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Assessment of Risk Factors to Predict the Duration of Tachypnea in the Management of Infants Hospitalized with Transient Tachypnea of Newborns

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ABSTRACT:
Purpose: The aim of this study was to determine risk factors to predict the duration of tachypnea in the management of infants hospitalized with transient tachypnea of newborns (TTN).
Material and Methods: This prospective study included newborns diagnosed with TTN separated into two groups of those with tachypnea lasting <72 hrs (Group 1) or ≥72 hrs (Group 2). The two groups were compared in respect of clinical and laboratory findings.
Results: The newborns in Group 2 were observed to have a lower birth weight and lower gestational age, and higher rate of SGA. These infants were determined to have a higher rate of antenatal steroid administration, longer duration of ventilation, and longer hospital stay. The cord blood gas oxygen levels were significantly lower in Group 2, TSH levels and the hemogram parameters of WBC, and PCT levels were significantly higher in Group 1.
Conclusions: Assessment of cord blood gas oxygen levels may be useful in predicting the clinical course of TTN.
Keywords: *Newborns, Transient tachypnea of newborns, Predictive factors, Prolonged tachypnea*

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INTRODUCTION

Transient tachypnea of the newborn (TTN) is the most common cause of respiratory distress in newborns (Keleş et al., 2013). It is believed that TTN is the result of delayed absorption of fetal pulmonary fluid from the pulmonary lymph system. Therefore, TTN is generally a self-limiting illness, but hypoxemia, respiratory failure, and pulmonary air leakage syndromes can increase the risk of morbidity (Derbent et al., 2011). However, with supportive therapy, TTN resolves itself spontaneously within days. As a result, TTN is a pulmonary disease with a good prognosis (Çakan et al., 2011). The estimated impact of this condition is between 0.5% and 2.8% of total deliveries (Derbent et al., 2011). Risk factors that play a role in the development of TTN; low birth weight, male gender, low gestational age, cesarean section (CS), low APGAR scores, perinatal asphyxia, maternal asthma, and maternal sedation (Kahvecioğlu et al., 2016).

Although the etiology and pathogenesis of TTN are still not fully understood, a delay in the absorption of lung fluid is considered to be the main problem. The presence of adequate fetal lung fluid is critical for normal pulmonary development during pregnancy. The fetal-lung fluid must be cleaned immediately after delivery, so that the fetus can complete the transition to extra-uterine life. This process begins 2-3 days before delivery. With the onset of labor, the basolateral membrane Na-K-ATPase in the pulmonary epithelium and the apical membrane Cl^- and Na^+ channels transform from a chloride-

releasing membrane to a sodium-absorbing membrane by reversing the lung fluid flow direction. At birth, oxygen, epinephrine, glucocorticoids and thyroid hormones interact, increasing the Na bearing ability of the epithelium and increasing the gene expression of the Na epithelial canal (ENaC). The inability of the fetal lung to shift from fluid secretion to fluid absorption the stage and immaturity of the expression ENaC can play an important role in the development of the TTN (Kasap et al., 2008; Neubauer, 2001). Other theories include pulmonary capillary leak syndrome resulting from mild asphyxia and myocardial dysfunction causing high filling pressures.

The diagnosis of TTN is made from follow-up in the first 6 hours and lasting for at least 12 hours, with chest x-ray showing compliance changes (increased ventilation, vascular congestion, fluid in fissures and costophrenic angle, flattened diaphragm) responding to ≤40% oxygen therapy. Other diseases that may cause respiratory distress (respiratory distress syndrome, meconium aspiration, neonatal sepsis, hypoglycemia, hypocalcemia, polyctemia, and congenital heart disease) should be eliminated (Çakan et al., 2011; Vanhole et al., 1997).

During treatment, newborns are monitored and oxygen support is given, with subsequent close follow-up for signs of tachypnea and other respiratory distress. If necessary, antibiotic treatment is administered in a laboratory and culture results are available. Tachypnea can resolve in 3 to 5 days if there are no complications (Çakan et al., 2011). The treatment of TTN is oxygen, nasal continuous positive airway pressure (NCPAP), asynchronous nasal intermittent mandatory ventilation (NIMV), and in some cases, intubated mechanical ventilation support (Coşar et al., 2016).

The decision for respiratory support treatment in newborns diagnosed with TTN in the neonatal intensive care unit (NICU) is difficult for caregivers of first- and second-level NICUs. The use of additional diagnostic tools that can assist neonatologists in the diagnosis and management of TTN will therefore be beneficial for the initiation of prompt and accurate treatment. Cord blood gas analysis may be one of the methods that can be used for this purpose so it was evaluated in this study as it has not been adequately addressed previously in literature. The aim of this study was to determine risk factors to predict the duration of tachypnea in the management of infants hospitalized with transient tachypnea of newborns.

Materials and methods

Purpose and Type of the Study

This prospective study enrolled preterm and term infants born at >34 weeks of gestation who were diagnosed with TTN between November 1, 2020, and November 1, 2021, in the newborn intensive care unit (NICU) of Sivas Cumhuriyet University. This study was approved by the Local Ethics Committee.

Sampling and Participant

Infants were excluded from the study if born at 34 weeks weighing <1,500 g, if diagnosed with perinatal asphyxia, meconium aspiration syndrome, congenital anomaly, metabolic disease, sepsis, taking antibiotics, congenital infection associated with TORCH complex (toxoplasmosis, others, rubella, cytomegalovirus, herpes), respiratory distress syndrome, congenital cardiac diseases, or non-respiratory reasons (hypocalcemia, persistent hypoglycemia, polycythemia) (Figure 1).

Data Collection Tools

For the infants included in the study, a record was made of birth weight, gender, gestational age, rate of small for gestational age (SGA), mode of delivery, maternal antibiotic use, antenatal steroid use, Apgar score, need for resuscitation during delivery, hemogram; leukocyte (WBC), procalcitonin (PCT), hemoglobin (Hb), thrombocyte (PLT), blood biochemistry (c-reactive protein) CRP, BUN, creatinine, sodium (Na), potassium (K), cord blood gases, Pa chest X-ray findings, , duration of tachypnea, respiratory rate, antibiotics used, blood culture, and perinatal risk factors. In terms of perinatal risk factors, it was questioned whether the mother had diabetes, asthma, multiple pregnancies, prolonged labor, pre-eclampsia, or any uterine anomaly.

Determination of cord blood gases

Cord blood samples (umbilical artery and vein) were collected in pre-heparinized 1 cc. syringes, capped

and transported to the laboratory. The acid-base status was determined within 10 min. of delivery with the ABL 90 FLEX blood gas analyzer (Radiometer Medical A/S, Denmark)

Definition of TTN

Transient tachypnea was defined as tachypnea that started within the first 6 hours after birth and continued for at least 12 hours with chest x-ray changes consistent with TTN (increased aeration, vascular congestion, fluid accumulation in fissures, and costophrenic angle).

Respiratory support therapy

Respiratory support was provided using conventional mechanical ventilation or non-invasive mechanical ventilation (NIMV). As the NIMV mode, nasal continuous positive airway pressure (nCPAP) or nasal intermittent positive pressure ventilation (NIPPV) mode was selected. The initial settings in both modes were frequency 40 breaths/min, positive end-expiratory pressure 5-6 cm H_2O, positive peak inspiratory pressure 18-20 cm H_2O, FiO_2 rate measured by pulse oximetry, and partial arterial oxygen saturation set to be 90 -95% for preterm and 95-99% for term infants. The TTN scoring system was used to assess the respiratory status of the infants (Malakian et al., 2018).

Peak inspiratory pressure was kept at a minimum, providing normal blood gas values (PCO_2: 40-50 mmHg and pH: 7.25-7.40). Blood gas analysis was performed in the first hour of mechanical ventilator support and then at four-hour intervals, and when normal blood gas normal values were reached (PCO_2: 40-50 mmHg and pH: 7.25-7.40), the frequency was gradually reduced to 20 breaths/minute. The criteria for termination of mechanical ventilator support were as follows: absence of respiratory acidosis in blood gas (PCO_2: ≤50 mmHg and pH ≥7.25); 90-95% oxygen saturation without pressure source; and respiratory rate <60/min in the absence of groaning and retraction. Recovery from TTN was accepted as the absence of clinical signs of respiratory distress, transcutaneous oxygen saturation >90% and respiratory rate <60/min without oxygen support.

The patients were grouped according to the duration of tachypnea as <72 hrs (Group 1) or ≥72 hrs (Group 2). The groups were compared in respect of the above-stated parameters.

Statistical Analysis

The study data were statistically analyzed using the IBM SPSS 23 (US) software. Data were examined with descriptive statistical tests. The normality of numerical variables was examined with the Shapiro-Wilk test. Descriptive measurements were expressed as numbers and percentages for categorical and median variables with interquartile range values for data that did not have a normal distribution. Non-parametric tests were applied to data that were not consistent with the normal distribution; the Mann-Whitney-U test for numerical data and the chi-square test for categorical data. A value of $p<0.05$ was considered statistically significant. A logistic regression analysis was used to identify independent factors affecting NICU admission due to TTN.

Ethical Approval

Before the research was conducted, the study proposal was submitted to the Sivas Cumhuriyet University Clinical Research Ethics Committee and approval decision dated 23.09.2020 and numbered 2020-09/10 was taken. Written permission was obtained from the management of division of neonatology, department of pediatrics, Sivas Cumhuriyet University Faculty of Medicine in Turkey, where the research would be conducted, and from the patients.

Results

In this prospective study all the cases were newborns diagnosed with TTN after delivery at Cumhuriyet University Hospital between November 1, 2020, and November 1, 2021. A total of 1215 newborns were admitted to the NICU during the study period, of which 1013 were excluded; newborns with major congenital anomalies (n= 4), perinatal asphyxia (n=20), or diseases other than TTN (n=989). Thus, analysis was made of a total of 202 newborns diagnosed with TTN, as 113 with tachypnea lasting <72 hrs, and 89 with tachypnea lasting ≥72hrs (Figure 1). The demographic and clinical data of both groups are shown in Table 1. The comparisons of cord blood gas analyses between the two groups of infants with

TTN are shown in Table 2. As seen in Table 3, the TSH thyroid hormone level was significantly higher in Group 1. The factors affecting NICU admission are shown in Table 4. WBC and PCT levels were determined to be significantly higher in Group 1 than in Group 2 (Table 5).

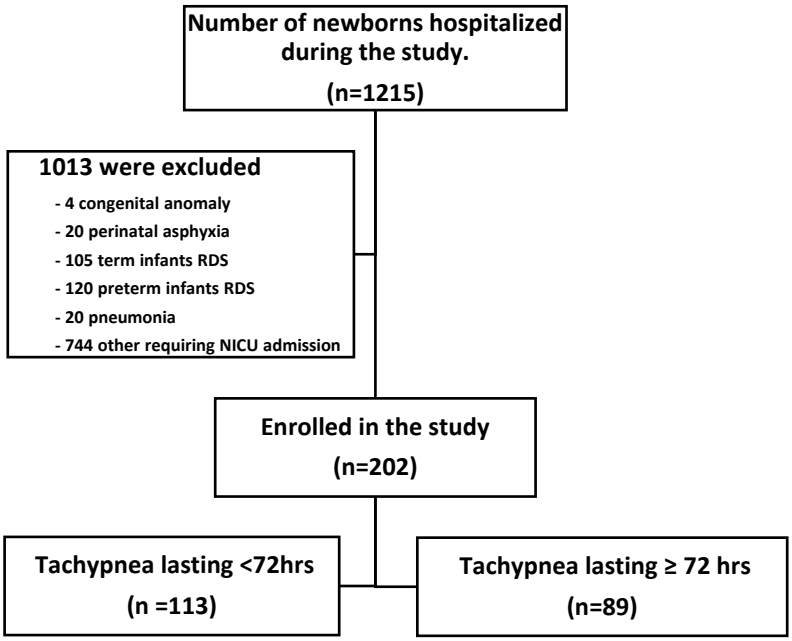

Figure 1. Flow diagram of the study

Table 1. Clinical characteristics of the study groups

Characteristics	Tachypnea lasting < 72 hrs (n =113)	Tachypnea lasting ≥ 72 hrs (n=89)	p value
Gender, n (%)			
Male	61 (54%)	52 (58%)	0.797
Female	51 (46 %)	37 (42%)	
Birth weight (g)	2823 (2357-3362)	2260 (1938-2742)	0.000
Gestational age (w)	37 (34-39)	34 (33-36)	0.000
Term/preterm, n (%)	59 (52%) /54 (48%)	19 (21%) /70 (79%)	0.000
SGA, n (%)	4 (3.5%)	13 (14%)	0.004
Apgar score, 5 min	8 (8-9)	9 (8-9)	0.148
Delivery mode			
Cesarean (%)	97 (85%)	82 (92%)	0.119
Birth action, n (%)	13 (12%)	15 (16%)	0.187
Presence of complicated pregnancy	7 (6%)	10 (11%)	0.056
Antenatal steroid administration,	28 (24%)	40 (45%)	0.002
Mode of Ventilation Therapy			
CPAP	6 (5%)	1 (1%)	0.142
NIPPV	63 (55%)	48 (54%)	
Duration of ventilation (d)	2 (1-2)	3 (2-4)	0.001
Modified Silverman score, median (range)	5 (3-7)	6 (3-8)	0.244
Duration of Hospital Stay, (d)	8 (6-11)	13 (11-18)	0.000

Mann–Whitney U test or t-test was used for data analyses. Data are stated as median with interquartile range values.
SGA: Small-for-gestational age, LGA: Large for gestational age, CPAP: Continuous positive airway pressure, NIPPV: Nasal intermittent positive pressure ventilation.

Table 2. Comparison of cord blood gas analyses between the two groups with TTN

Cord blood gases	Tachypnea lasting < 72 hrs (n =113)		Tachypnea lasting ≥ 72 hrs (n=89)		P values
	Mean± SD/n-%	Median	Mean ±SD/n-%	Median	
pH	7.31±0.08	7.32 (7.28-7.37)	7.33±0.06	7.34 (7.29-7.38)	0.543
PCO_2 (mm Hg)	42.7±9.9	41 (37-46)	42±8.5	42 (36-46)	0.827
PO_2 (mm Hg)	44±21.9	40 (32-48)	37±15.1	37 (28-42)	0.028
Lactate (mmol/L)	3.1±3.06	2.2 (1.8-3)	2.5±1.6	2.1 (1.5-2.9)	0.137
HCO_3 (meq/L)	23.3±21.5	21 (20-22)	21.2±2.38	21 (20-22)	0.943
BE (mmol/L)	-3.3±3.8	-3 (-5- -2)	-2±3.3	-3 (-4- -0)	0.073

Mann–Whitney U test/t-test. Data are expressed as mean±SD, and median with interquartile range values.

Table 3. Comparisons of thyroid hormone levels and transient tachypnea of the newborn

	Tachypnea lasting <72 hrs (n =113)	Tachypnea lasting ≥ 72 hrs (n=89)	P values
T4 level (ng/dL)			
Mean ±SD/n-%	1.44±0.30	1.40±0.37	0.466
Median	1.44 (1.19-1.73)	1.37 (1.14-1.66)	
TSH level (mIU/L)			
Mean ±SD/n-%	5.39±4.30	3.88±4.63	0.014
Median	3.83 (2.26-7.78)	2.88 (1.79-3.81)	
Male sex (n,%)	61 (51.6%)	52 (62.8%)	0.639

Data are reported as mean± SD and median with interquartile range, statistical significance determined by the Mann–Whitney U test, and frequency (%) with statistical significance analyzed by the Chi-square test.

Table 4. Factors affecting neonatal intensive care unit admission of TTN neonates, according to the duration of tachypnea.

Factor	Tachypnea lasting < 72 hrs (n =113)			Tachypnea lasting ≥ 72 hrs (n=89)		
	OR	95%CI	P	OR	95%CI	P
Gestational age	0.844	0.694-1.027	0.090	0.841	0.703-1.006	0.058
Male sex	0.839	0.482-1.460	0.534	0.838	0.481-1.460	0.534
T4 level	0.931	0.244-3.550	0.931	0.917	0.244-3.550	0.917
TSH level	0.937	0.848-1.036	0.937	0.938	0.852-1.034	0.199

Table 5. Comparison of hemogram parameter levels and transient tachypnea of the newborn

Hemogram parameters	Tachypnea lasting <72 hrs (n =113)	Tachypnea lasting ≥72 hrs (n=89)	P values
WBC (10^3/uL)			
Mean ±SD/n-%	17353±19332	14957±15161	0.009
Median	15700 (10760-19740)	12410 (10000-16470)	
Hb (g/dL)			
Mean ±SD/n-%	17.75±2.75	17.86±3.16	0.889
Median	18 (16-19)	18 (16-19)	
PLT (x 1,000/mm^3)			
Mean ±SD/n-%	290594±68429	297402±91334	0.744
Median	287000 (255000-332000)	292000 (246000-342000)	
CRP (mg/dl)			
Mean ±SD/n-%	3.2±0.38	2.86±4	0.954
Median	1.1 (0.38-3.4)	1.4 (0.37-3.15)	
PCT (ng/dl)			
Mean ±SD/n-%	1.34±5.7	0.33±0.91	0.028
Median	0 (0-0)	0 (0-0.18)	

Data are reported as mean± SD and median with interquartile range values, statistical significance determined by the Mann–Whitney U test.

WBC: White Blood Cells, Hb: Hemoglobin PLT: Thrombocyte, CRP: C-reactive protein, PCT: Procalcitonin

Discussion

The results of this prospective study demonstrated that the newborns in Group 2 (tachypnea lasting ≥72 hrs) have a lower birth weight and lower gestational age, and higher rate of SGA compared to those in Group 1. These infants also had a higher rate of antenatal steroid administration, longer duration of ventilation, longer hospital stay, lower cord blood gas oxygen levels, and lower TSH levels. In terms of hemogram parameters, the WBC and PCT levels were significantly higher in Group 1.

In previous studies, male gender, C/S delivery, low Apgar score, acidosis, and myocardial dysfunction have been stated as risk factors for prolonged tachypnea and TTN of the newborn has been reported to occur more frequently in preterm births and male infants (Kasap et al., 2008). The significant gender difference may be attributable to differences in lung growth and maturation in males and females, resulting in different susceptibilities. In another study, most of the newborns diagnosed with TTN were found to be male and delivered by cesarean section (Malakian et al., 2018). In the present study, gender was not seen to be a risk factor for the duration of tachypnea in TTN. However, most new with TTN were delivered by C/S, with a statistically significant difference determined between premature and term C/S rates.

Consistent with the reports of more frequent TTN in preterm births and male infants (Kasap et al., 2008; Malakian et al., 2018), the current study results showed significantly higher rates of TTN in preterm infants. It has been estimated that TTN is determined in approximately 10% of infants born at 33-34 gestational weeks and in 5% of those born at 35-36 gestational weeks. Although TTN is detected in premature infants, there are difficulties in differential diagnosis with RDS (Alhassen et al., 2021). In a multicenter double-blind study, a reduction in respiratory support therapy, mortality rate, surfactant use, bronchopulmonary dysplasia rate, and respiratory complications were found in newborn infants of $34^{0/7}$-$36^{6/7}$ weeks gestational age when beta-methasone injection was compared with a placebo treatment group (McDonald, 2017).

In the current study, cord blood PO_2 level was found to be significantly higher in Group 1. Cord blood gas data provides objectively correct information in the evaluation of the intrapartum hypoxic status of the infant and the fetal situation immediately before delivery (Blickstein & Green, 2007). Umbilical arterial blood best reflects fetal oxygenation and acid-base status, while blood gas measurements of the umbilical vein better reflect maternal status and placental function (Di Tommaso et al., 2014). In the study by Nodwell et al., the blood gases pH, O_2 saturation and hemoglobin were studied with the catheter they placed in the umbilical cord artery, vein, and placental cord. In this study; It was found that partial oxygen pressure (PO_2) and O_2 saturation were lower in the placental vein than in the umbilical vein, and that the PCO_2 was lower and the pH was higher in the placenta (Nodwell et al., 2005). It was reported in that study that placental cord blood provides an accurate estimation of fetal base excess and hemoglobin concentration at birth, but the measurement values for PO_2, O_2 saturation, PCO_2 and pH may be incorrect for reasons such as delayed cord clamping and cord compression. Tommaso et al. reported no significant difference in pH, PO_2, pCO_2, SaO_2 and Hb values in arterial blood between unclamped and clamped cords (Di Tommaso et al., 2014). In a study by Şener et al., cord pH and PO_2 levels were found to be significantly higher in newborns with high Apgar scores, and the rate of newborns hospitalized in the NICU with respiratory distress was significantly lower in this group (Şener et al., 1996).

The ongoing study describes a combination of thyroid hormones and TTN. The neonates with TTN lasting <72 hrs were seen to have significantly higher TSH levels than those with tachypnea lasting ≥72 hrs. Kayıran et al. found higher TSH levels in newborn infants with term TTN compared to the control group (Kayıran et al., 2019). Inability to fully mature hypothalamic-pituitary-thyroid axis may cause this delay in adaptation to extrauterine life (Fisher et al., 2000). In the current study, the serum T4 level was also low in the group with prolonged tachypnea, but not at a statistically significant level. This may have been due to the small size of the study group and the fact that it was a single-center study. Free and total T4 levels are low in premature infants and increase with gestation (Hume et al., 2004). There is a TSH

fluctuation that causes T4 concentrations higher than intrauterine periods in the first 4-5 days after delivery (Kayıran et al., 2019). Ulanovsky et al. reported an average T4 concentration below 14.4 µg/dl for early and term TTN newborns in blood samples taken 40 to 48 hours after birth (Ulanovsky et al., 2016). Similar to this study, Kayıran et al. detected serum T4 levels close to 13.9 ±2.9 µg/dl in newborn with TTN (Kayıran et al., 2019). According to Vanhole et al. low levels of thyroid hormones have been reported as associated with increased severity of the disease during the neonatal period (Vanhole et al., 1997). Paul et al. found that an inverse relationship between serum T4 levels and disease severity in their study on term and late premature infants (Paul, Mackley, & Yencha, 2010). Thyroid hormone therapy was not started in our newborns during the study, and only the effect of thyroid hormone level on TTN duration was examined. Considering the transient hypothyroidism that can be seen in newborns during this period, we did not initiate hormone therapy in any of our newborns whose thyroid function tests were checked.

In the present study, the WBC and PCT values of Group 1 were significantly higher than those of Group 2. In patients with clinical suspicion of sepsis, antibiotherapy was initiated, but as there was no culture positivity, antibiotherapy was terminated in the early period. Empirical antibiotic therapy for probable pneumonia is recommended for all neonates presenting with respiratory distress, as the clinical manifestations of TTN are not disease-specific and may be a precursor to other more serious respiratory tract pathologies (Weintraub et al., 2013).

However, this recommendation is not evidence-based. In order to minimize the emergence of resistant organisms, it has been standard practice to avoid starting antibiotics for sepsis in neonates with uncomplicated TTN without past risk factors or clinical suspicion of sepsis. An important benefit of strict antimicrobial management in neonates is the impact on the gut microbiome and immune system that develops as a result of perinatal antibiotic exposure. Newborn microflora is affected by many antenatal and postnatal factors such as maternal vaginal and gastrointestinal flora, mode of delivery, gestational week, nutrient source (breast milk, formula, parenteral nutrition), and antibiotic exposure(Palmer, Bik, DiGiulio, Relman, & Brown, 2007). It has been concluded that decisions about antimicrobial therapy should not be based on inflammatory markers alone such as C-reactive protein (CRP), cytokines (e.g. IL-6), and other acute-phase reactants (Bozkaya, Yiğit, & Yurdakök, 2019). Procalcitonin (PCT) is an inflammatory marker which has been reported to be useful in identifying bacteremia in children with pneumonia. (Machado et al., 2014). In a study by Bozkaya et al., statistically significant WBC and CRP levels were not detected in the TTN group, but the PCT level was found to be significant in terms of differential diagnosis in neonatal pneumonia (Bozkaya et al., 2019). In previous studies, no relationship was found between TTN and leukocyte count (Kasap et al., 2008). Catecholamines and steroids, which are thought to have an effect on the pathogenesis of TTN and cannot be secreted sufficiently at birth; The lack of these hormonal effects which would cause leukocyte levels to rise may have caused leukocyte levels to be low in these patients.

The study contained some limitations. First, this study had a prospective single-center design and included a relatively small sample size. Other limitations were that serum thyroxin samples were taken following TTN resolution, and it was not blinded because of the lack of block randomization. Larger prospective studies are needed to confirm these findings, to determine the factors influencing neonatal admission of newborns with TTN, and therefore to organize treatment.

In conclusion, assessment of cord blood gas oxygen levels can be helpful in predicting the clinical evolution of TTN. During the laboratory work-up and management of prolonged TTN in preterm and term infants, neonatologists need to consider the cord blood gas levels and the possibility of higher serum TSH values, and lower serum T4 levels with decreasing gestational age. Further studies with a larger sample, and assessment of these laboratory findings in terms of gestational age will be able to provide nomograms of cord blood gas levels and serum thyroxine levels.

Conflict of Interest

The authors declare no conflicts of interest.

Contributors

FK: Concept and designed the study, analyzed data and drafted the manuscript; GT: Collected the data and helped in data analysis; GÜ: Supervised cognitive and behavioral assessments.

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