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Original Article

Comparison of urine bisphenol A levels in transient tachypnea of the newborn and healthy newborns

Melek Büyükeren

Division of Neonatology, Department of Pediatrics, Gaziantep Cengiz Gökçek Obstetrics and Pediatric Hospital, Gaziantep, Türkiye.

ABSTRACT

Background. To investigate the relationship between neonatal urine bisphenol A (BPA) levels and the prevalence and prognosis of transient tachypnea of the newborn (TTN).

Methods. This prospective study was conducted between January and April 2020 in the Neonatal Intensive Care Unit (NICU) of Gaziantep Cengiz Gökçek Obstetrics and Pediatric Hospital. The study group consisted of patients diagnosed with TTN and the control group was made up of healthy neonates housed together with their mothers. Urine samples were collected from the neonates within the first 6 hours postnatally.

Results. Urine BPA levels and urine BPA/creatinine levels were statistically higher in the TTN group ($P < 0.005$). The receiver operating characteristic (ROC) curve analysis determined the cut-off value of urine BPA for TTN to be 1.18 μg/L (95% confidence interval [CI]: 0.667-0.889, sensitivity: 78.1%, and specificity: 51.5%) and the cut-off value of urine BPA/creatinine to be 2.65 μg/g (95% CI: 0.727–0.930, sensitivity: 84.4%, and specificity: 66.7%). Furthermore, the ROC analysis indicated that the cut-off value of BPA for neonates requiring invasive respiratory support was 15.64 μg/L (95% CI: 0.568–1.000, sensitivity: 83.3%, and specificity: 96.2%) and the cut-off value for BPA/creatinine was 19.10 μg/g (95% CI: 0.777–1.000, sensitivity: 83.3%, and specificity: 84.6%) among the TTN patients.

Conclusions. BPA and BPA/creatinine values were higher in the urine of newborns diagnosed with TTN which is a fairly common cause of NICU hospitalization, in samples collected within the first 6 hours after birth, which may be a reflection of intrauterine factors.

Key words: Bisphenol A, urine, newborn, transient tachypnea of the newborn, ventilation.

Bisphenol A (BPA) is an endocrine-disrupting monomer, that was developed as a synthetic estrogen.[1,2] BPA is found in many products, including plastics, food packaging, toothpaste, and thermal receipts.[3] People are exposed to BPA through their diet, inhalation, or dermal exposure.[4]

In addition to its serious side effects on the endocrine system, recent studies have begun to focus on the effects of gestational BPA exposure on neonatal outcomes.[5,6] The negative effects of intrauterine BPA exposure on lung development were demonstrated in a mouse model study.[7] In addition, cell culture studies have shown that BPA negatively affects the lung development via the ERß/NF-kB/GR signaling pathway and that this pathway affects lung alveolar epithelium via the sodium ion channel.[8] Studies have concluded that BPA inhibits epithelial sodium channel (ENaC) expression.[7-9]

A different study on intrauterine exposure found that neonatal urine BPA levels were correlated with BPA levels in maternal serum, breast milk, the placenta, and the umbilical cord.[5]

✉ Melek Büyükeren
melekbuyukeren@gmail.com

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Transient tachypnea of the newborn (TTN) is a condition that requires minimal intervention and spontaneously regresses within 24–72 h. Although the actual prevalence is unknown, it is estimated that 0.33%–0.50% of neonates have transient tachypnea at birth. The major risk factors are cesarean delivery, macrosomia, maternal diabetes, maternal asthma, multiple pregnancies, being male, and preterm, early term, and post term birth.[10,11]

At birth, the ENaCs located on the apical surface of the pulmonary epithelium open and absorb Cl and Na, thus absorbing pulmonary fluid. One of the known causes of TTN physiopathology is the decreased activity or immaturity of lung ENaCs.[11]

With reference to these studies, the current study was designed to investigate the association between newborn urine BPA levels and the presence and prognosis of TTN. The study aimed to investigate the relationship between urinary BPA levels and the incidence of TTN by comparing the BPA levels in urine samples of neonates with TTN with those of healthy neonates collected within the first 6 hours postnatally.

Material and Methods

Patients

Study group

This prospective study included patients with TTN who were hospitalized in the Neonatal Intensive Care Unit (NICU) of Gaziantep Cengiz Gökçek Obstetrics and Pediatric Hospital, between January and April 2020. After obtaining written consent from their parents, a single urine sample was collected from neonates who had been diagnosed with TTN and admitted to the NICU. Urine samples were collected within the first 6 hours postnatally. The demographic and neonatal data of the patients were recorded. The inclusion criterion was being hospitalized in the neonatal ICU with TTN. The exclusion criteria were as follows: acute respiratory distress due to any reason other than TTN (congenital pneumonia, neonatal pneumonia, apnea, congenital diaphragmatic hernia, pulmonary hypertension, etc.), congenital heart disease, chromosomal or metabolic diseases, requiring resuscitation in the delivery room, and the parents not giving written consent. The mothers of the patients did not have any diseases. There were no patients receiving antibiotic treatment.

Statistical power analysis revealed that there needed to be at least 26 patients in each group.

Within the 4 months that the study was scheduled to take place, there were 62 patients who conformed to the inclusion criteria and whose parents gave consent for participation. Among these, 2 patients were excluded from the study because they were determined to have congenital heart disease, and the family of 1 patient opted out of participation. Twelve patients were excluded from the study due to not being able to produce enough urine within the first 6 hours postnatally. Moreover, 11 patients who were diagnosed with congenital pneumonia and 4 patients who were diagnosed with early neonatal sepsis were also excluded from the study. The remaining 32 patients were included in the study.

Control group

The control group consisted of neonates born to healthy mothers within the same period of time whose postnatal examination was normal and who were housed together with their mothers (during the 24-h postnatal observation), and who had no health problems during the follow-up. After obtaining written consent from the families, a single urine sample was collected within the first 6 hours postnatally. The demographic and neonatal data of the subjects were recorded.

Due to the high birth rate in this hospital, patients from only 1 day of the week were included as controls. Urine samples were collected from neonates that were born on the second day of each week (Tuesday) during the

determined time period to healthy mothers, who were healthy themselves, and whose parents signed informed consent forms. During this time, the parents of 89 patients agreed to participation in the study. Of the patients, 48 failed to produce an adequate amount of urine. In addition, several patients were excluded due to the following reasons: 3 patients developed early neonatal sepsis, 3 patients developed indirect hyperbilirubinemia, 1 patient was not feeding properly, and 1 patient was admitted to the NICU with intestinal obstruction. Hence, 33 patients were included in the control group.

The study was granted ethical approval by the Ethics Committee of Gaziantep University Şahinbey Training and Research Hospital (No:2019/476).

Definition of transient tachypnea of the newborn

The duration of respiratory distress (tachypnea, nasal flaring, subcostal retraction, grunting) is the main determinant for the diagnosis of TTN.[12] TTN is a diagnosis of exclusion. A neonate with respiratory distress should be considered to have TTN after other potential causes have been ruled out. Tests that are used to rule out diagnoses other than TTN include preductal and postductal oxygen saturation, complete blood count (to exclude sepsis), blood culture, C-reactive protein, procalcitonin, blood gases, lactate, and posteroanterior lung radiography.[13] Since TTN is a benign and self-limiting condition, it does not require antibiotic treatment.[14]

In lung radiography, the presence of hyperinflation of pulmonary fissures, prominent perihilar vasculature, and interlobar septa or fluid support the TTN diagnosis.[13,15] If the tachypnea does not improve within 72 hours, TTN diagnosis is ruled out.[11]

Urine collection

Völkel et al.[16] reported that the urinary excretion half-life of BPA may be less than 6 hours, while Pottenger et al.[17] stated that this duration may range from 18 to 72 h, depending on the gender and dosage. In addition, Iribarne-Durán et al.[18] reported that neonates might be exposed to multiple sources of BPA and parabens in NICUs via inhalation, dermal, oral, and intravenous (IV)/parenteral routes. As a result I collected the urine samples from neonates in the first 6 hours postnally.

After obtaining consent, urine samples were collected by placing cotton balls in the diapers of the neonates, and urine was squeezed out of the cotton balls into a glass sample container using nitrile gloves (the cotton balls were not contaminated with feces). After being transferred into glass containers, the urine samples were stored at –20 °C until they were transported to the laboratory. The stored urine samples were transferred collectively on dry ice.

The study aimed to study the BPA levels and creatinine values in spot urine. Urine samples were not collected using invasive methods (bladder probing or suprapubic catheter insertion). For this study no blood was obtained from the patients. The routine follow-ups of the patients remained unchanged. In addition, the urine samples did not come into contact with any plastic derivatives during collection or transport.

Chemicals and reagents

BPA (99+% purity, Aldrich® brand) and D16-BPA (D16-BPA, ≥98% purity, Aldrich® brand) were purchased from Sigma-Aldrich. BPA β-Glucuronidase, reagents and mobile phases were obtained from Jasem Brand. An Agilent 6470 triple quadrupole LC–MS system (Agilent Corporation, MA, USA) equipped with 1290 Binary pump, 1290 multisampler and 1290 TCC therm. column compartments was used for all analyses. The system was controlled by MassHunter software (Agilent Corporation, MA, USA).

A method for measuring total BPA in human urine using LC-MS/MS after incubation and extraction was developed. BPA Glucuronide

was disintegrationed to BPA by breaking it down with enzymes. Thus total BPA result was obtained. The method is simple, requires less LC-MS/MS run time than previous methods, and yields more sensitive results. The presence of BPA Glucuronide indicated successful degradation of Bisphenol A.

Sample preparation

Human urine samples were stored at −20 °C and thawed on the first day of the extraction. Preparation of Glucuronidase Enzyme; Preparated 2mg/ml jasem glucuronidase enzyme with 1ml Jasem buffer reagent. Pipet 200 μL of urine was sampled into a glass centrifuge tube with cap and a 25 μL of internal standard and 50 μL Jasem Glucuronidase Enzyme was added and vortex for 5 seconds and incubated at 37°C for 3 hours. After incubation 250 μL of Jasem Reagent-1 was added and additionally vortex for 5 seconds. Then, centrifuged at 3000 rpm for 5 minutes. The supernatant was decanted into the HPLC vial and injected to the LC-MS/MS system.[19] Standard curves ranging from 1.00 to 100 ng/mL BPA and from 10 to 1000 ng/mL BPAG were run.

Urine analysis

To assess the impact of creatinine adjustment on the total variance of spot urine samples, urine creatinine levels were analyzed using a modified method developed and validated for creatinine analysis by Park et al.[19,20] Urine BPA levels were expressed in 2 forms: uncorrected BPA (μg/L) and corrected BPA/creatinine (μg/g creatinine), which was corrected by adjusting the measured BPA level by dividing it by the measured creatinine level (mg/L).

History concerning plastic exposure

Mothers of the neonates were questioned about the long-term use of plastic materials or their exposure to heat and the possible harms of plastic water bottles.

Results

The demographic data of the 32 TTN patients and the 33 healthy controls are given in Table I. The gender and mode of delivery of patients with TTN and healthy controls were not statistically different (p=0.492 and p=0.478, respectively). Also, the groups were statistically similar in the rate of birth with or without labor among the cesarean deliveries (p=0.515, Table I).

Birth weight, length, and head circumference, and gestational week were generally lower in the study group when compared to the control group, but these findings were not statistically significant (p=0.581, p=0.398, p=0.411, p=0.873, respectively; Table I). There were no abnormal findings in the genitourinary system examinations of all newborns. The 5-min Apgar scores of the TTN group were significantly lower than those of the control group (p=0.001). The groups were statistically similar in terms of the prevalence of low birth weight for gestation (p=0.999, Table I). There were no neonates with fetal placental doppler abnormalities in my study. The median length of NICU stay of the TTN patients was 10 days (interquartile range (IQR): 7–12.8), while the median duration of mechanical ventilation was 2 days (IQR: 1–2). The mortality rate was zero in both the study and control group. Patients in the study group did not require antibiotics during the follow-up period because they were diagnosed with TTN.

The spot urine BPA, creatinine, and BPA/creatinine values of the study and control groups are given in Table II. The median BPA results in the spot urine collected within the first 6 hours postnatally were 2.9 μg/L (IQR: 1.2–7.5) for the TTN group and 1.2 μg/L (IQR: 0.5–1.8) for the control group. The BPA levels were statistically higher in the TTN group (p=0.0001). The spot urine creatinine values of the 2 groups were not significantly different (p=0.091, Table II).

The spot urine BPA/creatinine ratio was significantly higher in the study group when compared to the control group (p=0.001). The

Table I. Demographic characteristics of the subjects.

Characteristics	Study group n=32	Control group n=33	P-value
Gender (male/female)	22/10	20/13	0.492
Mode of delivery (NVSD/CS)	9/23	12/21	0.478
The cesarean deliveries without labor among	11	8	0.515
Gestational age (weeks)*	38 (36.3-39)	38 (36.5-39.5)	0.873
Birth weight (g)*	2925 (2390-3395)	3100 (2400-3550)	0.581
Birth length (cm)*	50 (49-51)	50 (50-51)	0.398
Birth head circumference (cm)*	35 (34-35)	35 (35-35)	0.411
Apgar (5 min)*	8 (8-9)	10 (9-10)	0.001
Low birth weight for gestation	4	4	0.999
Mechanical ventilation (days)*	2 (1-2)	0	-
Length of NICU stay (days)*	10 (7-12.8)	0	-
Discharged/Exitus	32/0	33/0	-

*: Median (interquartile range), CS: Cesarean section, NSVD: normal spontaneous vaginal delivery.

Table II. Spot urine results of study and control groups.

Parameters evaluated in spot urine	Study group, median (IQR)	Control group, median (IQR)	P-value
BPA (μg/L)	2.9 (1.2-7.5)	1.2 (0.5-1.8)	0.0001
Creatinine (mg/L)	381.4 (227.9-576.2)	553.1 (360.3-654.2)	0.091
BPA/creatinine (μg/g)	8.0 (3.6-26.1)	2.0 (1.0–3.9)	0.0001

BPA: bisphenol A, IQR: interquartile range.

median BPA/creatinine ratio was 8.0 μg/g (IQR: 2.6–26.1) in the TTN group and 2.0 μg/g (IQR: 1.0–3.9) in the control group (Table II).

In the study group, 24 patients (75.0%) required noninvasive respiratory support and 6 patients (18.8%) required invasive respiratory support. Two patients (6.2%) were followed-up without requiring a mechanical ventilator. Since there were only 2 patients who did not require a ventilator, these patients were not included in the statistical comparison. The comparison of patients in the study group according to mechanical ventilator requirement (non-invasive and invasive) is given in Table III.

In the study group, patients that required invasive respiratory support were more likely to be male and delivered by cesarean section, but this finding was not statistically confirmed due to the small number of patients (Table III). The mean birth weight of patients who required invasive respiratory support was significantly lower than that of the patients who required non-invasive respiratory support (p=0.029). They also had a lower mean gestational week, but this finding was not statistically significant (p=0.065, Table III).

Urine creatinine levels were not found to be significantly associated with mechanical ventilation requirements (p=0.082). The spot urine BPA and BPA/creatinine values of the TTN patients who required invasive respiratory support were significantly higher than those of the patients who required non-invasive support (p=0.009 and p=0.001, respectively; Table III).

In order to assess whether the difference in the BPA levels between the study and the control groups was caused by the patients requiring invasive respiratory support, the 6 TTN patients who required invasive respiratory support were excluded, and the spot urine results were then re-assessed. These results are given in Table IV.

Table III. Comparison of the TTN patients according to mechanical ventilator requirements.

	Invasive respiratory support n (%)	Non-invasive respiratory support n (%)	P-value
Gender (male/female)	5/1	15/9	-
Mode of delivery (NVSD/CS)	1/5	8/16	-
Gestational age (weeks)*	36 (35-37.8)	38 (37-39)	0.065
Birth weight (g)*	2400 (2023-2533)	3200 (2496-3475)	0.029
BPA (μg/L)*	27.9 (14.6-89.3)	2.1 (1.2-5.3)	0.009
Creatinine (mg/L)*	202.5 (148.3-527.9)	416 (250.4-609.7)	0.082
BPA/creatinine (μg/g)*	98.5 (18.6-442.1)	6.1 (3.1-11.6)	0.001

*: Median (interquartile range).
BPA: bisphenol A .

Table IV. Comparison of the spot urine results after the exclusion of patients that received invasive support.

Parameters evaluated in spot urine	Study group median (IQR)	Control group median (IQR)	P-value
BPA (μg/L)	2.1 (1.2-5.8)	1.2 (0.5-1.8)	0.001
Creatinine (mg/L)	413.5 (246.7-588.6)	553.1 (360.3-654.2)	0.222
BPA/creatinine (μg/g)	6.1 (3.2-12.4)	2.0 (1.0-3.9)	0.0001

BPA: bisphenol A.

Table V. ROC curve parameters of the BPA and BPA/creatinine.

	BPA	BPA/creatinine
AUC	0,778	0,829
95% CI	0,667-0,889	0,727-0,930
p	0,0001	0,0001
Cut-off	1,18	2,65

AUC: area under the curve, BPA: bisphenol A, CI: confidence interval, ROC: receiver operating characteristic.

Table VI. ROC curve parameters of TTN patients who did or did not require invasive respiratory support.

	BPA	BPA/creatinine
AUC	0,837	0,917
95% CI	0,568-1,000	0,797-1,000
p	0,011	0,002
Cut-off	15,64	19,10

AUC: area under the curve, BPA: bisphenol A, CI: confidence interval, ROC: receiver operating characteristic, TTN: transient tachypnea of the newborn.

After the 6 TTN patients who required invasive respiratory support were excluded, the spot urine BPA and BPA/creatinine values of the remaining TTN patients (n = 26) and healthy controls (n = 33) were compared again, and it was observed that the spot urine BPA and BPA/creatinine values of the healthy subjects were still statistically significantly lower (p =0.001 and p=0.0001, respectively; Table IV).

The values of patients whose TTN duration was longer than 48 hours (n=11) and patients whose TTN duration was shorter than 48 hours (n=21) were compared. The median BPA results were 3.1 μg/L (IQR: 1.2–6.8) for the long-term TTN group (n=11) and 2.8 μg/L (IQR: 1.2–9.9) for the short-term TTN group (n=21). Also the median BPA/creatinine ratio was 4.6 μg/g (IQR: 3.2–21.9) in the long-term TTN group and 8.5 μg/g (IQR: 4.7–39.6) in the short-term TTN group. But these findings were not statistically significant (p=0.999, p=0.411, respectively).

The receiver operating characteristic (ROC) analysis results that aimed to determine the cut-off values for the patient (n = 32) and control (n = 33) groups are presented in Table V. The ROC curve is presented in Fig. 1.

The ROC curve analysis determined the cut-off value of BPA to be 1.18 μg/L (95% confidence interval (CI): 0.667–0.889, sensitivity: 78.1%, and specificity: 51.5%). The cut-off value of BPA/creatinine was calculated as 2.65 μg/g (95% CI:

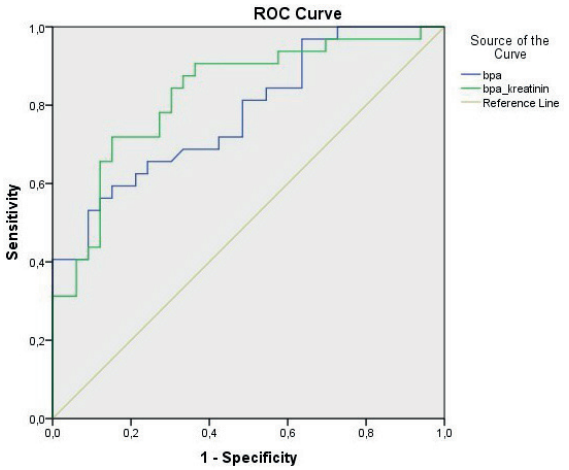

Fig. 1. Receiver operating characteristic curves of the BPA and BPA/creatinine values.

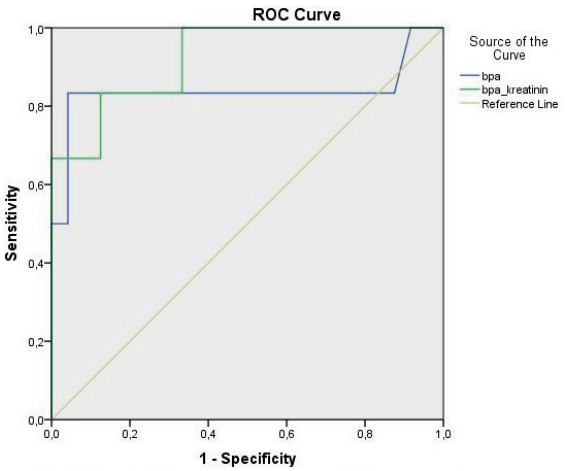

Fig. 2. BPA and BPA/creatinine receiver operating characteristic curves of newborns with transient tachypnea who did or did not require invasive respiratory support.

0.727–0.930, sensitivity: 84.4%, and specificity: 66.7%).

The ROC curve analysis results of TTN patients who did and did not require invasive respiratory support are presented in Table VI and Fig. 2.

For requiring invasive respiratory support, the ROC curve analysis determined the cut-off value of BPA to be 15.64 μg/L (95% CI: 0.568–1.000, sensitivity: 83.3%, and specificity: 96.2%) and the cut-off value for BPA/creatinine was 19.10 μg/g (95% CI: 0.777–1.000, sensitivity: 83.3%, and specificity: 84.6%).

Discussion

BPA exhibits estrogen hormone like properties that mimic endocrine-disrupting chemicals. BPA is mainly used in polycarbonate plastic production and is among the most commonly used materials.[4,21] A comprehensive study from the United States found at least 0.4 μg/L of BPA in 92.6% of human urine samples.[21,22] BPA is a common chemical that people are exposed to in everyday life, and its intrauterine effects are of interest to scientific research. Ranjit et al.[23] found that BPA exposure caused intrauterine growth restriction, and Wolff et al.[24] did not find a correlation between birth weight and BPA. In other words, different studies have obtained variable results.[25] In the current study, the birth weight, length, and head circumference findings of TTN patients (who had higher BPA levels) were not significantly different from those of the control group. There have been many studies investigating the relationship between BPA levels and endocrine disruption in newborns.[25,26] There have also been studies indicating that intrauterine BPA exposure may have adverse effects on fetal brain development.[27]

A study by Hijazi et al.[7,8] demonstrated that BPA has negative effects on fetal pulmonary development and stated that this effect was through pathways affecting the ENaC channel. There are ongoing studies that are investigating the pulmonary effects of BPA.

Even though TTN is a harmless and self-limiting condition, the tachypnea it causes can require oxygen support, non-invasive or (rarely) invasive respiratory support, and care in the neonatal intensive care unit.[14] TTN is a disease commonly observed in NICUs. An increased prevalence of cesarean sections was indicated to be one of the underlying causes of TTN and certain studies have mentioned genetic predispositions as another factor.[11] Reduced ENaC activity or ENaC immaturity on the apical surface of the pulmonary epithelium is one of the causes of TTN.

The BPA levels obtained in this study cannot clearly reflect intrauterine exposure because of the short half-life of BPA. However, there are no studies on the half-life of BPA in neonates. In addition, glucuronidation in the liver must work adequately for the removal of BPA from the body. As well known, neonates are insufficient in glucuronidation.[28] Therefore, urine BPA levels obtained in the early postnatal period raise the question of whether intrauterine reflection may occur. For this reason, there is a need for publications that will comprehensively investigate the relationship between amnion samples obtained from pregnant women in different trimesters and intrauterine exposure to BPA levels and TTN.

The control group was matched for gender, cesarean section, week of pregnancy, birth weights, and low birth weight for gestation.[10] This prevented the need for correcting the data for these variables while investigating the relationship between TTN and BPA.

BPA is also a known endocrine disruptor, but in this study no abnormal findings were observed in the genitourinary system examinations of any of the newborns.

Most of the mothers in this study had no idea about BPA and its possible harms. Although this was not measured, it could be because of the low educational status of the patients served at our hospital. It is necessary to raise societies awareness about this issue.

In lung cell culture studies; BPA is a pro-inflammatory factor via the estrogen receptor, and the BPA acts on the estrogen receptor to activate the Nuclear Factor kappa B signaling pathway. Nuclear Factor kappa B signaling pathway decreases glucocorticoid receptor activity. Therefore, ENaC expression is suppressed in lung epithelial cells. Studies have reported that suppression is temporary (8), but there is no information about its duration. Further studies are needed on this subject.

While there was no statistical difference between the spot urine creatinine values of the newborns admitted to the NICU with TTN and those of the healthy neonates who were housed with their mothers (p=0.091), there was a statistically significant difference between their urine BPA and urine BPA/creatinine values (p<0.005). The ROC curve analysis comparing the TTN and control groups determined the cut-off value of urine BPA for TTN to be 1.18 μg/L (95% CI: 0.667–0.889, sensitivity: 78.1%, and specificity: 51.5%) and the cut-off value of urine BPA/creatinine to be 2.65 μg/g (95% CI: 0.727–0.930, sensitivity: 84.4%, and specificity: 66.7%).

Infants with TTN usually need non-invasive respiratory support.[29] However, those with a severe clinical course may also need invasive respiratory support.[30] The spot urine BPA and BPA/creatinine results of TTN patients who required non-invasive and invasive respiratory support were compared and it was found that these values were significantly higher in patients who required invasive respiratory support (p<0.005). The ROC curve analysis comparing the TTN patients who required invasive and non-invasive respiratory support determined the cut-off value of urine BPA for requiring invasive respiratory support to be 15.64 μg/L (95% CI: 0.568–1.000, sensitivity: 83.3%, and specificity: 96.2%) and the cut-off value for urine BPA/creatinine to be 19.10 μg/g (95% CI: 0.777–1.000, sensitivity: 83.3%, and specificity: 84.6%).

Studies on BPA and newborns have indicated that total or free BPA levels are minimal in urine during the first few postnatal days. Sayıcı et al.[31] determined the median total BPA level in infant (aged >45 days) urine samples to be 0.13 μg/L (range 0.02–0.44). To the best of my knowledge, there are no other studies that have assessed BPA levels in urine samples collected within the first few hours of birth. However, many studies have been conducted with infants. For instance, Völkel et al.[32] investigated total BPA levels in the urine samples of infants and found it to be 17.85 μg/L. Calafat et al.[21] determined this value to be 1.70 μg/L. Herein, the urine BPA levels were found to be 2.9 μg/L (1.2–7.5) in the study group and 1.2 μg/L (0.5–1.8) in the control group.

Nachman et al.[33] determined glucuronide-conjugated BPA levels up to 11.21 μg/L in the urine of 6-day-old newborns. In their study, Lee et al.[5] collected urine samples within 2 days of birth and determined urine BPA levels to be 4.75 μg/L (0.93–14.5). I believe that BPA, whose half-life is known as 6 hours, will be affected by postnatal exposures which could be the reason for different results in different studies. In fact, maternal nutrition may also be effective in breastfeeding mothers, however more extensive studies are needed on this subject.

To the best of my knowledge, this study is the first to investigate the relationship between TTN and BPA; hence, it was not possible to compare these results with similar studies. Studies have shown that the incidence of allergic asthma and wheezing were higher among individuals who developed TTN as newborns.[34,35] Moreover, in their study, Spanier et al.[36] demonstrated the association between neonatal BPA levels and developing asthma later in life. All of these studies have suggested an association between TTN, wheezing/asthma in older ages, and neonatal BPA levels.

The results obtained in the current study may have been associated with the ENaCs located on the apical surface of the pulmonary epithelium. However, the effects of BPA on newborns need to be further investigated by further studies with larger samples that extensively evaluate cell cultures.

Another point to consider is that the urine samples obtained within the first few postnatal hours may be more valuable, but the collection of urine samples from newborns is very difficult with a high likelihood of fecal contamination.

Studying BPA from the pregnant women's urine just before birth or from the cord blood could support the hypothesis of intrauterine BPA exposure. This is one of the shortcomings of this study. Further studies are needed to analyze BPA in cord blood and newborn urine.

In conclusion, BPA and BPA/creatinine values were higher in the urine of newborns diagnosed with TTN than in those of healthy newborns (cut-off values 1.18 μg/L and 2.65 μg/g, respectively), in samples collected within the first 6 hours after birth, which may be a reflection of intrauterine factors. Furthermore, among patients with TTN, the prognosis of the patients with higher urine BPA levels was more severe.

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Ethical approval

The study was granted ethical approval by the Ethics Committee of Gaziantep University Şahinbey Training and Research Hospital (No:2019/476).

Author contribution

The author confirm contribution to the paper as follows: study conception and design: MB; data collection: MB; analysis and interpretation of results: MB; draft manuscript preparation: MB. The author reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The author declares that there is no conflict of interest.

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