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ORIGINAL ARTICLE

Association of cord blood bisphenol A (BPA) with cord blood adiponectin, leptin, fetal growth; adiposity and neoantal complications in a newborn cohort

Ceyhun Dalkan[a], Murat Uncu[b], Serpil Duran[a] and Nerin Nadir Bahçeciler[a]

[a]Department of Pediatrics, Faculty of Medicine, Near East University, Nicosia, Cyprus; [b]Department of Biochemistry, Faculty of Medicine, Near East University, Nicosia, Cyprus

ABSTRACT

Objective: To evaluate the relation between cord blood bisphenol A (BPA), leptin, adiponectin, birth weight, height, skin thickness, and postnatal results.

Method: This study was performed in near East University Medical Faculty, Nicosia, Cyprus with 150 healthy newborns. Cord blood leptin, adiponectin, BPA levels were measured by ELISA and birth weight, heights and back, waist, and arm skin thickness were measured and postnatal problems noted.

Results: One hundred eighty-seven newborns were included in the study. Mean ± SD of BPA, adiponectin, leptin levels were 48.3 ± 2.22 ng/mL, 65.60 ± 15.29 μg/mL and 3.08 ± 2.08 ng/mL. Mean birth weight, height, head circumferences were 3156.76 ± 493.45 g, 48.28 ± 2.04 cm, 34.14 ± 1.74 cm. The association anthropometric measurements, BPA, leptin, and adiponectin levels were not statistically significant ($p>.05$). The relation between cord blood leptin, adiponectin, and BPA levels and small for gestation, large for gestation and average for gestation groups were not significant ($p>.05$). Moreover, relation between back, waist and arm skin thickness and BPA, leptin, and adiponectin were not statistically significant ($p>.05$). However, newborns who were hospitalized and had newborn jaundice had higher BPA levels ($p<.05$).

Conclusion: In previous studies, higher BPA levels were associated with small for gestational age (SGA) birth, however, this relation was not noted in our study. Furthermore, there is no relation between skin thickness, BPA, leptin, and adiponectin. This difference may be as a result of higher cord BPA levels compared with previous studies.

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Adiponectin; adiposity; bisphenol A; cord blood; fetal growth; leptin

Introduction

Bisphenol A (BPA) has been widely used in the plastic and resin production industry such as water bottles, medical equipments, lining of food cans, and cosmetics. Exposure of products containing BPA to high temperatures is well known to cause leakage of this molecule to packed food and beverages [1–3]. BPA was reported to have estrogenic, antiandrogenic, and antithyroid effects and may disrupt insulin metabolism. BPA had been detected in placental blood, amniotic fluid, and cord blood. In addition, cord blood BPA levels were demonstrated to be positively correlated with maternal urine and blood BPA levels were correlated and cord blood BPA levels reflect the amount of BPA levels that fetuses were exposed during pregnancy [4].

Exposure to high levels of BPA had been reported to have metabolic, hormonal, reproductive side effects, such as infertility, hypothyroidism, premature puberty, type 2 diabetes, and obesity [5] In addition, intrauterine exposure to BPA leads to fetal developmental and metabolic adverse effects [3].

High-level BPA exposure had been reported to cause obesity in adults, while intrauterine BPA exposure was noted to cause low birth weight and small for gestational age newborns [6–8]. The underlying metabolic impact of BPA on adipocytes *in utero* life is not well known. The underlying physiologic functions and regulations of adipocyte-originated hormones, leptin, adiponectin in metabolic system has been recently recognized [9]. High leptin levels in adults are associated with obesity and large for gestational age in infants. High cord blood leptin levels have been positively correlated with birth weight, whereas low cord blood leptin levels have been associated with small for gestational age [10]. In adults, low adiponectin levels have been implicated in insulin resistance, type 2

CONTACT Ceyhun Dalkan dalkanc@yahoo.com Department of Pediatrics, Faculty of Medicine, Near East University, Nicosia, Cyprus

diabetes, and metabolic syndrome [11,12]. However, lower levels of adiponectin were found in small-for-gestational-age newborns and higher levels were found in large-for-gestational-age newborns [10]. The dose-dependent effect of BPA on adipocyte-originated hormones and anthropometric measurements adipocyte volume in newborns has not been evaluated to date.

Therefore, in this study, we examined the distribution of BPA levels in cord blood, and the impact of different levels of BPA on adipocyte-originated hormones (leptin and adiponectin). In addition, the effect of cord blood BPA level on anthropometric measurements, adiposity (measured by skin arm, back and waist thickness) and birth outcome were investigated.

Material and methods

Study population and anthropometric data

This study was designed as a cross-sectional study. Institutional Review Board approval was obtained prior to study (YDU/2015/32-215) and informed parental consent was obtained from each participant. All newborns that were born within the period of September 2015–September 2016 in near East University Hospital were planned to be included in the study. Infants who had congenital anomalies, perinatal asphyxia, and major surgical operation were excluded from the study. Mothers with obesity, diabetes, chronic kidney disease, epilepsy, chronic liver disease, hypertension, and chronic drug use were excluded from the study.

Pregnancy and birth history together with body mass and length data were obtained from the patients' hospital records. The body weight of each neonate and placental weight were determined to the nearest 1 g using an electronic scale. Body length was determined to the nearest 0.1 cm in the supine position with a length board. Head circumference was determined with a plastic tape to the nearest 0.1 cm. Arm, waist, and back thicknesses were measured by Holtain skinfold caliper. This work was supported by the Near East University DESAM department.

Blood sampling and BPA level measurement

Cord blood samples from umbilical vein were obtained with BPA-free polystyrene tubes from children at birth. Each blood sample was left to coagulate for 30 minutes, and then samples were centrifuged at 2000×*g* for 10 min at room temperature to obtain serum, which was stored in aliquots in BPA-free Eppendorf vials at −80 °C until analysis. On the day of analysis, the aliquots were brought to room temperature and thoroughly vortexed before the analysis.

Biological markers were analyzed by sandwich enzyme – linked immunosorbent assays (ELISAs) kits for human adiponectin (Human adiponectin ELISA, High Sensitivity Kit; BioVendor–Laboratorni medicina, Modrice, Czech Republic), Leptin (Leptin – ELISA, DIASource Immunoassays SA, Louvain-La-Neuve, Belgium), bisphenol A (General bisphenol A (BPA) ELISA kit, MyBioSource, Inc, San Diego, CA, USA).

All laboratory investigations were performed by a researcher unaware of the asthma diagnosis of the children. Five-milliliter samples of peripheral venous blood samples were obtained from all children. Each blood sample was left to coagulate for 30 minutes, then centrifuged for 15 minutes at 10,000 rpm and the extracted serum was collected and stored at −20 °C until analysis.

Leptin (ng/mL) and ghrelin (ng/mL) were measured by EIA (DRG Diagnostics, Inc, Marburg, Germany, and Raybiotec h, Inc, GA, USA respectively), whereas calprotectin (ng/mL) was measured by ELISA (Human Calprotectin ELISA kit, Cusabio Biotech, China) in serum samples. The methods of measurement were carried out according to the manufacturer instructions.

The standard curves are created by reducing the date

The methods of measurements were carried out according to the manufacturer instructions. ELISAs were read with a SpectraMax M5 (Molecular Devices, Sunnyvale, CA, USA). The standard curves are created by using computer software (Softmax Pro. 5.2) capable of generating four parameter logistic (4PL) curve-fit. Based on the BPA levels obtained the 50th and 90th percentiles of study group were calculated.

Birth outcomes

Postnatal follow up of neonatal complications

All participant newborns were followed for hypoglycemia, jaundice, asphyxia, respiratory distress, polycythemia, and neonatal intensive care unit admission. Hypoglycemia was diagnosed, if the capillary blood glucose level was less than 45 mg/dL; physiologic jaundice was diagnosed if jaundice started after the first 24 hours of life and if serum bilirubin level was more than 12–13 mg/dL in terms and 15 mg/dL, in preterms, if daily bilirubin increasing blood glucose levels were checked at the first, 2nd and 6th hours and venous hematocrit was checked in the 6th hour

of life in all newborns. Perinatal asphyxia was defined as the presence of at least 1 of the following: (1) umbilical artery pH or blood pH at 1 h of life ≤7 or base deficit ≥16; (2) 5-min Apgar score ≤5; (3) need for advanced resuscitation (intubation and/or chest compressions and/or administration of drugs).

Anthropometric and adiposity measurements

Gestational weeks were calculated by last due day and if necessary Ballard Score was used [13]. The newborns were assessed as (a) low birth weight (LBW) defined as a newborn's birth weight less than the 10th percentile; small for gestational age (SGA) defined as birth weight less than the 10th percentile, compared with the birth weight distribution in the same gestation week and gender according to the data of national newborn's birth weight percentiles by using normal ranges of Turkish children [14].

Statistical analysis

Statistical analysis was performed using SPSS version 22 for Macintosh (SPSS Inc, Chicago, IL, USA). The results are expressed as mean and standard deviation of the mean (SD). To determine the relationship between principal variables and the other continuous variables, Pearson correlation test was used. Mann–Whitney *U* test was used to determine the relationship between grouped variables. A *p* value less than .05 was considered statistically significant.

Cord blood leptin, adiponectin, birth weight, height, head circumference, waist, back, and arm thickness were compared with below and above the 10th, 25th, 50th, 75th, and 90th percentile of cord blood BPA levels.

Results

One hundred eighty-seven healthy newborns were included in the study. 49 were excluded based on exclusion criteria. Among the remaining 138 newborns, 61 (44.2%) were boys and 77 (55.8%) girls. The mean birth weight, height, and head circumference were 3156.76 ± 493.45 g, 48.28 ± 2.04 cm and 34.14 ± 1.74 cm, respectively. One hundred twenty-four newborns (89.9%) were AGA, 9 (6.5%) SGA and 5 (3.6%) LGA. The mean cord blood BPA level was 48.3 ± 2.22 ng/mL, while adiponectin level 65.60 ± 15.29 μg/mL and leptin level was 3.08 ± 2.08 ng/mL (Table 1). The 90th and 50th percentile of the cord blood BPA levels of the whole group were found to be 8.33 ng/mL and 48.3 ng/mL, respectively. There was no statistically significant difference between cord blood leptin and adiponectin levels, birth weight, head circumference, arm, back, and waist thicknesses when newborns below and above the 50th and 90th percentile of cord blood BP levels were compared ($p>.05$) (Table 2, 3).

In addition, the mean BPA levels of neonatal outcomes; respiratory distress, polycythemia, hypoglycemia, pathologic jaundice, and neonatal intensive care unit admission were compared (Table 4). The mean cord blood BPA levels were significantly higher in newborns with polycythemia (7.85 ± 0.31; 4.7 ± 2.18 ng/mL in control $p=.04$), newborns who had pathologic jaundice (6.46 ± 2.59, 4.73 ± 2.18 in control, $p=.04$) and admission of NICU (5.536 ± 2.37, 4.51 ± 2.1 in control, $p=.03$). These results showed that neonatal complications were more common during pregnancy in newborns with higher exposure of BPA during pregnancy.

Table 1. Characteristics of the study group.

Characteristics (*n*: 138) (*n*: 138)	Mean ± SD
Birth weight (gr) (Mean ± SD)	3156.76 ± 493.45
Birth height (cm) (Mean ± SD)	48.28 ± 2.04
Head circumference (mm) (Mean ± SD)	34.14 ± 1.74
Arm thickness (mm) (Mean ± SD)	5.14 ± 3.59
Back thickness (mm) (Mean ± SD)	4.72 ± 1.27
Waist thickness (mm) (Mean ± SD)	4.19 ± 2.45
Girl/ Boy (n/n)	77/61
BPA (ng/mL) (Mean ± SD)	48.3 ± 22.23
Adiponectin (μg/mL) (Mean ± SD)	65.60 ± 15.29
Leptin (ng/mL) (Mean ± SD)	3.08 ± 2.08
AGA (%)	89.9
SGA (%)	6.5
LGA (%)	3.6

Table 2. Comparison of cord blood leptin, adiponectin, birth weight, height, head circumference, waist, back and arm thickness based on > and < mean BPA level (48.3). (BW: birth weight, BH: birth height, HC: head circumferences).

	BPA <48.3	BPA >48.3	*p*
Adiponectin	49.2 ± 55.08	81.5 ± 207.1	.193
Leptin	2.77 ± 1.58	3.38 ± 2.45	.074
BW	3179.97 ± 411.17	3134 ± 566.18	.602
BH	48.67 ± 1.59	47.89 ± 2.36	.025
HC	34.37 ± 1.77	33.90 ± 1.70	.122
Arm thickness (mm)	4.78 ± 1.03	5.51 ± 4.98	.238
Back thickness (mm)	4.28 ± 3.1	4.1 ± 1.54	.7
Waist thickness (mm)	4.67 ± 1.22	4.77 ± 1.33	.7

Table 3. Comparison of cord blood leptin, adiponectin, birth weight, height, head circumference, waist, back, and arm thickness > and <90th percentile BPA level (83.3). (BW: birth weight, BH: birth height, HC: head circumferences).

	BPA <83.3	BPA >83.3	*p*
Adiponectin	66.57 ± 160.5	56.8 ± 46.1	.6
Leptin	3.05 ± 2.08	3.36 ± 2.12	.6
BW	3170.98 ± 479.1	3022.29 ± 618.9	.4
BH	48.35 ± 1.98	47.57 ± 2.58	.3
HC	34.35 ± 1.67	33.08 ± 2.17	.08
Arm thickness (mm)	5.18 ± 3.74	4.77 ± 1.57	.7
Back thickness (mm)	4.19 ± 2.55	4.26 ± 1.22	.9
Waist thickness (mm)	4.69 ± 1.16	5.05 ± 2.13	.3

Discussion

It has been recently demonstrated that BPA can cross the placental barrier in humans; and maternal and placental BPA levels are correlated. In addition, prenatal BPA exposure had been demonstrated to have some harmful effects on pregnancy, fetus, and neonate [15]. Furthermore, BPA exposure is a risk factor for development of obesity, hypothyroidism, gonadal abnormalities, infertility, and malignancy in adults. Currently, *in utero* BPA exposure was demonstrated to be a neonatal risk factor for SGA birth, preterm birth, and a neonatal hypothyroidism. In adults, by release of adiponectin and leptin, BPA was found to be the main reason for obesity. In addition, it has an impact on insulin resistance, which triggers adipocyte differentiation, and increases obesity.

Hereby, based on the recent scientific data on adults and newborn, we aimed to determine the dose-related impact of BPA on fetal growth, adiposity, and neonatal complications.

Cord blood BPA levels were divided into percentiles form 10th–90th and simultaneous cord blood adipokine proteins (leptin and adiponectin) were measured (Figure 1). Leptin, adiponectin and skin thickness of newborns were compared to find possible dose-dependent effect of BPA on adipocyte tissue volume. In addition, the association between prenatal BPA exposure and neonatal complications were evaluated.

There were no significant differences in cord blood leptin, adiponectin levels, birth weight, and skin thickness based on the comparison of different cord blood BPA levels. On the other hand, newborns NICU admission, jaundice and polycythemia had higher mean cord blood of BPA level.

Several studies have examined the correlation between birth weight, height, and BPA. According to Troisi et al. study [7], BPA concentration of oven-dried placental tissue and birth weight was checked. Low birth weight and SGA newborns had significantly higher placental BPA. In another study, dry blood spots were used to check BPA levels and compared with infant outcomes [16]. They observed negative associations between BPA and birth size. In the current study, no association was detected between cord blood BPA and SGA. According to Woods et al. study [17], they measured maternal urine and blood chemicals at 16 and 26 weeks gestation and checked the correlation between birth weight and noted no correlation between them. However, third-trimester exposure was not controlled in their study. We suggest that, the measurement of cord blood BPA levels better reflects fetal exposure to BPA as all the BPA in

Table 4. Comparison of cord blood BPA levels based on presence or absence of neonatal complications.

	BPA mean ± SD +	BPA mean ± SD −	*p*
Respiratory distress (*n*: 30)	51.96 ± 22.8	45.44 ± 21.2	<.05
Polycytemia (*n*: 5)	78.05 ± 3.1	47.39 ± 21.8	.04
Hypoglycemia (*n*: 19)	52.83 ± 20.05	46.51 ± 22.34	>.05
Jaundice (*n*: 15)	64.6 ± 2 5.9	47.3 ± 21.8	.04
NICU admission (*n*: 40)	55.36 ± 23.7	45.1 ± 21.01	.03

*Mann–Whitney *U* test.

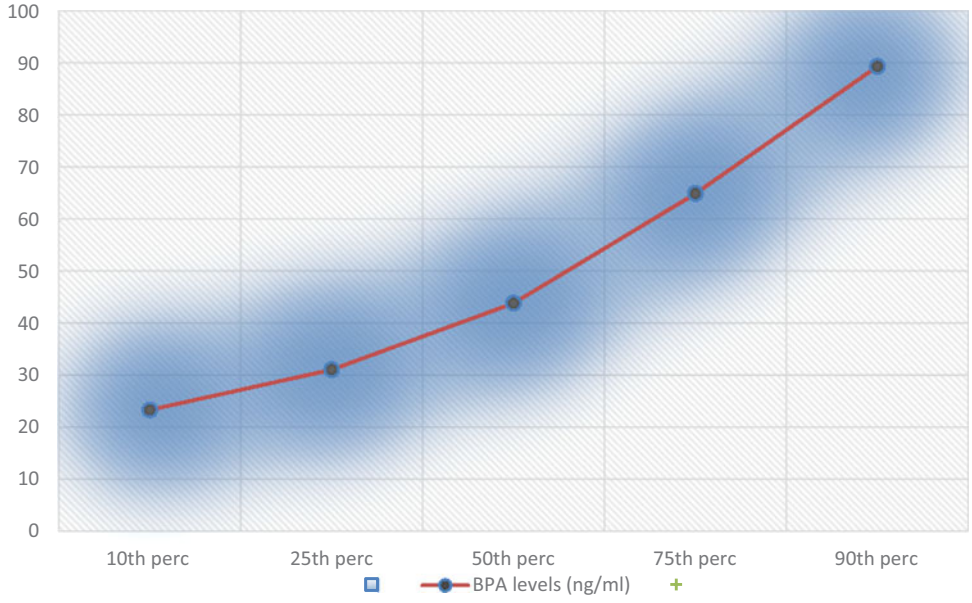

Figure 1. 10th, 25th, 50th, 75th, and 90th percentile values of measured cord blood BPA levels were calculated. All study parameters of newborns that had lower or higher BPA levels than each percentile were compared with no statistically significant differences (data not shown for 10th, 25th, and 75th percentiles).

placental tissue may not pass over to the neonatal circulation. If we checked first and second trimester maternal BPA levels, this would increase the power of our study.

In another study [6], a positive correlation between maternal BPA levels and low birth weight was detected. Highest maternal BPA exposed males had higher risk for LBW. We suggest that evaluation of cord blood BPA, rather than maternal BPA more accurately reflects the extent of exposure in fetal life.

Previous studies have demonstrated that BPA exposure modified the regulation of metabolism *via* peroxisome proliferation pathway, adipogenesis and changing insulin secretion by pancreatic β-cells. Large epidemiologic studies have shown highly significant relation between BPA and obesity or obesity-related disorders [5–10]. Metabolic related biomarkers such as leptin, adiponectin, tumor necrosis factor alpha (TNF-α) and interleukin-6 were used to check metabolic functions. Adipocytes produce adiponectin and leptin and placenta also produces leptin [4,6–9]. However, in-utero exposure level and fetal, neonatal outcomes are not well-known. In addition, studies about the relation between BPA and adiponectin and leptin for newborns are limited and relation is uncertain. Minatoya et al. [18], compared maternal first-trimester blood BPA levels and cord blood leptin, adiponectin levels. They demonstrated a positive correlation between maternal BPA and cord blood leptin/adiponectin levels. This previous study compared only first-trimester maternal blood BPA levels and cord blood adipocyte molecules, whereas in our study cord blood levels of BPA, leptin, and adiponectin were studied. The measured levels in this study reflect the first 3 months of fetal BPA exposure, while cord blood level reflects the amount of BPA directly transporting to the fetus during pregnancy. Using first, second, and third-trimester maternal blood or urine and cord blood samples for BPA, adiponectin, leptin measurements in addition to follow-up of in-utero growth of the fetus until birth may delicate the dynamic impact of BPA on adiposity and growth.

Epidemiologic studies reported that BPA is an endocrine disruptor that has an obesogenic effect in adults by increasing adipocyte tissue through adipocyte hormones [6]. Therefore, skin thickness of newborns was evaluated in addition to BPA, adipocyte hormones, and birth weight. According to our knowledge, this the first study evaluating the relation between BPA and arm, back and waist skin thickness of newborn. Back and waist thicknesses were higher in the group whose BPA was >90th percentile; with no statistically significant difference. Prospective cohort studies should be planned to detect this relation.

This study has several limitations. First, the level of plasma BPA was only detected at a single time in connection with delivery from cord blood. Another limitation of our study was the relatively small study sample, larger series that contains more SGA and LGA cases are needed to confirm our results.

In conclusion, possible impact of high cord blood BPA on neonatal complications has been reported for the first time. More exposed newborns developed more polycythemia, NICU admission, and jaundice which implicate possible systemic side effects of BPA on newborns. Nearby, no dose depend neonatal effect of BPA exposure was detected based on objective parameters of obesity. It is clear that high dose BPA exposure has harmful effects on newborns.

Disclosure statement

No potential conflict of interest was reported by the authors.

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