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ORIGINAL ARTICLE

High Urinary Bisphenol A Levels may be a Risk Factor for Infantile Colic: a case-control study

Los niveles elevados de bisfenol A en orina podrían ser un factor de riesgo para el cólico infantil: un estudio de casos y controles

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What do we know about the subject matter of this study?

People are frequently exposed to bisphenol in their daily lives. It is thought to have negative effects in addition to its endocrine-disrupting effect.

What does this study contribute to what is already known?

Urine BPA values of infants with infantile colic were higher than those of healthy infants. According to this study, BPA may be associated with the development of infantile colic.

Abstract

Objective: To investigate the relationship between infantile colic and urinary Bisphenol A (BPA) levels in infants aged under 3 months. **Patients and Method:** A group of 20 infants with a recent diagnosis of infantile colic, according to ROMA IV criteria, without treatment and a control group of 33 healthy infants were evaluated. Gestational age, birth weight, age at urine sampling, daily weight gain and consumption of packaged products by the mothers of the infants included in the study were recorded. Urine BPA levels were measured by liquid chromatography-mass spectrometry in an isolated urine sample. **Results:** The sex, median gestational age, mode of delivery, birth weight, weight at the time of urine sampling, daily weight gain and mother's packaged product consumption were not significant different between control and colic group. The urine BPA results of infants diagnosed with infantile colic (median 20,4 µg/g/creatinine, IQR 8,9-34,1) were significantly higher than the urine BPA results of the healthy infants (median 9,1 µg/g/creatinine, IQR 4,9-16,3) ($p < 0,05$). The model established as a result of the regression analysis was not statistically significant (Model Significance: $F = 0,861$; $p = 0,530$; $R^2 = 0,101$). **Conclusion:** The etiology of infantile colic is still poorly understood and is speculated to be associated with disrupted microbiota. Our results suggest that BPA is associated with the development of infantile colic.

Keywords:
Bisphenol A;
Infantile Colic;
Microbiota;
Infant

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Introduction

Bisphenol A (BPA), one of the most widely used synthetic compounds in the world, is a plastic monomer and a synthetic estrogen with endocrine-disrupting effects[1,2]. It is found in numerous everyday products, including contact lenses, dental composites, toys, medical equipment, glasses, and pacifiers[3]. People are exposed to BPA through diet, inhalation, or dermal exposure[4]. BPA can also migrate to foods through direct contact. Some of these include plastic packaging, kitchenware, and jar lids[5]. Several longitudinal studies explored the postpartum effects of intrauterine BPA exposure (including cognitive and neurodevelopmental effects) by following infants from birth throughout childhood[6,7]. Studies also demonstrated that BPA is associated with allergic diseases and migraines[8,9]. In another study, BPA levels were found to be high in urine samples collected after birth from newborns diagnosed with transient tachypnea of the newborn in the Neonatal Intensive Care Unit[10]. All these studies indicate the broad clinical effect of BPA on children.

Infantile colic is described as constant or excessive crying and is one of the most challenging problems of infancy[11]. Parents may see crying as evidence of a disease or an indicator of their inability to care for their child[12]. Infantile colic is a benign, self-limiting condition that spontaneously resolves over time[11]. Although its etiology is not fully elucidated and most infants resolve spontaneously, it has been also observed to be concomitant with certain diseases, such as migraines and allergic diseases[13,14]. Since the diseases that have been associated with BPA exposure and the diseases that colicky infants are likely to develop when they grow up are similar, we considered investigating the potential association between infantile colic and BPA[8,9,13,14].

Subsequently, we decided to investigate the association between BPA and infantile colic by assessing the urine BPA levels of infants aged less than 3 months who were presented to the Gaziantep Children's Hospital and were diagnosed with infantile colic. Both recently diagnosed patients with infantile colic and healthy control babies are included in the study.

Patients and Method

Patients

This study was prospectively conducted in the Gaziantep Children's Hospital between January 2020 and May 2020. The study included patients aged <3 months who were admitted to the Gaziantep Children's Hospital with infantile colic. Demographic data were recorded.

The exclusion criteria were as follows: congenital heart disease, chromosomal disorders or syndromes, metabolic diseases, parents not giving consent for participation, preterm birth, history of admission to the neonatal intensive care unit or the hospital ward, comorbidities, and receiving supplements other than vitamin D.

BPA levels

Zhang et al. stated that, in humans, serum BPA levels are correlated with urinary BPA levels[15]. In our study, we planned to examine BPA levels in the urine samples of infants due to the noninvasive nature of this method. In their study, Völkel et al. found the half-life of BPA to be 6 hours[16]; therefore, we collected urine samples at least 6 hours after the last dose of vitamin D. Although not all patients used the same amount or type of vitamin D supplement, six hours were considered to exclude the possibility of BPA being used as a possible preservative in some vitamin D preparations.

Definition of infantile colic

In this study, we accepted the definition proposed by the Rome IV criteria[17]: being aged <5 months when the symptoms start and stop; recurrent and prolonged periods of crying, fussing, or irritability that start and stop without obvious cause and cannot be prevented or resolved by caregivers; no evidence of poor weight gain, fever, or illness; caregiver reports crying/fussing for ≥ 3 hours per day ≥ 3 days/week on telephone or in face-to-face interview; and total daily crying is confirmed to be ≥ 3 hours when measured by at least one prospectively kept 24-hour diary.

If an otherwise healthy infant with a normal physical examination who has normal development, weight, head circumference, length, and urinalysis results and who does not have vomiting symptoms, respiratory distress, or any symptoms that may suggest gastrointestinal pathology (e.g., bloody stool) conforms to the above criteria, the infant is diagnosed with infantile colic[18].

Study group

This group consisted of patients diagnosed with infantile colic through the exclusion of other possible diagnoses during outpatient clinic check-ups. Patients hospitalized were not included in the study. A spot urine sample was collected before the initiation of the supplement treatment prescribed by the physician (the supplement treatment was planned by the physicians who followed the newborns without intervention from the researchers).

During the 4-month inclusion period, 59 patients fulfilled the inclusion criteria and their families gave consent for participation. We excluded 11 patients from the study because their last dose of vitamin D was

given less than 6 hours before the urine sampling. Seven patients were excluded from the study due to receiving a supplement (6 patients were using probiotics and one patient was using fish oil.) Three patients were excluded since their parents did not remember the time of the last dose of vitamin D. One breastfeeding patient was excluded because his mother consumed herbal teas to address infantile colic. The parents of two patients did not give consent for participation in the study. Furthermore, 9 patients were excluded because the urine sample could not be collected, 5 due to not being able to deliver enough urine, and 1 whose urine sample was determined to be too small immediately before the analysis. The remaining 20 patients were recently diagnosed with infantile colic.

Control group

The control group included healthy infants who were presented to the outpatient clinic for routine follow-up. These subjects had normal health, were not described as having infantile colic symptoms, and did not use any medication other than vitamin D. All subjects were aged under 3 months. The subjects' demographic data were recorded.

During the 4 months of study, 127 babies conformed to the inclusion criteria and whose families gave consent for participation. Out of these, 49 babies were excluded because they had been given vitamin D less than 6 hours before and 15 were excluded since their parents did not remember the time of the last dose of vitamin D. The parents of 4 babies did not give consent for participation in the study. Furthermore, 11 babies were excluded because a urine sample could not be collected, and 13 due to not being able to deliver enough urine. Two babies were excluded because the follow-up examination revealed 1 case of urinary tract infection and 1 case of bronchiolitis. The remaining 33 patients were included in the control group.

The infants were divided into three groups according to type of feeding: breastfeeding, formula, and combined feeding (breastfeeding and formula). The mothers of infants who were being breastfed (with or without formula) were asked about any supplements they consumed to address infantile colic. The babies of mothers using such supplements were excluded from the study. Mothers of breastfeeding infants were also asked about the number of packaged foods they consumed per day.

Since all subjects were aged <3 months old, none of the subjects had switched to solid foods. According to the protocol described by the Turkish Ministry of Health, prophylactic iron supplementation is initiated at the 4-month follow-up. Therefore, none of our subjects were receiving iron supplements.

Urine collection

After obtaining consent, urine samples were collected by placing cotton balls in the diapers of the babies, and urine was squeezed out of the cotton balls into glass sample bottles using nitrile gloves. After being transferred to glass bottles, the urine samples were stored at -20°C until they were transported to the examination center. The stored urine samples were transferred collectively to the examination center on dry ice.

The study aimed to evaluate only urine BPA levels and spot urine creatinine. Urine samples were not collected using invasive methods (e.g., bladder probing or suprapubic catheter insertion). Blood was not collected from the subjects for the study. The routine follow-up of the subjects remained unchanged. In addition, the urine samples did not come into contact with any plastic derivatives during collection or transport.

Urine analysis

Urine BPA levels were expressed in two forms: uncorrected BPA (μg/L) and corrected BPA/creatinine (μg/g creatinine), the latter of which was corrected by adjusting the measured BPA level by dividing it by the measured creatinine level (mg/L). Bisphenol A (99+% purity, Aldrich®) and D16-Bisphenol A (D16-BPA, ≥98% purity, Aldrich®) were purchased from Sigma-Aldrich. Bisphenol A βglucuronidase, reagents, and mobile phases were obtained from Jasem. LC-MS/MS was preferred for measurements.

Ethics

All subjects' parents gave informed written consent to participate before initiation of the study. The study was granted ethical approval by the Ethics Committee of Gaziantep University (2019/477) and subsequently, permission from the Scientific Research Application Review Commission of the Provincial Health Directorate of Gaziantep.

Results

Table 1 shows the demographic characteristics of the 20 recently diagnosed colicky patients and the 33 healthy controls. The study and control groups were not statistically different in terms of sex and type of delivery ($p = 0.974$ and $p = 0.592$, respectively). The gestational week and birth weight findings of the two groups were also similar ($p = 0.668$ and $p = 0.907$, respectively). The median (IQR) age at the time of urine sample collection was 35 days (27-54) for the control group and 41 days (29-58) for the recently diagnosed infantile colic group This difference was not statistically significant ($p = 0.443$). Weight gain per day, measured according to the weight on the day of urine

Table 1. Demographic characteristics of the infants and comparison of urine results of the groups

Characteristics		Control group, n (%) n = 33	Newly diagnosed patients with infantile colic, n (%) n = 20	p
Sex				
Male		18 (54.5)	11 (55)	0.974
Female		15 (45.5)	9 (45)	
Type of delivery				
NSVD[a]		19 (57.6)	13 (65)	0.592
C-section		14 (42.4)	7 (35)	
Diet	Breastfeeding	11 (33.3)	3 (15)	
	Formula	9 (27.3)	3 (15)	0.037
	Breast milk + formula	13 (39.4)	14 (70)	
		Median (IQR 25-75)	Median (IQR 25-75)	
Gestational weeks		38.4 (38.1-39.1)	38.3 (38.02-38.9)	0.668
Birth weight (g)		3200 (2960-3465)	3215 (2963-3565)	0.907
Age at the time of urine sampling (days)		35 (27-54)	41(29-58)	0.443
Weight at the time of urine sampling (g)		4285 (3950-4625)	4548 (4273-4774)	0.483
Daily weight gain (g)		29.5 (25.2-38.2)	29.9 (26.1-38.1)	0.769
Mother's packaged product consumption/day (among breastfeeding infants)*		1.0 (1.0-1.0)	1.0 (1.0-2.0)	0.145
Parameters evaluated in spot urine	BPA (µg/L)	2.5 (1.6-10.0)	7.0 (4.0-19.5)	0.021
	Creatinine (mg/L)	345.6 (232.8-928.8)	437.5 (201.6-1106.4)	0.769
	BPA/creatinine (µg/g)	9.1 (4.9-16.3)	20.4 (8.9-34.1)	0.035

*Product processed and packaged in plastic wrap; NSVD: Normal Spontaneous Vaginal Delivery; C-section: Cesarean section. BPA: urinary Bisphenol A.

collection, was not statistically different for babies (p = 0.769). Median (IQR) weight gain per day was 29.5 g/day (25.2-38.2) for the control group and 29.9 g/day (26.1-38.1) for the recently diagnosed infantile colic group (table 1). However, weight at the time of urine collection was not significantly different between the groups (p = 0.483). We compared the packaged food consumption rates of the mothers of breastfed babies finding it was higher in the study group (17 patients in the newly diagnosed group and 24 patients in the control group), also this difference was statistically significant (p = 0.037; table 1).

Table 1 shows the spot urine BPA, creatinine, and BPA/creatinine results of the recently diagnosed infantile colic patients, and healthy control groups. The spot urine creatinine levels of recently diagnosed infants and healthy controls were not statistically different (p = 0.769). However, urine BPA and BPA/creatinine were significantly higher in recently diagnosed patients with infantile colic than in the control group (p = 0.021 and p = 0.035, respectively; table 1).

Figure 1 shows the spot urine BPA/creatinine results of the two groups.

The BPA/creatinine ratio was considered as a dependent variable. Gestational age, birth weight, age at the time of urine sampling, daily weight gain, and the packaged food consumption rates of the mothers of breastfed babies were considered independent variables. According to table 2, the BPA/creatinine value is not affected by the variables. The model established as a result of the regression analysis was not statistically significant (Model Significance: F = 0.861; p = 0.530; $R^2 = 0.101$).

Discussion

Infantile colic is a benign and self-limiting condition that is characterized by prolonged bouts of crying and spontaneously resolves around 5 months of age, but it is a challenging condition both for parents and doctors. Despite numerous studies, the etiology of infantile colic is still not fully understood[11].

In the literature, it has been observed that both children with BPA exposure and patients diagnosed with infantile colic present with similar diseases (aller-

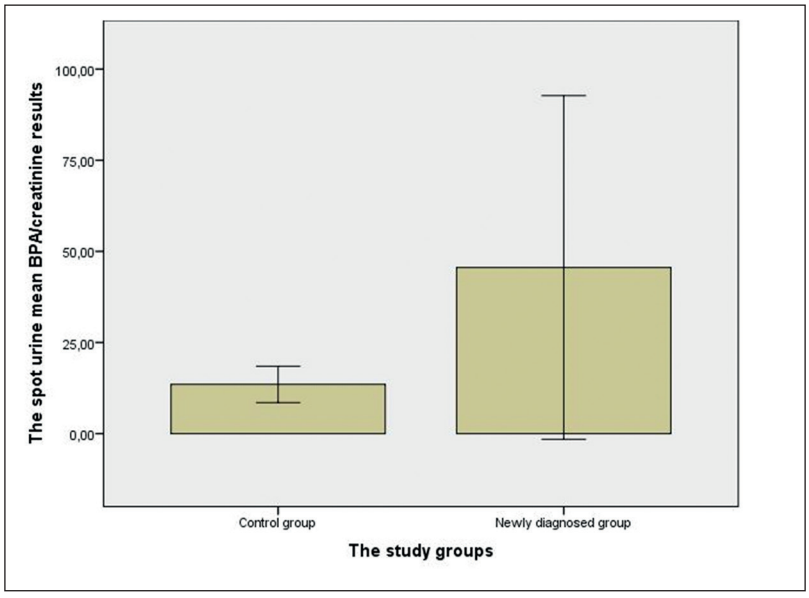

Figure 1. The spot urine BPA/creatinine results of the groups (Error Bars: 95% CI).

Table 2. Simple linear regression analysis by BPA/Creatinine value

	Regression Coefficient						
	β	Se	z β	t	p	%95 Confidence Interval for β	
						Lower Bound	Upper Bound
Constant	75.827	435.267		.174	**0.862**	-800.320	951.974
Gestational weeks	-3.813	11.725	-0.048	-0.325	**0.746**	-27.415	19.788
Birth weight (g)	0.079	0.093	0.431	0.843	**0.403**	-0.109	0.266
Age at the time of urine sampling (days)	3.552	2.560	0.761	1.388	**0.172**	-1.601	8.706
Weight at the time of urine sampling (g)	-0.085	0.081	-0.889	-1.054	**0.298**	-0.248	0.078
Daily weight gain (g)	2.723	3.392	0.433	0.803	**0.426**	-4.105	9.551
Mother's packaged product consumption/day	-3.985	14.681	-0.039	-0.271	**0.787**	-33.536	25.567

Model Significance: F=0.861; p=0. 530; R2=0.101. Durbin-Watson= 1.885. β: Regression Coefficient; se: Standard error; *z*β: Regression Coefficient (Standardized); R^2: Coefficient of Determination; Dependent variable: BPA/creatinine ratio.

gic disorders and migraine) at later ages.[8,9,13,14] Therefore, we planned to investigate the relationship between infantile colic and BPA. In our study, we found that urinary BPA levels of infants under 3 months of age and diagnosed with infantile colic were higher than the control group. In two groups were similar in terms of sex, type of delivery, gestational week, birth weights, age at the time of urine sampling, and weight gain per day. We found that the creatinine results were statistically similar, whereas the BPA and BPA/creatinine results of the study patients were statistically higher (p = 0.021 and p = 0.035, respectively).

The study by de Siqueira CD et al. showed a high concentration of BPA in the breastmilk of lactating mothers which might be through the use of plastic containers as food/drink packages[19]. In our study, in the colic group, packaged food consumption rates of mothers of breastfed babies were determined significantly higher compared to the control group (p = 0.037). We suggest that infantile colic may be triggered due to the increase in the consumption of packaged products by breastfeeding mothers. The spot urine analysis results of recently diagnosed patients were compared with those of controls. It was determined

that creatinine values of the subjects were not significantly different, but the urine BPA and BPA/creatinine results of the babies diagnosed with infantile colic were significantly higher ($p = 0.021$ and $p = 0.035$, respectively). There were no similar studies in the literature for comparison. However, our results supported our hypothesis. There are limited studies and data on urine BPA concentrations in infants. Mendonca et al. assessed 29 healthy children aged 2-15 months and reported a mean urine BPA level of 2.3 μg/L[20]. Völkel et al. found that the urine BPA level of infants aged 1-5 months was below 0.45 μg/L[21]. In our study, the median urinary BPA level (IQR) was 2.5 μg/L (1.6-10.0) in the control group comprising 33 healthy babies aged <3 months. This value was 7.0 μg/L (4.0-19.5) in recently diagnosed patients. Our results were consistent with those reported by Mendonca et al.[20]. Moreover, Calafat et al. indicated that the mean BPA level of 40 low-birth-weight babies was 30.3 μg/L[22]. The discrepancy between these results and ours can be explained by the fact that low-birth-weight newborns were followed in the NICU and thus were more likely to be exposed to BPA.

When we consider the diseases associated with infantile colic, one of the hypotheses that aim to explain the comorbidity of migraine and abdominal migraine with infantile colic involves the disruption of the microbiota[23]. Allergies are also commonly associated with infantile colic[14], and the disruption of the microbiota is reported to contribute to the etiology of allergies[24]. Perhaps the disruption of the microbiota is the major underlying cause, which can potentially result from BPA exposure. The reasons behind the comorbidity of these conditions and the probiotic mechanisms of action are subjects for investigation in future scientific research.

Chen et al. demonstrated the negative effects of BPA on the microbiota of zebrafish[25], and Javurek et al. reported similar findings in mice, noting that probiotics could be an effective treatment option[26]. The results of these two studies support our hypothesis that BPA may be involved in the disruption of the microbiota and contribute to infantile colic pathogenesis. Similarly, the study of Rhoads et al. reported dysbiosis in patients with infantile colic[27].

To the best of our knowledge, this is the first study to investigate the relationship between infantile colic and urinary BPA levels; therefore, we were unable to compare our results with those of similar studies.

We conclude that the urine BPA and BPA/creatinine values of the recently diagnosed patients with infantile colic were statistically higher than those of healthy infants. This suggests that the etiology of infantile colic may be associated with numerous factors, including BPA exposure. In our study, there was no significant difference in risk based on covariates between the colic/control groups, and we also think that there was no difference in BPA exposure between the groups. However, BPA can come from different components and be absorbed through different pathways. Therefore, new more comprehensive studies are needed.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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