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Changes in Vitamin D Status during the First Two Weeks of Life in Preterm Infants on TPN: A Cross Sectional Study

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Abstract

Background: Given the high prevalence of vitamin D(vitD) deficiency in preterm infants on total parentral nutrition (TPN) and the negative effects of this deficiency, the vitD status and the risk factors of vitD deficiency should be evaluated and studied in order to prevent the deficiency of vitD and its complications.

Methods: This study was a cross sectional study in which 25(OH)D, calcium (Ca), phosphorus (P), and alkaline phosphatase (Alk) levels were measured in infants of GA<37 weeks receiving TPN in the first 24 hours after birth and two weeks after receiving TPN. Maternal 25(OH)D, Ca, P, and Alk levels were also measured in the first 24 hours after delivery. Moreover, the relationship between neonatal and maternal vitD, Ca, P, and Alk was measured before and after TPN.

Inclusion criteria: infants with no asphyxia, that were expected to undergo TPN for two weeks. Infants did not receive corticosteroids and anticonvulsants. Mothers did not receive medication during pregnancy.

Results: The mean of 25(OH)D level in infants was significantly decreased after 2 weeks; therefore, the mean at birth, in the group of GA<30 weeks before and after TPN was 49.44±32.12 ng/ml and 34.99±23.15 ng/m and in the group of GA≥30 weeks before and after TPN was 33.64±16.24 ng/ml and 26.26±9.86 ng/ml, respectively.

The neonatal vitD status at birth and at two weeks of age had a strong, direct and significant relationship with maternal vitD at the time of delivery, but the neonatal P, Ca and Alk level had a direct and significant correlation with maternal P, Ca and Alk level only at the time of birth, and unlike vitD, this relationship decreased significantly after two weeks.

Conclusion: It seems that the cause of this significant decrease in vitD status cannot be attributed to vitD deficiency in mothers only, rather this decrease is relevant to the lack of fat-soluble vitamins such as vitD in TPN solutions available in our country. The main recommendation of the present study is that by adding fat-soluble vitamins to TPN from the first days of life, the deficiency of these vitamins in preterm infants on TPN and its complications can be prevented.

Keywords: Vitamin D deficiency; Hypocalcemia; Premature infant; Preterm neonate; Total parentral nutrition; TPN

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Introduction

During a normal pregnancy, it is expected that vital elements, such as vitamins, proteins, lipids, and minerals that are necessary for the growth and development be transported from placenta to fetus. This transition should normally take place in forty weeks of pregnancy. Meanwhile, medical sciences face the phenomenon of preterm and premature infants all over the world [1]. Given the high prevalence of preterm delivery and the subsequent preterm infants (Gestational age (GA)<37 weeks) and the importance of neonatal mortality and morbidity statistics in the assessment and improvement of the health status of the country, and the cost of treatment, the study of preterm infants is very necessary. The less the gestational age and birth weight of these infants, leads to more problems that they would face at the time of birth and after discharge from the hospital. As some of these babies are not able to have oral intake and are candidates for nutrition on Total parentral nutrition (TPN). The common problem in this group of infants is vitamin D(VitD) deficiency and, consequently, hypocalcaemia and osteopenia [2].

Preterm infants are born with lower vitD stores as VitD is a fat-soluble vitamin that is mostly transferred to the fetus during the third trimester [3], so more amount of vitamin D supplementation is needed, so they could grow and develop adequately [4]. Normally Breast milk provides 25% of the calcium, phosphorus and vitamin D needed for the baby. However, preterm infants are even deprived of this insignificant amount because of their long-term nutrition on TPN [5]. Unfortunately, despite the many advances in feeding of premature

infants in the world, the administration of vitamin D to preterm infants on TPN does not start from the first days after birth in NICU Centers in our country, but the time and dose of its administration is a matter of personal style and is administered 14 days after birth or even later [6], whereas according to protocol for a Cochrane review, the vitamin D should be administered from the first days of birth to three to six months corrected age and its dose must be from 400 to 1000 units per day [7].

As matter of fact, vitamin D deficiency in infants is effectively preventable. Since, firstly, numerous studies have strongly confirmed the relationship between the vitamin D intake and the circulating vitamin D concentration [8,9]; secondly, Vitamin D levels are also reliably measurable with 25-Dihydroxycholecalciferol [10]; thirdly, vitamin D supplement is available as either oral or intramuscular administrations [11]. In this study, we plan to examine the changes in vitamin D level before and after TPN and its possible contributing factors in order to reduce the prevalence of vitamin D deficiency and its complications in preterm infants.

Methods

This was a cross-sectional study that was conducted on 49 preterm infants under TPN admitted to NICU of Shahid Akbar Abadi Hospital in south of Tehran, Iran, which is a referral and educational center. Random sampling method was used from June to October in 2018. This case study was approval by the Ethics Committee of Iran University of Medical Sciences (Ethic number: IR.IUMS.FMD. IREC.1396.8921215070) and the neonates were entered to the study process after obtaining the informed consent from their parents.

The inclusion criteria included: preterm infants (GA<37 weeks) that were expected to undergo TPN for at least two weeks. The preterm infants with asphyxia; infants that received corticosteroid and antihypertensive drugs (Phenobarbital and Phenytoin) in two weeks after birth were excluded from the study. Also we excluded subjects with major congenital and chromosomal abnormalities. On the other hand, the mothers with long-term use of high-dose corticosteroids and antihypertensive drugs (Phenobarbital, Phenytoin) during pregnancy; mothers with gestational hypertension, preeclampsia, and gestational diabetes were also excluded from the study. The primary outcome was relevant to the study of serum 25(OH)D levels and the secondary outcome was relevant to the serum levels of calcium, phosphorus, alkaline phosphatase. In order to measure the primary and secondary outcomes of the study, 2 cc venous blood samples were taken from each neonates on the morning of the first day and on the 14th day of birth, besides, blood samples were taken from mothers in the first 24 hours after delivery; then the samples were evaluated for the serum 25(OH)D level using radioimmunoassay technique(RIA) and for the level of phosphorus, calcium and alkaline phosphatase using ELISA method in the Laboratory of Akbar Abadi hospital. The subjects under study underwent TPN according to the current protocol in Iran, which included: 5% or 10% dextrose water, amino acid, intralipid and vial of sulovit fromfirst day; calcium gluconate (4 cc/kg) and sodium glycerophosphate (1 cc/kg) from the 2nd day; NaCl 20% and KCl 15% from the 3rd day; and vitamin K once a week.

In this study, given the 95% confidence level (at the significance level of 0.05) and the study power of 90%, the mean serum 25(OH) D levels before receiving TPN was 16.37±5.29 and 14 days after was 20.78±5.44; the sample size was computed to be 30 individuals, however, regarding sample attrition it was estimated to be at least 40 people and ultimately it was equal to 49 neonates [12].

The results for quantitative variables were expressed as mean ± SD, and for the qualitative variables as percentages. The comparison between quantitative variables was performed by t test and in case of abnormal distribution by Mann-Whitney test. The comparison between qualitative variables was also performed by Chi-square test or Fisher's exact test. The correlation between quantitative variables was investigated using Pearson correlation coefficient and Spearman rank correlation. STATA 14.1 was used to analyze the data. The significance level was less than 0.05.

Results

In this study, neonates were divided into two groups of GA<30 weeks with 30 neonates (61.22%) and GA≥30 weeks with 19 neonates (38.78%), besides, mothers, according to their serum 25(OH)D levels at the time of delivery, were divided into two groups of below 30 ng/ml with 22 cases (44.90%) and above 30 ng/ml with 27 cases (55.10%) (Table 1).

Neonatal serum 25(OH)D levels in both groups of GA<30 (P value:0.02) and GA≥30 weeks (P value:0.04) were significantly reduced after two weeks of receiving TPN (Table 2).

Serum 25(OH)D levels in neonates in both groups of mothers with serum 25(OH)D<30 ng/ml, and of mothers with serum 25(OH)D≥ 30 ng/ml were decreased significantly after two weeks of receiving TPN (P value:0.01) (Table 3).

There was a direct, strong and significant relationship between maternal serum 25(OH)D levels in the first 24 hours after delivery and neonatal serum 25(OH)D levels at birth (r=90%). There was a direct, strong and significant correlation between the maternal serum 25(OH) D levels in the first 24 hours after delivery and neonatal serum 25(OH) D levels until two weeks after birth (r=85%). While no strong and long-term relationship was observed in level of calcium, phosphorus and alkaline phosphatase. Of course, there was a significant relationship between maternal and neonatal calcium, phosphorus and alkaline phosphatase at birth (P value<0.05); this relationship was not significant at 2 weeks of age regarding calcium and alkaline phosphatase (P value>0.05); however, regarding phosphorus, the relationship was significant (Pvalue:0.01) although there was no strong correlation (r=33%) (Table 4).

Discussion

The prevalence of VitD deficiency (25(OH)D <30 ng/ml) in neonates was 30.61% at birth; it reached 53.06% after two weeks of receiving TPN. Preterm infants are more at the risk of metabolic bone diseases in comparison to term infants. The incidence of metabolic bone diseases in neonates below 1000gr is reported as 55% and in neonates below 1500 gr is reported as 23%. [13]. Osteopenia caused by prematurity is a multifactorial problem, including inadequate vitamin D intake [14,15]. VitD is a fat-soluble vitamin which is involved in

Table 1. Demographic Information of Neonates.

Mean ± SD	Frequency (%)	Variables
	30 (61.22)	GA<30 weeks
	19 (38.78)	GA ≥ 30 weeks
	16 (32.65)	Normal vaginal delivery
	33 (67.35)	Cesarean section
	15 (30.61)	25(OH)vit D3<30 ng/ml
	34 (69.39)	25(OH)vit D3 ≥ 30 ng/ml
29.87±1.97		GA (week)
1193.26±221.86		Weight birth (gram)

Table 2. Changes in Neonatal VitD levels after Two Weeks of Receiving TPN based on Gestational Age.

P	CI 95%		MD	VitD after two weeks of TPN	VitD before TPN	Frequency (%)	GA
	Upper	Lower					
0.02	49.63	34.8	42.22±28.70	23.15±34.99	32.12±49.44	30 (61.22)	GA<30 weeks
0.04	34.48	25.42	29.95±13.77	9.86±26.26	16.24±33.64	19 (38.78)	GA>30 weeks

Table 3. Changes in Neonatal VitD levels after Two Weeks of Receiving TPN based on Maternal VitD.

P	CI 95%		MD	Neonatal VitD after TPN	Neonatal VitD before TPN	Frequency (%)	Maternal VitD
	Upper	Lower					
0.01	25.56	19.5	9.96±22.53	6.30±19.32	11.93±25.69	22 (44.90)	25(OH)D< 30 ng/ml
0.01	56.85	42.41	26.44±49.63	20.91±41.58	29.21±57.68	27 (55.10)	25(OH)D≥30 ng/ml

Table 4. The Correlation between the Maternal and Neonatal VitD, Ca, P and Alk.

Alk after TPN	Alk before TPN	P after TPN	P before TPN	Ca after TPN	Ca before TPN	VitD after TPN	VitD before TPN	
						r=0.85	r=0.90	Maternal VitD
						p<0.001	p<0.001	
				r 0.03	r=0.35			Maternal Ca
				p=0.7	p=0.01			
		r=0.33	r=0.51					Maternal P
		p=0.01	p<0.001					
r=0.28	r=0.40							Maternal Alk
p=0.05	p=0.004							

many physiological processes [3]. VitD levels are essential for bone health [16], and has a prominent role in skeletal development, enamel formation [17,18], lung growth, alveoli supply [19,20], maturation of the immune system [3], regulation of cell proliferation, apoptosis, and angiogenesis, and in general, in fetal development [17,18]. In cases of vitD deficiency, calcium and phosphorus absorptions are poor [21] and by receiving vitD supplement, the calcium absorptions increases from 50% to 71% [22]. It should also be noted that preterm infants have only a small amount of fat-soluble vitamins at birth because the transfusion of these vitamins through placentahad a shorter time. For the same reason, the supply of these vitamins by PN is very important [23].

Standardized TPN is routinely used in NICU in many countries. In the study by Bolisetty et al., published in 2012, it was suggested that there are 61 standardized total intravenous nutrition formulas for infants in 2009 [24]. This is despite the fact, very few NICU in Iran have standardized nutrition methods [6].

In our study, the serum 25(OH)D levels in infants decreased significantly in both groups of GA<30 and GA≥30 weeks after two weeks of receiving TPN-that lack fat-soluble vitamins. In Iran, vitamin D introduction for preterm infants on TPN begins 14 days after birth or even later [6]. However, it is recommended that preterm births have to be considered as a nutritional emergency [23] and vitD supplement should introduced from the first days of life [3,7,25]. The approximate amount of vitD that is provided by standardized TPNin other countries is 160 IU\kg\d [24,26].

In advanced countries, the onset of vitD supplementation has begun from the first days of life, and the controversial issue is the dosage, safety, and effectiveness of vitD supplements in preterm infants. Despite multiple years of research and numerous publications, there is still a lack of consensus in regard to how much vitD infants should receive and how long they should receive it. For example, in the study by Monangi et al., he measured serum 25(OH)D levels in infants of GA≤30 weeks at birth and at 36 weeks postmenstrual age (PMA). A dose of 200 IU of vitD per day was given to infants. It was finally reported that 64% of babies at birth and 35% at 36 weeks PMA had serum levels below 20ng/ml, and in fact the author concluded that the cause of suboptimal serum 25(OH)D levels is that the 200IU of vitD supplement per day is inadequate [4]. Similar to the study mentioned, a randomized double-blind trial study was conducted in north of India that compared the effect of 800 vs 400 IU of vitD 3 per day. Prevalence of vitD deficiency in the 800IU group was significantly lower than in the 400IU group [27]. Practical guidelines for the supplementation of vitD and the treatment of deficits in Central Europe that has been recently published, notice that preterm infants should receive a dose of 400 to 800 IU per day from the first days of life until accomplishing the corrected gestational age of 40 weeks, and this should be continued at a dose of 400 units per day [28]. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended administering a dose of 800 to 1000 IU of vitamin D in these infants [29]. In general, it can be argued that American Academy of Pediatrics (AAP) and the Institute of Medicine (IOM) have supported a serum level of 50 nmol/l for vitD as an adequate amount for the ideal skeletal health [30,31].

According to the present study findings, it can be concluded that the serum 25(OH)D levels in infants under TPN is significantly reduced during the first two weeks of their life. Moreover, it should be noted that this reduction is not affected by the infants' weight or age, the type of delivery, or even the sufficient or insufficient level of maternal vitD status [32]. In other words, in all neonates regardless of their gestational weight, gestational age and delivery type, serum 25(OH)D levels was significantly reduced in two weeks (P value<0.05). The interesting point is that during a study conducted in south of India in 2014, vitD deficiency in preterm infants, even with a daily dose of 400IU, reached from 12.6% at birth to 52.2% at 6 weeks of age (P value<0.001) [33].

VitD deficiency in pregnant women can lead to born of infants with insufficient vitD status [34,35]. Several studies have confirmed that neonatal vitD storage at birth is dependent on maternal levels [9,36-39). In this study, as with other studies, there was a strong correlation between maternal and neonatal vitD levels (r=90%) and our study showed that vitD status in neonates is affected by maternal vitD status (at the time of delivery) until two weeks of age (r=85%). That is, infants whose mothers had higher serum 25(OH)D levels at the

time of delivery, had higher serum 25(OH)D levels until two weeks of age in comparison to infants whose mothers had lower serum 25(OH) D levels (41.58±20.91 v 6.30±19.32). Of course, serum 25(OH)D levels even in infants whose mothers had sufficient serum 25(OH)D levels reduced significantly after two weeks of receiving TPN(P value:0.01). In several studies, including the study by Khattab et al., and the study by Thomas AK et al., there is a correlation between maternal and neonatal calcium levels, maternal and neonatal phosphorus, and neonatal and maternal alkaline phosphatase [40,41]. This is consistent with our study. However, this correlation, unlike vitD, has a significant decline over the two weeks. In other words, unlike vitD status which is affected by maternal vitD status event at two weeks of age, the correlation between neonatal calcium, phosphorus and alkaline phosphatase levels and maternal calcium, phosphorus and alkaline phosphatase levels at the time of delivery decreased at two weeks of age and the correlation is insignificant (Table 4).

The sample size of the present study was limited due to the restrictions such as the lack of parental cooperation in taking samples or neonatal death before reaching the 2 weeks of age. However, some useful results obtained from our study that could be considered as an introduction to future studies to change care and treatment policies in this vulnerable group.

Conclusions

Significant decrease in vitD status in Iranian infants may be due to the fact that, unlike other countries in Iran, TPN lacks fat-soluble vitamins in the first two weeks after birth. Due to the strong correlation between maternal and neonatal vitD status, it can be concluded that by the improvement of prenatal care and proper introduction of vitamin D supplementation to pregnant women we can prevent vitD deficiency in neonates. Unlike vitD, which was affected by the maternal vitD status even at two weeks of age, the correlation between neonatal calcium, phosphorus and alkaline phosphatase at two weeks of age with maternal calcium, phosphorus and alkaline phosphatase levels (at the time of delivery) decreased, Which seems to be due to TPN containing calcium and phosphorus solutions in Iran.

In the present study, the recommended suggestion is to add fat-soluble vitamins to TPN in order to prevent the deficiency of these vitamins in preterm infants on TPN and their complications. Moreover, given the strong correlation between maternal and neonatal vitD status, it is recommended to optimizing maternal vitD status during pregnancy in order to minimize vitD deficiency in these women in Iran.

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Abbreviations

VitD: Vitamin D; TPN: Total parentral nutrition; GA: Gestational age; Ca: Calcium; P: Phosphorus; Alk: Alkaline phosphatase; PMA: Postmenstrual age

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