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RESEARCH ARTICLE

Association of maternal exposure to bisphenol A with her β-hCG level and neonatal anthropometric measures

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Abstract

Bisphenol A (BPA) is one of the organic compounds that might interfere with estrogenic receptors, which would make difficulties in pregnancy hormones and fetal growth. Human chorionic gonadotropin (β-hCG) is one of the important pregnancy hormones that might be affected by environmental pollutants. The aim of this study is to investigate the probable impacts of maternal exposure to BPA on anthropometric measures of newborns. This cross-sectional study was conducted in 2019–2020 in Isfahan, Iran. During the first trimester of pregnancy, we measured the urinary BPA concentration and serum β-hCG level of 120 pregnant women, who were randomly selected from participants of a birth cohort. BPA concentration was measured using gas chromatography–mass spectrometry (GC-MS). Serum blood sample was derived and used for β-hCG analysis. Anthropometric measurement of neonates was conducted at the time of birth. BPA and β-hCG level were grouped by quartiles, and their associations with birth weight, height, and head circumference were tested using multiple linear regression model. The adjustment was done for urine creatinine, gender, and gestational age, as well as maternal age, body mass index, and education level. Data of 119 pairs of mothers and infants were available for the present study. The mean (SD) age of mothers was 29.19 (5.75) years; 56.3% of newborns were boys. Geometric mean of urinary BPA and β-hCG concentrations were 0.36 ng/g crea. (creatinine) and 17736 mIU/ml, respectively. Across the BPA tertiles, the differences in mean values were not significant for none of the anthropometric measurements and gestational age (GA). Furthermore, no significant association existed between unadjusted and adjusted tertiles of BPA and β-hCG with abovementioned birth outcomes. It seems that the non-significant association found in this study is because of low levels of urinary BPA levels than in other studies; the adverse effects on infants might be related to high concentration of BPA passed from placenta. Future longitudinal studies with large sample size are necessary to document the adverse health effects of maternal exposure to endocrine disruptor chemicals including BPA.

Keywords Bisphenol A · Anthropometry · Fetus · HCG-beta · Urine

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Introduction

Phenols broadly comprise chemical compounds with hydroxyl groups bonded to an aromatic hydrocarbon. Bisphenol A (BPA), 4,4-isopropylidenediphenol or 2,2-bis-(4-hydroxyphenyl) propane, the most studied phenolic compounds, is used in polycarbonate plastics, epoxy resins, and thermal paper with numerous applications in a wide range of consumer products including canned food and plastic water bottles, toys, food containers, thermal papers, and medical equipment (Amin et al. 2019; Aung et al. 2019; Catenza et al. 2021; Mustieles et al. 2020; Yang et al. 2021).

Industrial wastewater, indoor air, and landfill leachates are potential sources of environmental contamination by BPA (Lee et al. 2014a). Human exposure to BPA occurs across

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dermal contact, ingestion, and inhalation of contaminated environment media (Yang et al. 2021). Bisphenol A has been listed as an endocrine-disrupting chemicals (EDCs) and compounds intervening with the endocrine system and is associated with disruption of various metabolic, reproductive, and neuroendocrine systems (Derakhshan et al. 2021). It is an imitation of estrogen causing a hormonal response even at low doses and may cause an imbalance in endocrine system (Brugnera et al. 2010).

The estrogenic role of BPA in the body may lead to toxic effects on development or the reproductive process. the effect of BPA on fetal development is of great concern because there is growing evidence that BPA has irreversible effects on gestational age (GA) and birth outcomes including birth length and birth weight (Lee et al. 2014b; Yang et al. 2021).

Pan et al. reported that prenatal BPA exposures were associated with adverse effects on embryonic growth measures and found that maternal urinary BPA level were negatively associated with birth length, and this effect was stronger in female infants (Yang et al. 2021). Vicente et al. observed a strong negative association between maternal BPA exposure and offspring birth size (Mustieles et al. 2018).

In the study of Lee et al., univariate regression analysis demonstrated that maternal urinary levels of BPA was significantly associated with birth weight and more pronounced in male infants (Lee et al. 2014b).

The meta-analysis conducted by Cheng-Yang et al. suggested that prenatal BPA exposure does not have significant association with continuous birth weight (Hu et al. 2018). Another meta-analysis by Zhitong et al. revealed that BPA exposure had positively associated with birth weight but not with head circumference, birth length, and gestational age (Zhou et al. 2019a).

HCG is a very complex molecule with two subunits, α and β, that is synthesized by the placenta. The in vitro studies found that EDCs such as aspara-Nonylphenol (p-NP) and BPA could change hCG production and exert their fetal effect. Therefore, it could be extrapolated that hCG could become a useful clinical biomarker for maternal exposure to EDCs (Adibi et al. 2015; Mannelli et al. 2014; Paulesu et al. 2018).

The presence of any defect in hCG production during pregnancy is associated with many problems for the fetus, one of which is impaired fetal growth. The placenta is a carrier between the fetus and the mother that carries fluids and gases but is unable to block the transfer of many man-made chemicals that have entered the mother's body. As a result, many environmental pollutants cross the placenta and affect fetal health and growth. One of the compounds that affects the activity of the endocrine glands as well as the growth of the fetus is the BPA compound, which is able to cross the placenta. In the blood, it reacts and causes changes in placental development as well as the secretion of hCG hormone, and the changes made affect the growth and health of the fetus and can lead to consequences such as premature birth. Studies in human cells show that this hormone could be a potential biomarker for the activity of endocrine disruptors during pregnancy. Due to the increasing use of products containing BPA, in this study, by measuring the level of BPA in the urine of pregnant women in Isfahan and their serum hCG, the possible effect of exposure to BPA during pregnancy as a disruptor of endocrine activity on the infant growth profile was checked.

Materials and methods

This is a nested cross-sectional study of the PERSIAN birth cohort in Iran. Study subjects were 120 pregnant women from the PERSIAN birth cohort enrolled in 2018–2019. Urine samples (20 mL volume) were gathered in the first trimester of pregnant women. Each sample was divided to two parts for BPA and creatinine analysis. Blood samples, hold at −80 °C, were analyzed for hCG. For analysis of BPA, 10 μL of β-glucuronidase was added to 10 mL of samples. They were placed in incubator at37 °C for 12 h. After shaking, 2.5 mL of samples was separated and diluted by deionized water to doubly ratio. At the next step, 0.5 g sodium chloride, 500 mL asetonitril, and 50 μL aseto-benzene were added to samples and centrifuged in 5000 RPM for 1 min. Extracted samples from previous stage were transferred to specific vials, and 50 μL of MSTFA was added for sample derivatization and was put to oven at 50 °C for 1 h. Finally, 1 μL of the sample was injected to GC-MS for analysis (Amin et al. 2017)

Gas chromatography (GC), Agilent Company, Model 7890, equipped to mass spectrometry (MS), Agilent Model 5975, split/split less mood, was used for BPA analysis. The limits of detection (LOD) and quantification (LOQ) and relative standard deviation (RSD, %) for BPA detection were 0.1(μg/l), 0.35 (μg/l), and 8.9%, respectively.

Serum measurements

During 2019–2020, 120 pregnant women referred to Prenatal Clinic or Emergency Department of Amin Hospital in Isfahan, Iran, with complaints of fluid discharge were enrolled. The information were collected by a data form including demographic data, results of speculum examination, fern and nitrazine test, HCG dipsticks (Acon Inc. from USA), and ELISA (dbc HCG ELISA, Diagnostics Biochem Co., Canada) results with accuracy of 99% and cut-off value of 25 mIU/mL and Cortez (CORTEZ DIAGNO STIC Co.,USA) and DIMA (DIMA Gesellschaft Fur Diagnostika Co., Germany) with cut-off value of 20 mIU/mL. The validity of data was confirmed by content validity method. Control solutions were utilized for confirming the validity of HCG dipsticks and ELISA method (Kariman et al. 2011).

Statistical analysis

Continuous variables were expressed as means (standard deviation (SD)) and categorical data as number (percentage). The normality of data was assessed graphically using statistical tests. Comparisons between means of anthropometric measures and GA according to tertiles of BPA and β-hCG were performed using one-way ANOVA. The two independent sample t-test and Mann-Whitney test were used for comparing BPA and β-hCG across gender, preterm, and low birth weight for normal data and abnormal data, respectively. The association between the adjusted BPA and β-hCG with anthropometric measurements and GA was evaluated using multiple linear regression models. The models were adjusted with creatinine, gender, gestational age, maternal age, maternal BMI, and maternal education level. The data analyses were performed using statistical software STATA 12.0 (STATA Corp, College Station, Texas, USA). P-values less than 0.05 were considered to be statistically significant.

Results

Data of 119 mothers and infants were available for the present study. Table 1 shows characteristics of mothers and their infants in the study. In total, 56.3% of infants were boys. The mean (SD) maternal age of participants was 29.19 (5.75) years. Geometric mean and the percentiles of urinary BPA and β-hCG concentrations during first trimester of pregnancy are presented in Table 2. The mean value of urinary concentrations of BPA and β-hCG across categories of discrete variables is shown in Table 3. The mean of urinary concentrations of BPA for mothers with preterm infants was significantly higher than others (P = 0.009). BPA in the first, second, and third tertiles was < 0.275, 0.275–0.395, and > 0.395 (ng/g crea.), respectively. The tertiles for β-hCG were < 15230, 15230–33910, and > 33910 (m IU/mL), respectively. Table 4 shows comparison of the anthropometric measurements including birth weight (BW), birth length (BL), head circumference (HC), Ponderal index ((weight/(height^3))*100) (kg/m^3), and gestational age (GA) across tertiles of urinary BPA and β-hCG concentrations. The differences in means of tertiles were not significant for any anthropometric measurements and GA (P > 0.05). Tables 5 and 6 show association between unadjusted and adjusted tertiles of BPA and β-hCG with anthropometric measurements and GA, respectively. There were no significant associations between unadjusted and adjusted tertiles of BPA and β-hCG with all outcomes (P > 0.05) except for PI that difference in average of PI's between third and first tertiles of β-hCG (after adjusting other variables in model) was significant beta = 0.26 (SE = 0.11) and P = 0.02 (Table 6). Moreover, we performed analyses using urinary concentrations of BPA and β-hCG as the continuous variables, and there were no significant associations with any of the outcomes except association between PI and adjusted β-hCG (beta = 5.00E-06, SE = 2.01E-06; P = 0.017) (Table 6).

Table 1 Characteristics of mothers and infants in the study

Mothers	Mean or frequency	SD or %
Age (y)	29.19	5.75
BMI (kg/m^2)	24.68	4.01
< 18.5	10	8.5
18.5–23	30	25.6
> = 23	77	65.8
Education level		
Under high school	24	20.2
High school	55	46.2
Universal education	40	33.6
Infants		
Gender (boy)	58	56.3
Weight (g)	3125.86	366.37
Height (cm)	50.21	2.61
Head (cm)	34.39	1.14
Low birth weight	5.00	4.30
Preterm	9.00	7.60

BW, birth weight; BL, birth length; HC, head circumference; PI, Ponderal index; GA, gestational age

Model 1, unadjusted model; Model 2, adjusted with creatinine, gender, maternal age, maternal educational level, maternal BMI, and gestational age; BW, birth weight; BL, birth length; HC, head circumference; PI, Ponderal index; GA, gestational age

Model 1, unadjusted model; Model 2, adjusted with creatinine, gender, maternal age, maternal educational level, maternal BMI, and gestational age; BW, birth weight; BL, birth length; HC, head circumference; PI, Ponderal index; GA, gestational age

Discussion

In this study, the maternal urinary BPA concentrations were measured for assessing the correlation between the urinary BPA concentration and hCG hormone levels, gestational age, and infants anthropometric characteristics. Some studies showed that placenta plays an important role in transportation of gases and fluids in pregnancy, being able to produce and metabolize hormones, and finally, plays a basic role in pregnancy progress. Besides, it was reported that high doses of BPA may pass from placenta and affect fetus growth and health, decrease or increase disorders of βhCG, and damage

Table 2 Urinary concentrations of BPA and β-hCG during first trimester of pregnancy in the present study

		Range		Percentile					
	Geometric mean (GM)	Min	Max	10th	25th	50th	75th	90th	95th
BPA (ng/g crea.)	0.36	0.07	2.01	0.19	0.26	0.33	0.46	0.93	1.44
β-hCG (m IU/mL)	17735.90	220	97450	3750	12280	22400	36950	58336	70618

offspring anthropometric measures (BW, BL, HC, Ponderal index, and gender) (31).

In the present study, as shown in Table 2, the geometric mean of BPA was 0.36 m IU/ML, lower than its value in the study conducted by Lee et al., in Korea (1.29 μg/L (1.87 μg/g creatinine)) (Lee et al. 2014b); Braun et al., in Cincinnati, Ohio (median: 2.0 μg/L) (Braun et al. 2011b); Wenqian et al., in China (median: 4.70 μg/L and 2.25 μg/L for case and control mothers) (Huo et al. 2015); and Adam J. et al., in Ohio (geometric mean: 2.4 μg/g creatinine) (Spanier et al. 2012).

There were no significant associations between unadjusted and adjusted tertiles of BPA and β-hCG with birth outcomes ($P > 0.05$). Urinary BPA concentrations were not related to hCG hormone (Tables 4 and 5). These results are in line with those of Casas et al. (Casas et al. 2016).

However, some studies found that the urinary BPA concentration was associated with the mentioned parameters; for example, Maohua et al. provided evidence suggesting that maternal BPA exposure can be associated with decline in offspring birth weight (Miao et al. 2011). Moreover, Lee et al. found the sex-specific associations in exposure to BPA with birth outcomes, such as birth length and birth weight (Lee et al. 2014b). Pan et al. also reported the sex-specific relationship between BPA exposures and germinal growth parameters, and stronger impact was reported for female newborns (Yang et al. 2021). BPA can bind to receptors of estrogen, while estrogen plays an important role in fetus growth; consequently, exposure to BPA can affect fetal growth by disrupting the endocrine (Yang et al. 2021). The result of meta-analysis conducted by Zhitong et al. demonstrated that prenatal BPA exposure increases the birth weight probably with stimulating glucocorticoid receptor (GR) activity in 3T3-L1 preadipocytes and with occupying the estrogen receptor (ER) (Zhou et al. 2019b).

In this study, we did not find any association between the urinary BPA concentration and infants' anthropometry measures. It can be related to the short half-life of BPA in the serum, approximately 6 h, and eliminated to the urine within 24 h (Lassen et al. 2013; Taylor et al. 2011); thus, its concentration varies during and across days. We used the spot urine sample, and the fluctuation is higher in spot urine samples than in long-term samples (Khoshhali et al. 2020).

Another study confirmed that BPA is detectable in human biological fluids like serum, follicular fluids, and amniotic fluid and showed high concentration of BPA causes preterm delivery (Ikezuki et al. 2002). Moreover, the results of the in vitro research study by Chiara et al. showed that BPA has toxic effects on endometrial maturation cells, endometrial stromal cells, macrophage migration inhibitory factors, secretion, and hormone chorionic gonadotropin/luteinizing hormone receptor (hCG/LH-R), and this toxicity decreases the number of cell viability (Mannelli et al. 2015). Previous studies showed that transferred BPA from placenta is able to affect it and cause change in β-hCG secretion level to lower or higher than normal range. Furthermore, it was observed that the rate of FSH in exposed women is lower than control group (5.3: 7.6 MI+U/ml). It was reported that BPA may affect hCG and gonadotropin similarly (Alonso-Magdalena et al. 2006).

Table 3 The mean value of urinary concentrations of BPA and β-hCG across categories of discrete variables

Variables		Bisphenol A			β-hCG		
		Mean	SD	P	Mean	SD	P
Gender	Girls	0.41	0.27	0.918	34456.73	24084.89	0.054
	Boys	0.43	0.33		23897.97	17974.00	
Education level	Under high school	0.51	0.42	0.609	30864.00	28219.10	0.698
	High school	0.43	0.33		25466.03	19816.57	
	Universal education	0.41	0.32		26193.70	16426.67	
Preterm	No	0.42	0.32	0.009	27295.06	21081.85	0.507
	Yes	0.67	0.53		20864.00	14872.60	
Low Birth weight	No	0.44	0.34	0.664	26714.76	20026.52	0.11
	Yes	0.31	0.06		74170.00	0.00	

Table 4 Comparison of the anthropometric measurements and gestational age across tertiles of urinary concentrations of BPA and β-hCG

	BW (g)		BL (cm)		HC (cm)		PI		GA (week)	
BPA (ng/g crea.)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T_1	3079.36	363.53	50.23	2.50	34.37	1.40	2.44	0.30	38.00	0.88
T_2	3123.33	387.13	49.82	3.06	34.36	1.04	2.54	0.36	37.95	0.78
T_3	3176.18	350.21	50.59	2.19	34.43	0.95	2.46	0.32	37.74	1.07
P for trend	0.250		0.545		0.804		0.758		0.216	
β-hCG (m IU/mL)										
T_1	3114	343	50.59	2.24	34.50	1.14	37.79	0.98	2.41	0.29
T_2	3230	330	50.83	1.80	34.44	1.00	37.79	0.93	2.47	0.29
T_3	3117	394	50.20	2.88	34.29	1.12	38.00	0.80	2.49	0.39
P for trend	0.977		0.574		0.522		0.751		0.665	

In this study, measured BPA and β-hCG did not have any significant relation. The in vitro study conducted by Mannelli et al. revealed that direct BPA exposure triggered the release of β-hCG by placental cells (Mannelli et al. 2014). Adibi et al. found that higher first trimester urinary MBzP, MnBP, and MCOP were significantly associated with higher and lower hCG in women carrying female and male fetuses, respectively (Adibi et al. 2015).

In the present study, the mean concentration of BPA was 0.36 ppb, whereas in the study by Shelley et al., BPA mean concentration was higher than 2.22 μg/L and showed significant relation with decreased number of oocyte (overall and mature) (Ehrlich et al. 2012).

It was reported that high concentration of BPA causes hormonal, reproductive, physiological, and gender disorders; for example, 10 μg BPA/kg/day causes fast decrease induction of glycemic cells correlates with increase in plasma insulin and β-cell insulin in the estrogen receptor–dependent manner (Hanaoka et al. 2002), and 100 μg BPA/kg/day causes metabolic disorders relevant to glucose homeostasis and risk factor for diabetes in pregnancy and pancreatic functions in offspring (Alonso-Magdalena et al. 2010). Urinary assay of BPA is one of the research indexes to assess the β-hCG in pregnancy and offspring anthropometry. Following the increased BPA in urine, hormonal disorders become obvious into decrease or increase in hCG and offspring disorders into decrease and increase of weight, height, gender, and head circumference. Furthermore, disorders in amniotic fluid and placenta enzymes by the increase by BPA affect logged BPA to placenta (Braun et al. 2011a; Levine et al. 2011).

Study strengths and limitations

This is the first Iranian study in Isfahan to assess associations between maternal BPA exposure and hCG hormone levels and infants anthropometric measures. Strengths of this study include the population-based design, high-quality urinary BPA assays, direct anthropometric measurements, and assessment of multiple potential confounders.

Table 5 Association between urinary concentrations of BPA and anthropometric measurements and gestational age

	BW			BL			HC			PI			GA		
BPA	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P
Model 1	Ref.			Ref.			Ref.			Ref.			Ref.		
Tertiles: T1															
T2	43.97	83.21	0.60	−0.41	0.59	0.49	−0.01	0.26	0.97	0.11	0.07	0.16	−0.05	0.20	0.81
T3	96.83	83.75	0.25	0.36	0.60	0.55	0.06	0.26	0.80	0.02	0.07	0.76	−0.26	0.21	0.22
Continuous	96.61	103.59	0.353	0.10	0.74	0.896	0.12	0.32	0.716	0.05	0.09	0.582	−0.13	0.25	0.603
Model 2	Ref.			Ref.			Ref.			Ref.			Ref.		
Tertiles: T1															
T2	56.11	89.97	0.54	−0.19	0.71	0.80	0.02	0.31	0.95	0.09	0.09	0.32	0.00	0.25	1.00
T3	129.25	86.97	0.14	1.03	0.69	0.14	−0.12	0.30	0.68	−0.05	0.09	0.61	−0.23	0.24	0.34
Continuous	148.42	118.04	0.212	1.10	0.95	0.249	−0.13	0.40	0.738	−0.06	0.12	0.647	−0.05	0.33	0.889

Table 6 Association between urinary concentrations of β-hCG and anthropometric measurements and gestational age

	BW			BL			HC			PI			GA		
β-hCG	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P
Model 1	Ref.			Ref.			Ref.			Ref.			Ref.		
Tertiles: T1															
T2	116.57	105.28	0.27	0.24	0.69	0.73	−0.06	0.32	0.85	0.05	0.10	0.59	0.00	0.26	1
T3	3.10	106.37	0.98	−0.40	0.70	0.57	−0.21	0.32	0.52	0.07	0.10	0.47	0.21	0.26	0.43
Continuous	9.08E-05	0.002	0.966	−4.67E-06	1.37E-05	0.735	−5.26E-08	6.35E-06	0.993	7.51E-07	1.90E-06	0.694	2.87E-06	5.22E-06	0.584
Model 2	Ref.			Ref.			Ref.			Ref.			Ref.		
Tertiles: T1															
T2	150.95	111.19	0.18	−0.07	0.85	0.93	−0.30	0.43	0.49	0.12	0.10	0.25	0.12	0.34	0.74
T3	−7.44	112.05	0.95	−1.86	0.86	0.04	−0.48	0.44	0.28	0.26	0.11	0.02	0.23	0.35	0.52
Continuous	0.003	0.002	0.245	−2.3E-05	1.72E-05	0.181	1.56E-06	8.43E-06	0.855	5.00E-06	2.01E-06	0.017	2.45E-06	6.64E-06	0.714

The spot urine sampling that may not be the best biomarker of maternal BPA exposure and does not control effect of other pollution during pregnancy is the most powerful limitations of present study.

Conclusion

Taken together, across the BPA tertiles, the differences in mean values were not significant for none of anthropometric measurements and gestational age (GA). Furthermore, no significant association existed between unadjusted and adjusted tertiles of BPA and β-hCG with birth outcomes.

Author contribution MA contributed in the concept, conducting the study, and revising the manuscript. Z Gh contributed in the concept, conducting the study, and drafting the manuscript. M Kh conducted the statistical analysis and revision of the manuscript. ET contributed in conducting the study and revising the manuscript. BD contributed in conducting the study and drafting the manuscript. AF contributed in conducting the study and revising the manuscript. NR contributed in conducting the study and revising the manuscript. RK contributed in the concept, conducting the study, and revising the manuscript. All authors approved the final draft of the manuscript for submission and accept the responsibility of its content.

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Data availability All data generated and analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval IR.MUI.RESEARCH.REC.1398.630 (http://ethics.research.ac.ir/IR.MUI.RESEARCH.REC.1398.630)

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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