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Vitamin D Status in Preterm Neonates in The NICU of Al-Imamein Al-Kadhimein Medical City

Zainab A. Hussain[1] *FICMS*, **Areej A. A. Mohammad**[2] *CABP*

[1]Al-Imamein Al-Kadhimein Medical City, Baghdad Al-Karkh Health Directorate, Iraqi Ministry of Health, Baghdad, Iraq,
[2]Dept. of Pediatrics, Collage of Medicine, Al-Nahrain University, Baghdad, Iraq

Abstract

Background Vitamin D is a fat-soluble vitamin that played an important role in bone metabolism (mineralization). It was considered a prohormone and had important role in the optimal function of many organ systems and may be a risk modifying factor for many chronic diseases.

Objective To assess the level of vitamin D in preterm neonates and its relation with different neonatal and maternal factors.

Methods A cross sectional study conducted at the Neonatal Intensive Care Unit (NICU) in Al-Imamein Al-Kadhimein Medical City, in Baghdad during a period from 1st of march 2022 to 1st of October 2022, seventy preterm neonate admitted to NICU were included and divided into groups according to their gender, gestational age, cause of admission and maternal factors such as gravidity, maternal health and supplementation with vit D or not during pregnancy, and the neonatal serum vitamin D level was measured to assess its relationship with these different neonatal and maternal factors.

Results Among the total number of 70 preterm neonate included in current study, number of females were 33 (47.2%), males were 37 (52.8%). Vitamin D level in preterm neonates was significantly low in the group in whom mother did not take vitamin D supplement during pregnancy (mean 8.56) versus (11.54) in neonates whom their mothers supplemented with vitamin D during pregnancy. Regarding the maternal health, there was no significant association with neonatal vitamin D ($p = 0.08$), there were no significant association between maternal parity and neonatal vitamin D deficiency ($p = 0.091$). Regarding the neonatal factors there were no significant association between vitamin D level and the gender ($p = 0.47$), gestational age ($p = 0.2$) and cause of admission of the preterm neonates to neonatal intensive care unit ($p = 0.478$).

Conclusion There was significant relation between neonatal serum vitamin D level and maternal use of vitamin D supplement during pregnancy. No significant relation between serum vitamin D and neonatal gender, gestational age, cause of neonatal admission, maternal health and gravidity.

Keywords Preterm, gestational age, vitamin D.

List of abbreviations: ALP = Alkaline phosphatase, BPD = Bronchopulmonary dysplasia, BW = Birth weight, CBC = Complete blood count, CXR = Chest X ray, CHD = Congenital heart disease, GA = Gestational age, GDM = Gestational diabetes mellitus, GIT = Gastrointestinal tract, IDA = Iron deficiency anemia, LBW = Low birth weight, MBD = Metabolic bone disease, NEC = Necrotizing enter colitis, NICU = Neonatal intensive care unit, PDA = Patent ductus arteriosus, PTH = Parathyroid hormone

Introduction

Prematurity refers to neonates born at less than 37 weeks' gestation. Preterm birth is the leading cause of neonatal mortality and the most common reason for antenatal hospitalization [(1)]. The world health organization (WHO) defines term neonate from 37 completed weeks to less than 42 completed

weeks. Preterm birth as any birth before 37 completed weeks of gestation, or fewer than 259 days since the first day of the women's last menstrual period (LMP) and this can be further subdivided on the basis of gestational age: early preterm (28 - 32) weeks and late preterm (33 – <37) [2]. Low birth weight (LBW) is defined by WHO as a birth weight less than 2500 gm very LBW born weighing less than 1500 gm [3].

Vitamin D level in preterm neonates

Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism (mineralization). It is also considered a prohormone and has important roles in the optimal function of many organ systems and may be a risk modifying factor for many chronic diseases, including rickets, respiratory distress syndrome (RDS), and autoimmune disease like, type 1 diabetes [3,4,5]. Vitamin D receptors are present all over the human body, from bones and muscles to the central nervous system [6,7].

The main source of vitamin D for the body is sunlight exposure, but it can also be extracted from diet or food supplement such as fish oils. Maternal and neonatal vitamin D deficiency is high in Arabs and significantly associated with each other. One study showed that almost 85% of Arab pregnant women and 88% of their neonates had vitamin D deficiency or insufficiency [8]. That may be due to measures that decrease sun exposure, such as covering the skin with clothing, applying sunscreen and seasonal factor such as when the winter sun away from the equator is ineffective at mediating vitamin D synthesis. Maternal vitamin D deficiency is one of the major risk factors for neonatal vitamin D deficiency [9]. Vitamin D deficiency is common among infants, and pregnant and non-pregnant mothers in the worldwide [10,11]. The Food and Nutrition Board's current recommendation for adequate intake of vitamin D is 200 IU/d for both pregnant and no pregnant individuals aged 0–50 years [12].

The 25-hydroxy vitamin D [25(OH)D] is an important steroid hormone [13], and the management of its deficiency is crucial mainly during pregnancy because it will affect fetal development besides bone metabolism [14], 25(OH)D exhibits ant proliferative, proapoptotic, and immunomodulatory properties. Additionally, it plays a role in cell development and embryogenesis and helps in fetal lung maturation [15,16]. There is no consensus regarding the optimal level of 25(OH)D in pregnant women or neonates. The US Institute of Medicine defines 25(OH)D levels of 50 nmol/L as adequate [17], whereas others advocate a threshold of 75 nmol/L [18] and up to 100 nmol/L as optimal during pregnancy [19]. Recently developed recommendations define vitamin D deficiency and insufficiency as <30 and 30 to 50 nmol/L, respectively [20].

The American Academy of Pediatrics guidelines recommend supplementation of 200–400 IU/day in enter ally fed preterm infants [21], whereas in Europe, according to European Society for Pediatric Gastroenterology, Hematology and Nutrition (ESPGHAN) guidelines, supplementation of vitamin D for preterm infants should reach 800–1000 IU/day [22]. Recently, separate guidelines have been published for Central Europe. Preterm infants fed enter ally should receive vit D supplementation of 400–800 IU/day within the first days of life and continue up to 40 weeks of gestational age (GA). This should be followed by 400 IU/day [23]. The various states of vitamin D status were defined as: deficient (<25 nmol/L); insufficient (25-50 nmol/L); sufficient (50-75 nmol/L) and desirable (>75 nmol/L) [24].

The aim of this study was to assess the level of vitamin D in preterm neonates and its relation with different neonatal and maternal factors.

Methods

A Cross-sectional study was conducted at the Neonatal Intensive Care Unit (NICU) in Al-Imamein Al-Kadhimaein Medical city in Baghdad during a period from 1st of march 2022 to 1st of October 2022, the age of preterm

neonates was between 1-3 days without any supplement, feeding or parenteral nutrition. This study includes seventy preterm neonates from about 250 neonates admitted to the NICU at this interval, those with RDS depending on clinical features and X-ray findings, others with early onset sepsis diagnosed by clinical features, C-reactive protein (CRP), complete blood count (CBC), blood culture, chest x-ray (CXR), neonates of diabetic mother, and neonatal jaundice. Mothers' data were collected from mothers themselves by direct questionnaire included: age, gravidity, antenatal care, mode of delivery, chronic illnesses, and maternal vitamin D use during pregnancy. Healthy mothers 47 (67.1%) those mothers without history of chronic illness or pregnancy related complication, while 14 (20%) had history of lower urinary tract infection in the third trimester diagnosed by urinalysis, 6 (8.5%) of mothers had gestational diabetes mellitus (GDM), (4.2%) had gestational hypertension. The evaluated neonatal data were collected in the NICU from case sheets soon post-delivery or during the first three days of life and included the following: name, GA, gender, birth weight and diagnosis. The preterm neonates divided according to gestational age to early preterm (28 - 32) weeks and late preterm (33 - <37) completed weeks of gestation [4]. The preterm neonates also divided according to body weight to LBW is defined by WHO as a birth weight less than 2500 g, very LBW born weighing less than 1500 gm [5]. Two ml of venous blood sample taken from the neonates by gel tube to measure the serum vitamin D level, in the Lab of the Medical City by Atelic solution, 1300 ml solution device with pediatric median 25 (OH)Vitamin D: 23.8 ng/ml.

Inclusion criteria

- One to three days old preterm neonates admitted to NICU.
- The neonate did not receive any supplement, feeding or parenteral nutrition.

Exclusion criteria

- Term neonates.
- Neonates with congenital anomalies.
- Neonates on vitamin D drops.
- Neonates older than three days old.

Ethical approval:
All mothers were verbally informed about the study and they were asked permission to make their neonates being part of the study. All personal information's were kept anonymous. Data were exclusively used for the sake of this study.

Statistical Analysis

In this cross-sectional study, most of data were parametric and expressed as mean ± standard deviation (SD), while some of data were non-parametric and illustrated as frequency and percentage. Comparison of parametric data (vitamin D level) among 3 groups was done using ANOVA (analysis of variance) with post hoc Tukey test to compare between each pair of groups. While unpaired t-test was used to compare vitamin D level between 2 groups. P value less than 0.05 was considered the level of significance. Statistical package of social sciences (SPSS) version 23 was used to do the analysis.

Results

The general characteristic of cases according to GA, birth weight, and gravidity were shown in table (1). Regarding GA, (61.4%) of them were late preterm (GA 33-36 week), 72.9% of them were LBW and (75.7%) of them were product of multigravida mother.

Table 1. demographic characteristics of the cases

Parameter	Category	No.	%
Gestation age (wk)	28-32	27	38.6
	33-37	43	61.4
Birth weight (kg)	<1.5	13	18.6
	≥1.5 – 2.5	51	72.9
	≥2.5	6	8.5
Gravidity of mothers	Primigravida	17	24.3
	Multigravida	53	75.7

N=70

The females constituted 33 (47.2%) of sex of newborn, while 37 (52.8%) were males, the comparison of neonatal Vitamin D between them using unpaired test revealed non-significant p value (p = 0.477) as shown in table (2).

Table 2. Comparison of neonatal vitamin D according to sex of the premature neonates by unpaired t test

Parameter	Female N=33 Mean±SD	Male N=37 Mean±SD	P value
Vitamin D (ng/ml)	10.0±2.85	10.65±4.52	0.477

Regarding the cause of admission of the preterm neonates to the hospital, 46 (65.7%) of them admitted due to RDS, 19 (27.1%) sepsis,5 (7.1%) others include (infant of diabetic mother and jaundice). There were no significant differences in the level of vitamin D between the three groups and even between each two groups as shown in table (3).

Table 3. Comparison of neonatal vitamin D according to cause of admission to hospital of premature neonates

Parameter		RDS N=46 (65.7%)	Sepsis N=19 (27.1%)	Others N=5 (7.1%)
Vitamin D (ng/ml)	Mean±SD	9.97±3.01	11.25±5.63	10.34±1.01
	P value *		0.478	
	P value **		0.445	0.977
	P value ***			0.885

Others: include infants of diabetic mother and jaundice, * p value by ANOVA (among three study groups), ** p value between RDS group with each of the two other study groups by post hoc Tukey test, *** p value between sepsis group and others group by post hoc Tukey test

The majority of mothers were taken supplement during pregnancy 42 (60%), while the rest did not take supplement. The neonatal vitamin D level was significantly higher level in those who were taken supplement than those who did not take supplement, unpaired ttest revealed significant p value (p <0.001) as shown in table (4).

Table 4. Comparison of neonatal vitamin D according to supplement taking by mother of premature neonates by unpaired t test

Parameter	With supplements N=42 (60%) Mean±SD	Without supplements N=28 (40%) Mean±SD	P value
Vitamin D (ng/ml)	11.54±4.5	8.56±0.93	<0.001

There was no significant difference in preterm neonate's vitamin D level when comparison done according to medical history of mother of preterm neonates, where 47 (67.1%) of mothers were healthy, 14 (20%) had urinary tract infection (UTI) in third trimester, 6 (8.5%) had gestational diabetes, 3 (4.2%) had hypertension as shown in table (5).

Table 5. Comparison of neonatal vitamin D according to medical history of mother of premature neonates

Parameter		Healthy N=47 (67.1%)	UTI N=14 (20%)	GDM N=6 (8.5%)	Gestational HT N=3 (4.2%)
Vitamin D (ng/ml)	Mean±SD	10.12±3.04	9.24±1.33	13.57±8.94	12.53±5.46
	P value *			0.083	
	P value **		0.864	0.150	0.696
	P value ***			0.089	0.507
	P value ****				0.979

* p value by ANOVA (among three study groups), ** p value between Healthy group with each of the three other study groups by post hoc Tukey test, *** p value between UTI group with GDM and HT groups by post hoc Tukey test, **** p value between GDM group with HT group by post hoc Tukey test

The majority of mothers were multigravida 53 (75.7%), and primigravida mothers were 17 (24.2%). There was no significant difference in vitamin D of preterm neonates from both groups of mothers (p = 0.091) as shown in table (6).

Also, there was no significant difference in neonatal vitamin D in those with very LBW 13 (18.5%), those with LBW were 51 (72.8) and those with appropriate birth weight for age 6 (8.5%) (p = 0.091) as shown in table (7).

Table 6. Comparison of neonatal vitamin D according to gravidity of mothers of premature neonates by unpaired test

Parameter	Primigravida N=17 Mean±SD	Multigravida N=53 Mean±SD	P value
Vitamin D (ng/ml)	8.99±1.6	10.78±4.21	0.091

Table 7. Comparison of neonatal vitamin D according birth weight of premature neonates

Parameter		VLBW N=13 (18.5%)	LBW N=51 (72.8%)	Appropriate for age N=6 (8.5%)
Vitamin D (ng/ml)	Mean±SD	8.39±0.56	10.8±4.31	10.68±1.54
	P value *		0.123	
	P value **		0.104	0.435
	P value ***			0.997

VLBW: <1.5 kg, LBW: ≥1.5 & <2.5 kg, Normal: ≥2.5, * p value by ANOVA (among three study groups), ** p value between VLBW group with each of the two other study groups by post hoc Tukey test, *** p value between LBW group and normal group by post hoc Tukey test

Regarding the comparison of neonatal vitamin D according to GA of preterm neonates, number of neonates with GA <33 week were 27 (38%.5) and GA ≥33 week were 43(61.4%). No significant p value was revealed (p = 0.2) as shown in table (8).

Table 8. Comparison of neonatal vitamin D according to gestational age of premature neonates by unpaired t test

Parameter	GA (28-33) N=27 Mean±SD	GA (34-37) N=43 Mean±SD	P value
Vitamin D (ng/ml)	9.61±4.88	10.81±2.93	0.201

Discussion

Vitamin D level had a relation with many health problems, so, it is important to study its level in preterm neonates and its relation with different neonatal and maternal factors.

In this study, there was no association between neonatal vitamin D level and sex (p = 0.4), which is nearly similar to finding in an Iranian study done by Mosayebi et al. (2021), in which they did not found statistically significant of any association between serum vitamin D level and neonatal sex. The mean serum value of vitamin D was similar among both sexes (p=0.305) [25].

In the study, there was no significant association between RDS and neonatal vitamin D level deficiency, which is similar to the finding in a study at Czech Republic done by

Matejek et al. (2020), in which vitamin D level does not lead to a higher or lower risk of RDS (p = 0.7) [26]. This finding disagreed with the finding of a study in China done by Zang et al. (2022), in which vitamin D deficiency is likely to be a high-risk factor of RDS [27]. This may be due to some limitation such as there are certain differences in the GA, birth weight and specific time of blood draw of the included research subjects, regional and ethnic differences.

There was no significant association between vitamin D level in neonate and sepsis, that is not corresponding with a study that done by Yang et al. in China at 2016, in which rate of vitamin D deficiency among the neonates in the early onset sepsis group was significantly higher than that of the control [28].

The significant difference in neonatal vitamin D according to supplement taken by mother of preterm neonates during pregnancy is agree with the study in Iran done by Mosayebi et al. (2021) [25].

In this study, the medical history of mother of preterm neonates showed no significant difference in vitamin D level in the preterm neonates, that was corresponding with the study done by Park et al. (2015) in Korea [29], in which there were no significant differences in 25-OHD concentrations between infants with and without maternal history of diabetes and preeclampsia.

Other factors that were assessed in the study included GA, birth weight, and parity, none of these factors were seen to be associated with vitamin D deficiency in the neonate, these findings are in line with studies [30,31], where GA, birth weight, and parity not shown to be associated with vitamin D deficiency in the newborn. However, in Jordan, lower GA was found to be associated with vitamin D deficiency in the neonates this study was done by Khuri-Bulos et al [32]. This difference could be due to the smaller sample size in this study in contrast the large sample size used in the study done in Jordan.

In this study, there was limited ability to measure maternal vitamin D due to limited kit in the hospital.

In conclusion, there was no significant relation between serum vitamin D level and sex, GA, birth weight cause of admission, maternal health and gravidity. While there was a significant relation between neonatal serum vit D level and maternal use of vitamin D supplement during pregnancy.

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Author contribution

Dr. Hussain: Collection of data, analysis of them. Interpretation of results and discussion of them done by both authors.

Conflict of interest

The authors declare there is no conflict of interest.

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Correspondence to Dr. Areej A. A. Mohammad
E-mail: areejmhd965@gmail.com
areej.abdulabbas@ced.nahrainuniv.com
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