Arch Iran Med. August 2020;23(8):530-535

doi 10.34172/aim.2020.55

http://www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

Open Access

Original Article

Comparison of Umbilical Cord Serum Vitamin D Levels between Infants with Transient Tachypnea of the Newborn and those without Respiratory Distress

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Abstract

Background: Transient tachypnea of the newborn (TTN) is one of the most frequent causes of respiratory distress in neonates. A relationship has been shown between vitamin D deficiency and respiratory disorders in neonates. This research was carried out to evaluate the serum level of vitamin D in TTN newborns and their mothers compared to the control group.

Methods: This case-control research was conducted during 2016-2019 in a general hospital affiliated with Mashhad University of Medical Sciences, Iran. Thirty-four infants with TTN and 82 neonates in the control group as well as their mothers were investigated. The levels of umbilical cord serum vitamin D in infants with TTN and also their mothers were compared to the control group.

Results: The mean levels of serum vitamin D in infants with TTN and their mothers were 8.11 ± 4.32 and 12.6 ± 10.12 ng/mL, respectively ($P<0.001$), whereas they were 19.21 ± 12.71 and 25.96 ± 16.6 ng/mL in the newborns of the control group and their mothers, respectively ($P<0.001$). The mean differences (95% CI) of neonatal and maternal vitamin D level between the two groups were 11.10 (7.92–14.28) and 13.36 (7.90–18.08), respectively. In the TTN group, 100% of the infants had vitamin D levels less than 30 ng/mL (79.4% had severe, 17.6% had moderate and 2.9% showed mild deficiency). However, vitamin D levels lower than 30 ng/mL were observed in 76.4% of the neonates in the control group (28.8% had severe, 31.1% showed moderate and 16.3% had a mild deficiency) ($P<0.001$).

Conclusion: The serum vitamin D levels of infants with TTN and their mothers were significantly lower than the control group. Therefore, TTN in infants may be reduced through the treatment of vitamin D deficiency in mothers.

Keywords: Newborn, Respiratory distress, Transient tachypnea of the newborn, Vitamin D deficiency

Cite this article as: Boskabadi H, Maamouri G, Kalani-moghaddam F, Ataee Nakhaei MH, Zakerihamidi M, Rakhshanizadeh F. Comparison of umbilical cord serum vitamin D levels between infants with transient tachypnea of the newborn and those without respiratory distress. Arch Iran Med. 2020;23(8):530–535. doi: 10.34172/aim.2020.55.

Received: August 18, 2019, Accepted: June 2, 2020, ePublished: August 1, 2020

Introduction

Transient tachypnea of the newborn (TTN) is one of the most frequent causes of respiratory distress in neonates, which involves 3.6 to 5.7 infants per 1000 term newborns. The onset of tachypnea or the evidence of respiratory distress is regarded as clinical manifestations of TTN. Such presentations can be seen within the first hours of life and resolve spontaneously within 72 hours with no need for any intervention; however, serious complications are possible in some cases.[1] TTN results from delayed postnatal clearance of fetal lung fluid. The passive transport of sodium through the epithelial sodium channels (ENaCs) in type II pneumocytes is the accepted mechanism for fetal lung fluid clearance. Following adrenergic stimulation before labor and epinephrine release, ENaC is activated and calcium ions may act as a secondary intracellular messenger in this process. When sodium enters type II pneumocytes through the ENaC channel, it migrates toward the interstitial space via the basolateral Na/K ATPase, resulting in water and chlorine passive efflux.[2-4] Immaturity of the ENaCs is considered as the main reason for the failure of lung fluid reabsorption.[5,6] Although the pathophysiology of TTN is basically associated with delayed clearance of lung fluid, mild insufficiency of the surfactant system has been shown to reduce the amount of surfactant and/or its function. Therefore, TTN may be a multifactorial disease caused by delayed clearance of lung fluid and varying degrees of surfactant abnormalities.[7]

TTN is known to be associated with certain risk factors, including cesarean delivery, male gender, history of asthma or diabetes mellitus in the mother, macrosomia, and late preterm birth.[1,8] Recently, the correlation between TTN

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and maternal and neonatal vitamin D deficiency has been indicated in two studies.[9,10]

Vitamin D is a steroid hormone which is essential for the balance of minerals, bone metabolism, and neuromuscular function. In recent years, due to the identification of vitamin D receptors in different cells of the body, other effects of this vitamin have been identified increasingly. Several studies have demonstrated that vitamin D plays a vital role in regulation of more than 1000 genes involved in many biological processes, including angiogenesis, inflammation, and immune function.[11,12] It has been also shown that it is crucial to the development of fetal lung via different mechanisms, such as surfactant metabolism, epithelial-mesenchymal interactions, and calcium regulation in type II pneumocytes.[13-15]

The maternal vitamin D level is a determinant factor for its concentration in the fetus and infant.[16] Vitamin D deficiency has been widely reported throughout pregnancy and is associated with increased risk of poor fetal growth,[17] neonatal sepsis,[18] and higher rate of respiratory tract infections.[19] Respiratory distress syndrome (RDS), retinopathy of prematurity (ROP) and cerebral hemorrhage are other common newborn problems in which vitamin D is involved.[20,21] The relationship between vitamin D and TTN has not been studied widely; accordingly, this research was done to evaluate the serum levels of vitamin D in TTN newborns and also their mothers and compare them to a control group.

Materials and Methods

This case-control research was conducted during 2016–2019 in a general hospital affiliated with Mashhad University of Medical Sciences, Iran. The sample size was estimated at 34 patients, based on a study by Singh *et al.*[22] through two independent samples formula in infants with TTN (Mean ± SD: 11.32 ± 8.2) and infants without respiratory distress (22.66 ± 13.15), type I error (alpha) of 1%, and power (beta) of 90%. All preterm neonate (gestational age <37 weeks) born in this time period and their mothers were entered to the study consecutively. The following potential confounders were considered as the exclusion criteria: apparent congenital anomalies, congenital infections, severe asphyxia, cardiopulmonary resuscitation in the delivery room, infants with respiratory distress who did not meet the TTN criteria, and history of maternal substance abuse, diabetes or asthma. Those diagnosed with TTN and also their mothers were assigned to the case group. The control group included infants who did not meet the TTN criteria and had no respiratory distress, alongside their mothers. TTN was diagnosed in the infants based on the presence of clinical conditions (tachypnea/retraction of the accessory muscles of respiration/ grunting/ nasal flaring) through the first hours of birth lasting for more than 12 hours and resolving spontaneously within 48–72 hours. The changes observed in chest X-ray images included perihilar streaking, fluid in the interlobar fissure, hyperinflation and flattening of the diaphragm, and other causes of respiratory distress (such as pneumonia, RDS and pneumothorax) were ruled out.[1]

A researcher-made checklist was used to collect the demographic information of neonates and their mothers, such as delivery method, birth weight, maternal age, gestational age, gender, underlying maternal-related conditions (high blood pressure, asthma, diabetes, etc), pregnancy-related complications, parity, a history of respiratory problems in siblings, a history of vitamin D supplementation during pregnancy, first- and fifth-minute Apgar score, clinical signs of the infant on admission (tachypnea, retraction of the accessory muscles of respiration, nasal flaring, grunting and hypoxia), need for resuscitation and ventilation, duration of oxygen therapy and duration of hospitalization in the neonatal intensive care unit (NICU).

From the infants, 1.5 mL of whole blood was collected from the umbilical cord to measure vitamin D levels. Blood samples were also taken from mothers for the same purpose. Samples were centrifuged and the collected serum samples were stored at -20°C and sent to the laboratory for further analysis. The enzyme-linked immunosorbent assay (ELISA) through ELISA Reader (model RT2100c, Germany) was employed to evaluate the serum levels of 25-hydroxyvitamin D. A vitamin D level of less than 30 ng/mL was considered as vitamin D deficiency. Levels less than 10 ng/mL were considered as severe, 10 to 20 ng/mL as moderate and 20 to 30 ng/mL as mild deficiency.[23]

After collecting data and entering data into SPSS version 23, tables, figures, and statistical indices were used to analyze the results and evaluate the relationship between variables. For this purpose, after checking the normal distribution of data, Pearson's correlation coefficient and independent *t* test were used for normally distributed data. For non-normally distributed data, non-parametric statistics, including the Mann-Whitney coefficient was used. To analyze the relationship between variables and nominal scale, the Chi-square test was used. In the current study, *P* values less than 0.05 were considered significant.

Results

Thirty-four neonates with TTN and 82 neonates as the control group were evaluated. In the TTN group, 35.3% of the subjects were male and 64.7% were female, whereas in the control group, 44.9% were male and 55.1% were female. No significant difference was observed between the two groups in delivery method, maternal age, gestational age, birth weight, first- and fifth-minute Apgar score, underlying maternal conditions, and pregnancy-related complications ($P > 0.05$; Table 1). Blood cultures were negative for all subjects and there was no evidence of intra-ventricular hemorrhage on ultrasound imaging of the brain.

Table 1. Demographic Characteristics of the Study and Control Groups

Variable		Control Group	TTN Group	Mean Difference 95% (CI)	*P* value
		Mean ± SD/No. (%)	Mean ± SD/No.(%)		
Gestational age (wk)		32.64 ± 1.76	32.26 ± 1.56	0.381 (-0.309–1.072)	0.27
Apgar at first minute		7.53 ± 1.51	7.01 ± 1.52	0. 59 (-0.08–1.267)	0.09
Apgar at fifth minute		8.68 ± 1.12	8.44 ± 1.05	0.242 (-0.195–0.678)	0.28
Weight (g)		1535.4 ± 351.07	1606.61 ± 256.12	-71.21 (-187.7–45.29)	0.22
Maternal age (y)		28.04 ± 6.4	28.32 ± 6.45	-0.279 (-2.956–2.397)	0.83
Sex	Male	35 (44.9%)	12 (35.3%)		0.34
	Female	43 (55.1%)	22 (64.7%)		
Pregnancy complications	Yes	41 (50%)	21 (72.7%)		0.21
	No	41 (50%)	8 (27.3%)		
Type of delivery	NVD	49 (60.3%)	26 (%76.2)		0.16
	CS	32 (39.7%)	8 (23.8%)		

NVD, natural vaginal delivery; CS, cesarean section.

The average serum vitamin D level was 12.6 ± 10.12 and 25.95 ± 16.6 ng/mL in mothers in the TTN and control groups, respectively. In addition, the mean serum vitamin D level in neonates of the TTN group was 8.11 ± 4.32 ng/mL, whereas it was 19.21 ± 12.71 ng/mL in neonates of the control group (Table 2 and Figure 1).

In general, 69.5% of the mothers had vitamin D levels of less than 30 ng/mL (32.6% had severe, 29.5% had moderate, and 7.4% had mild deficiency). Among the infants, 83.4% showed vitamin D levels of less than 30 ng/mL (43.9% had severe, 27.2% had moderate, and 12.3% showed mild deficiency).

In the TTN group, 56% of the mothers showed severe and 27% showed moderate vitamin D deficiency, whereas it was 20% and 31% in mothers of the control group, respectively ($P = 0.002$). In the TTN group, 100% of the infants had vitamin D levels of less than 30 ng/ml (79.4% had severe, 17.6% had moderate and 2.9% showed mild deficiency). However, vitamin D levels of lower than 30 ng/mL were observed in 76.4% of the neonates in the control group (28.8% had severe, 31.1% showed moderate and 16.3% had mild deficiency), whereas 23.8% of them had normal levels ($P < 0.05$) (Table 3 and Figure 1).

Discussion

According to the results, about three quarters of the mothers and four fifths of the newborns had vitamin D deficiency, of whom 62% of the mothers and 71% of the infants showed significant (moderate and severe) vitamin D deficiency. The incidence of vitamin D deficiency has been reported at 30% to 88% in infants as well as mothers worldwide.[20-26] In a study in Iran, 552 mothers and infants were examined for serum vitamin D levels and the results showed that 66% of the mothers and 93% of the newborns had vitamin D deficiency.[27] Our findings demonstrated a high prevalence of vitamin D deficiency among Iranian mothers and newborns, which is consistent with the mentioned study. Accordingly, prevention and timely diagnosis of this concern should be considered. Several factors can be involved in the high incidence of vitamin D deficiency in the studied subjects, including lack of exposure to the sun, low maternal vitamin D intake (seafood, such as fish and shrimp) and prematurity in infants.

Vitamin D levels were significantly lower in mothers and infants in the TTN group compared to the control group. In fact, vitamin D levels were nearly 2.5 times greater in the infants without TTN as well as their mothers in

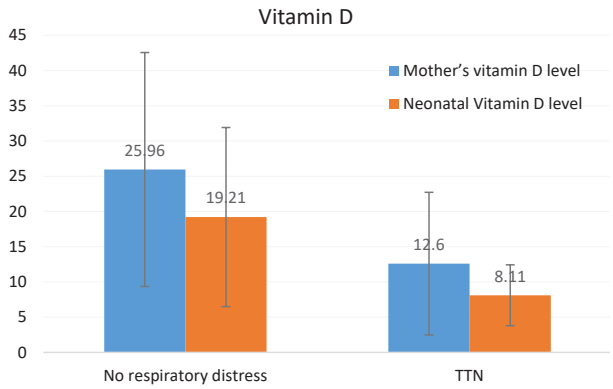

Figure 1. Comparison of Vitamin D Serum Levels between the Cases and the Controls.

Table 2. Mean and Standard Deviation of 25OHD Serum Level in the Neonates and the Mothers of Both Group

Variable	Total	Control Group	TTN Group	Mean Difference (95% CI)	*P* Value
		Mean ± SD	Mean ± SD		
Maternal vitamin D level	95	25.96 ± 16.6	12.6 ± 10.12	13.36 (7.9 – 18.08)	<0.001
Neonatal vitamin D level	114	19.21 ± 12.71	8.11 ± 4.32	11.1 (7.92 – 14.28)	<0.001

Table 3. Serum Levels of 25OHD in the Neonates and the Mothers of Both Group

Variable		Control Group No. (%)	TTN Group No. (%)	Test Results
Maternal vitamin D level (n = 95)	Severe vitamin D deficiency	12 (19.7)	19 (55.9)	$\chi^2 = 14.68$ *P* value = 0.001
	Moderate vitamin D deficiency	19 (31.1)	9 (26.5)	
	Mild vitamin D deficiency	6 (9.8)	1 (2.9)	
	Normal vitamin D level	24 (39.3)	5 (14.7)	
Neonatal vitamin D level (n = 114)	Severe vitamin D deficiency	23 (28.8)	27 (79.4)	$\chi^2 = 14.68$ *P* value < 0.001
	Moderate vitamin D deficiency	25 (31.3)	6 (17.6)	
	Mild vitamin D deficiency	13 (16.3)	1 (2.9)	
	Normal vitamin D level	19 (23.8)	0 (0.0)	

Severe vitamin D deficiency: the level of less than 10 ng/mL; Moderate vitamin D deficiency: 10 to 20 ng/mL; Mild vitamin D deficiency: 20 to 30 ng/mL; Normal vitamin D level: more than 30 ng/mL.

comparison to the other group ($P < 0.001$). Nearly 80% of the mothers in the TTN group had severe or moderate vitamin D deficiency, whereas it was 50% among mothers in the control group ($P = 0.002$). Moreover, moderate or severe vitamin D deficiency was observed in 97% of the newborns in the TTN group; however, 60% of the infants in the control group were suffering from moderate or severe vitamin D deficiency ($P < 0.05$). Fifty-one newborns with TTN and 59 healthy infants were evaluated for the level of vitamin D deficiency by Konca et al. They demonstrated that the average level of vitamin D was 5.8 ± 3.5 ng/mL and 8.7 ± 4.0 ng/mL in the newborns in the case and control groups, respectively ($P < 0.01$). They also concluded that lower serum vitamin D levels may be involved in TTN pathogenesis. Regarding the possible mechanism of this correlation, they noted that vitamin D deficiency may reduce the expression of ENaC and the synthesis of surfactants, which leads to TTN incidence.[9] Thirty infants with TTN and their mothers were studied for vitamin D deficiency by Omran et al. They compared the results with the control group and reported that there was a significant difference in vitamin D level between the two groups; vitamin D levels in the TTN infants and their mothers were 7.74 ± 3.17 and 15.05 ± 4.71 ng/mL, respectively, whereas in the control group, they were 16.08 ± 5.41 and 29.08 ± 5.41 ng/mL, respectively ($P < 0.0001$). They concluded that TTN can be linked to low blood levels of vitamin D.[10] Our findings indicating a correlation between vitamin D deficiency and TTN in newborns are consistent with the results obtained by these investigations.

The vital role of vitamin D in pulmonary maturation has been shown in recent animal studies.[28,29] They have explained that the structure and performance of the lungs can be affected by its deficiency in the fetus and the neonate.[30] A study by Nguyen et al in a rat model showed that 1, 25-dihydroxycholecalciferol, by activation of 1,6-bisphosphatase fructose and the gluconeogenesis pathway, reduces the glycogen content of cells and disrupts the synthesis and secretion of surfactants. So, lung maturity can be influenced by vitamin D levels.[14] The mechanisms by which vitamin D can affect fetal lung development were studied by Chen et al in a rat model. They reported that deficiency of vitamin D interferes with the structure and function of the lung by disrupting the production of surfactants, impairing the response to oxidative stress, and affecting the synthesis of collagen at the time of alveoli formation.[15]

The correlation between vitamin D deficiency and neonatal respiratory diseases has been considered in recent human studies, such as RDS as well as lower respiratory tract infection (LRTI). In this regard, it has been indicated that there is a correlation between vitamin D deficiency and increased risk of respiratory complications in mothers and newborns.[31,32] Dinlen et al studied the serum level of vitamin D in 30 neonates with LRTI and 30 healthy newborns admitted to the NICU. They showed that LRTI was correlated with vitamin D deficiency. They suggested that supplementing pregnant women with vitamin D and also supplementing through early childhood can be effective in respiratory system function in infants.[31] Another study was done on blood levels of vitamin D in 160 preterm neonates of less than 34 weeks' gestation with RDS and their mothers. The findings indicated that vitamin D levels in the case group were significantly less than the control group, indicating a significant association between vitamin D blood levels and RDS.[21]

Due to the limited numbers of studies on the relationship between vitamin D deficiency and TTN, the underlying mechanisms involved in this correlation have not been completely understood. The main cause of TTN is delayed lung fluid absorption at the time of birth, although studies have shown the decreased level of surfactants or their dysfunction. Due to the influence of vitamin D in lung function and maturation, its deficiency may affect the function of ENaC and reduce lung fluid reabsorption at birth. On the other hand, by affecting type II pneumocytes, the deficiency may also influence the synthesis and secretion of surfactants and ultimately, contribute to the incidence of TTN or other respiratory problems in infants. Such mechanisms can be suggested to explain the link between vitamin D deficiency and TTN

in newborns; however, further investigations should be conducted for confirmation or rejection.

Further studies with larger sample sizes may result in a better understanding of this association. The effectiveness of supplementing with vitamin D during pregnancy and also its preventive role against development of TTN was not evaluated in our research. No study has been yet done on the effect of vitamin D deficiency in the clinical progression and severity of TTN, which indicates the need for further studies in the future.

In conclusion, vitamin D in infants is not only effective in bone metabolism but also in various systems in the body, such as the respiratory system. There is a positive correlation between maternal and neonatal vitamin D deficiency; therefore, its deficiency in the mother can affect the neonate, as well. Based on our findings, the TTN group showed a significantly lower level of vitamin D than the control group. Nearly all TTN infants and fourth fifths of their mothers were suffering from severe and moderate deficiency. These findings emphasize the importance of vitamin D for lung maturation and function and it can be concluded that vitamin D deficiency may be involved in the prevalence of TTN. Accordingly, it seems that accurate management of vitamin D during pregnancy can possibly reduce the risk of TTN in infants.

Authors' Contribution

HB conceptualized and designed the study, drafted the initial manuscript, critically reviewed the manuscript, supervised data collection and approved the final manuscript as submitted. GAM carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. MZ carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. MA designed the study and carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. FR designed the data collection instruments, and coordinated and supervised data collection at two of the four sites, critically reviewed the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interests. The authors take full responsibility for the content and writing of this article.

Ethical Statement

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Approval code: IR.MUMS.MEDICAL.REC.1397.53) followed by obtaining the consent from the parents of studied infants.

Funding/Support

The Vice-Chancellor for Research of Mashhad University of Medical Sciences sponsored this research.

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