

Although some studies did not document such significant associations [29, 57], but our findings are in line with the study of the Messerlian et al. who showed that head circumference decreased by 0.27 cm (95% CI: -0.54, 0) for each logarithmic unit increase in MeP [28]. It should be acknowledged that the decrease in head circumference of neonates is negligible in the current and previous studies, however its impact might be important at population level and further clinical studies should be done to verify its clinical impacts.

The underlining mechanisms by which parabens may alter neonatal anthropometric indices are not well understood. As a member of EDCs [59, 60], it is probable that parabens may exert their effects on neonatal measurements by influencing the activity of key effector hormones including estriol, progesterone, sex hormone binding globulin and thyroid-stimulating hormone [59–61]. For instance, the balance of maternal thyroid hormones has been demonstrated to play a vital role in fetus development [62]. In this regard, the concentrations of maternal urinary parabens have shown to be significantly associated with decreased levels of thyroid hormones [63]. Similar results have also been documented by several *invivo* studies [64–66]. In addition, some studies revealed that parabens may also induce estrogenic response to tissue as an estrogen receptor agonist or antagonist, which may disrupt the regulation of estrogen-dependent transcriptional signaling pathways [67]. Such disruptions during the pregnancy might be accounted for some abnormal neonatal measurements at birth. It has also been shown that maternal estriol level is positively associated with neonatal head circumference [68]. Therefore, the changes in the levels of aforementioned hormones may be associated with changes in neonatal head circumference, however further studies are warranted to elucidate the molecular basis of these assumptions.

Neonatal weight at birth is another parameter which is used to evaluate fetal growth. In the present study we found that maternal urinary BuP concentration is significantly associated with neonatal weight. For neonates of both sexes, the crude model showed significant association [$\beta = 4.3$, 95% CI: 1.6, 6.9], and remained significant after adjustment for the confounding variables such as educational level, maternal BMI and gestational age [$\beta = 3.8$, 95% CI: 1.1, 6.4]. The current study also showed that BuP had a significant effect on the weight of female neonates. Furthermore, our results showed that by each unit of increase in BuP concentration, 3.9 g [95% CI: 0.7, 7.1] of neonatal weight was increased in the adjusted model. Similarly, Aker et al. in USA found that maternal BuP levels was associated with higher birth weight in both male and female neonates [63]. In line with our findings, Philippat et al. [3] has conducted a study in France and showed that the total concentration maternal urinary parabens was linked with increased male neonatal weight. Ferguson in USA [56] has also revealed that there is a positive association between BuP concentration in maternal urine and birth weight in male neonates.

The strong association of maternal urinary BuP with neonatal measurements obtained in this study might be explained by the higher frequency and amounts of BuP in this study compared to the previous investigations, We also found a weak but significant association (0.28 and p-value = 0.002) between the urinary levels of parabens with the use of cosmetic products indicating a higher amounts of BuP in the used products. Moreover, the increase of neonatal weight due to the maternal exposure to parabens might because of the obesogenic effects of these compounds. It has been demonstrated that EDCs, including parabens, could increase weight by changing lipid homeostasis toward lipid accumulation and adipogenesis. Additionally, the weight gain by the exposure to these compounds might be a result of increased adipocytes numbers and size, and altered endocrine pathways responsible for the control of adipose tissue metabolism [16].

Mechanistically, there are evidences indicating that parabens could stimulate adipocyte differentiation in 3T3-L1 cells [61]. Of note, the adipogenic potency of parabens has been shown to be increased with the increase in the length of the alkyl chain [61], which is associated with PPARγ activation [69]. The mentioned facts are in accordance with the results of our study showed that BuP, a paraben with a long alkyl chain, had significant effects on neonatal weight. In addition, by affecting steroid hormones, parabens can also change fat deposition and lipid storage and thus could lead to the expansion of adipose tissue [70]. Furthermore, it has been shown that maternal exposure to parabens can also promote obesity later in life; indicating that the exposure to these compounds during pregnancy may result in life-time adverse health issues. Given to the mentioned notes, birth weight is important parameter and could provide a forecast of an individual health status in the future; therefore both low and high birth weights might be associated with later health problems and should be prevented. Based on the abovementioned notes, the impact of maternal exposure to environmental chemicals on birth weight should be strongly considered at public health level.

Study limitations and strengths

This study has some limitations. First, the urine sampling was performed by spot sampling that could not accurately reflect the level of exposure of pregnant women to parabens. However, given the fact that pregnant women are exposed to cosmetics and foods and that their consumption habits cannot be easily changed [40], one can rely on spot sampling and it is recommended that the approach of this study be used to determine the concentration of urinary parabens in different trimesters of pregnancy and by combined sampling. The second limitation is that, some isomers of parabens such as (n-PrP vs. iso-PrP, n-BuP vs. iso-BuP) were not measurable by the method used in this study, therefore the sum of the parabens isomers was reported; but a study conducted by Błędzka et al. [71] showed that the toxic effect of n-PrP versus iso-PrP and n-BuP was equal, thus reporting the total parabens would not raise a problem. However, this survey is the first study of its kind not only in Iran but also in the MENA region. Furthermore, we used well designed questionnaires covered a large number of variables pertaining to the exposure of pregnant mothers to parabens and different aspects of their lives and completed by face-to-face interviews. It should be stressed that our the significant associations found between the concentration of parabens and neonatal weight and head circumference in this study may stem from the advantages of the used questionnaires.

Conclusions

These findings of this study showed some associations between the concentrations of urinary parabens of pregnant mothers with birth weight and head circumference. It is suggested that maternal exposure to parabens might have impact on the fetal growth. However, these findings are based on cross-sectional data, thus the results should be interpreted with caution. Additionally, the clinical impact of the current findings should be verified in the longitudinal studies. The current findings underscore the necessity of providing more strict regulations in industries for limiting parabens use in their products, and the importance of public education for women of reproductive age for using paraben-free compounds.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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