ORIGINAL REPORT

Prevalence of Maternal Vitamin D Deficiency in Neonates with Delayed Hypocalcaemia

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Abstract- Maternal vitamin D deficiency is one of the major risk factors for neonatal vitamin D deficiency followed by neonatal hypocalcaemia. The aim of this study is to determine the relationship between delayed neonatal hypocalcaemia and maternal vitamin D deficiency. This is a descriptive cross-sectional study. Target population of this study included all term and preterm neonates with delayed hypocalcaemia (after the first 72 hours of birth) admitted to Ali-Asghar Hospital. The sample size was 100 neonates included in the study. Demographic, clinical and paraclinical data including Ca, P, PTH and level of maternal and neonatal vitamin D were recorded according to patients records. 67 neonates (67%) were term and 33(33%) were preterm neonates. The mean of serum calcium in neonates was 6.49± 0.68mg/dL (in the range of 4.3-7.8 mg/dL). 85% of neonates and 74% of mothers had vitamin D deficiency. 100% of neonates born to mothers with vitamin D deficiency were hypocalcaemia. A statistically significant difference was seen between the mean values of serum Ca (6.67 in term vs. 6.12 in preterm neonates) and vitamin D in term and preterm neonates was 16.34 vs. 20.18 (P= 0.0001 and P=0.01 respectively). Also, a significant correlation was seen between maternal and neonatal level of vitamin D (P=0.0001, r=0.789). With regard to the socio-cultural status in Iran besides women's clothing style and nutritional deficiencies before and during pregnancy, health authorities and policy makers are responsible to focus their serious attention on hypocalcaemia and hypovitaminosis D in neonates.

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Introduction

According to the standard definition of neonatal hypocalcaemia,which is the total level of calcium less than 8 mg/dL in preterm and less than 7 mg/dL in term neonates (1), several causes of this disease are taken into account. Hypocalcaemia can be/is divided into two groups of early and delayed. According to references, early neonatal hypocalcaemia occurs within the first 24 and 48 hours of birth) which usually happens before the onset of adequate milk intake. There is a direct relationship between level of serum calcium and gestational age, so the incidence of hypocalcaemia is higher in rather premature neonates (2).

Early neonatal hypocalcaemia mainly occurs in neonates with low birth weight, especially in cases of neonatal asphyxia, diabetic mothers, intrauterine growth retardation, prolonged and difficult labors and women receiving anticonvulsants during pregnancy (1).

Delayed hypocalcaemia is less prevalent in neonates rather than its early type. Symptoms usually present within the first 5 and 10 days of birth and might be seen until the sixth week (of life). According to references, incidence of hypocalcaemia after the fourth day of birth is classified under delayed hypocalcaemia (1). Causes of delayed hypocalcaemia, which differ from, its early type include hyperphosphatemia, hypomagnesaemia, vitamin D deficiency, hypoparathyroidism and other causes (1) and this type of hypocalcaemia(delayed) occurs less in breastfed neonates due to less content of phosphate in breast milk (2).

During pregnancy and breast feeding, fetus and neonate are supplied with a large amount of maternal calcium. Since bone metabolism and calcium directly

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depend on vitamin D, its adequacy during pregnancy and breast feeding is of paramount importance (3). In some of the previous studies, vitamin D deficiency with or without relative hypoparathyroidism was known as the main cause of delayed hypocalcaemia. Vitamin D deficiency resulted from its maternal deficiency was not uncommon (4). In a study conducted by Behjati *et al.*, (2003) prevalence of delayed and early hypocalcaemia was studied on 796 neonates. The results showed that 33.5% of neonates were hypocalcaemia, 85 (31.8%) and 182 (68.2%) of which had early and delayed hypocalcaemia respectively (5). Most of the previous studies have shown high prevalence of hypovitaminosis D in neonates and its direct relationship to maternal level of vitamin D (5-10).

Maternal vitamin D deficiency is one of the major risk factors for neonatal vitamin D deficiency followed by neonatal hypocalcaemia. Maternal vitamin D deficiency is remarkably more prevalent in women with low dairy product or pregnancy supplement intake as well as the women residing in the Middle East and South Asia where women's exposure to sunlight is less due to the clothing style (1). As Iran is located in this region, paying serious attention to this matter is extremely necessary. With regard to the details mentioned above and the fact that such a study has never been conducted in Iran, this study aims to determine the relationship between neonatal delayed hypocalcaemia and maternal vitamin D deficiency.

Materials and Methods

This is a descriptive cross-sectional study on the target population of the term and preterm neonates with delayed hypocalcaemia (after the first 72 hours of birth) admitted to Ali-Asghar Hospital. Inclusion criteria were as follows:

1- Delayed hypocalcaemia

2- Incidence of symptoms after the first 72 hours of birth

And exclusion criteria were early hypocalcaemia (less than 72hours) and presence of diabetes in the mother.

According to previous studies in which rate of neonatal delayed hypocalcaemia was estimated to be 10% (margin of error: 0.05, confidence interval: 95%), sample size of 100 neonates was considered sufficient based on the following formula. Simple probability sampling method was applied. All hypocalcaemia neonates admitted to Ali-Asghar Hospital were included in this study (April of 2008-Oct. of 2010). Demographic, clinical and paraclinical data including Ca, P,PTH, maternal and neonatal level of vitamin D were recorded based on hospital records and processed by $SPSS_{17}$. All stages of research were carried out with regard to principals of confidentiality and Helsinki Resolution and approved by the ethics committee. Since stages of diagnosis and treatment did not change, no special ethical limitation was considered. Finally, data were analyzed by t-test and Pearson's correlation coefficient. Values less than 0.05 were considered significant.

Results

According to results of the study, the sample size (100 neonates) was equally divided into two groups of boys (50) and girls (50). Of those, 67(67%) were term and 33(33%) were preterm neonates. 85% of neonates and 74% of mothers had vitamin D deficiency. 100% of neonates born to mothers with vitamin D deficiency were hypocalcaemia. Mean of serum calcium in neonates was 6.49±0.68 mg/dL (in the range of 4.3-7.8 mg/dL). 100% of studied neonates were hypocalcaemia (level of serum calcium less than 8 mg/dL in term and less than 7mg/dL in preterm neonates).

Mean of serum phosphorus in neonates was 6.00±1.96mg/dL (ranged 141.0-1152.0 U/L), mean of serum alkaline phosphatase was 491.0±197.57 U/L (in the range of 141.0-1152.0 U/L), mean of serum PTH was 42.99±21.49 pg/dL (ranging from 10.50-120.0 pg/dL) and mean of serum 25 (OH) D was 17.61±7.56 nmol/L (in the range of 3.90-41.0 nmol/L). Values less than 25 nmol/L were considered as vitamin D deficiency and 85% of neonates suffered from this deficiency accordingly. Of this 85%, 24 (24%) had only vitamin D deficiency, 41(41%) had both vitamin D deficiency and relative hypothyroidism, 25(25%) had vitamin D deficiency along with hypomagnesaemia, 4 (4%) had vitamin D deficiency along with transient hypocalcaemia and just 1 (1%) case of vitamin D deficiency accompanied by pseudo-hypoparathyroidism was found in the target population. Mean of serum magnesium was 1.73±0.25 mg/dL (in the range of 1.04-2.20 mg/dL).

Mean of serum calcium in mothers was 9.27±0.67 mg/dL (ranged 8.0-11.0 mg/dL). According to the results hypocalcaemia was not seen in mothers (level of serum calcium less than 8 mg/dL). Mean of serum phosphorus in mothers was 4.10±0.50 mg/dL (3.0-5.5 mg/dL), mean of serum alkaline phosphatase was 305.70±126.84 U/L (39.0-670.0 U/L), mean of serum PTH was 53.41±31.56 pg/dL (32.0-333.0 pg/dL) and

mean of serum 25 (OH)D was 19.87±7.74 nmol/L(3.90-40.0nmol/L). Considering values less than 25nmol/L as vitamin D deficiency, 74% of mothers in this study suffered from vitamin D deficiency. According to results of t-test,statistically significant difference was found between mean of serum calcium (6.67 in term *vs* 6.12 in preterm neonates) and vitamin D in neonates(16.34 in term vs. 20.18 in preterm neonates)(*P*=0.0001, *P*=0.01 respectively) (Table 1)

No significant difference was found in levels of serum calcium, phosphorus, alkaline phosphatase, PTH, vitamin D and magnesium in neither groups of the study (girls & boys)/in neither gender (Table 2).

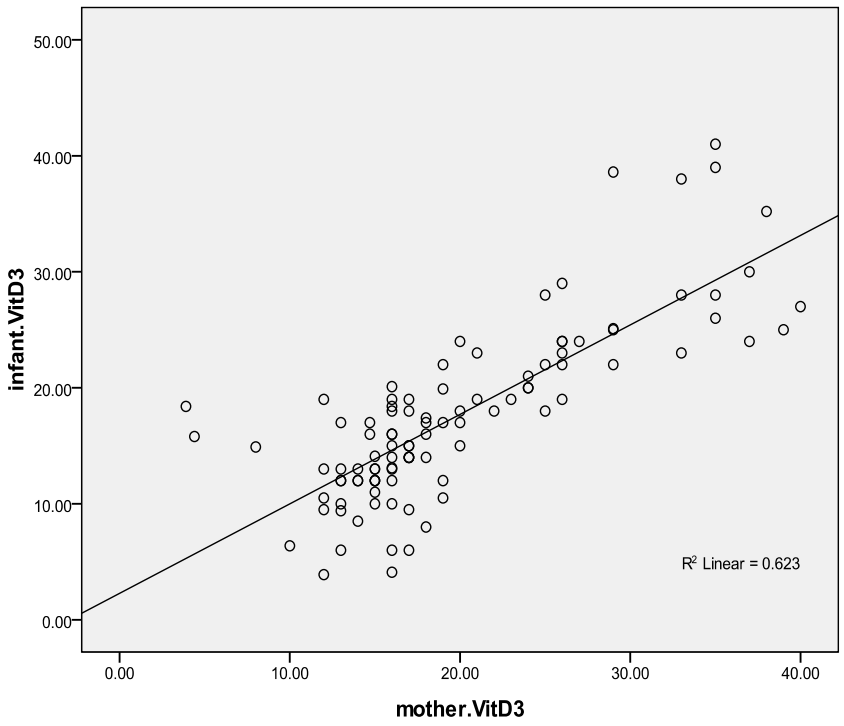
According to results of Pearson's test, a significant correlation was seen between level of vitamin D in neonates and mothers (*P*=0.0001, r=0.789) (Figure 1).

Also with regard to results of Pearson's test of correlation, no significant correlation was found between neonatal and maternal level of serum calcium (*P*=0.936, r=-0.008).

In addition, there was a significant correlation between neonatal level of vitamin D and age of neonates. (*P*=0.007, r=0.269). But no significant correlation was found between level of serum calcium and age (*P*=0.76, r=-0.031)

Table 1. Comparison of paraclinics value between term and preterm.

	Term	**Preterm**	***P*. value**
	Mean±SD	**Mean±SD**	
Calcium	6.67±0.61	6.12±0.69	0.0001
Phosphorus	5.84±2.2	6.33±1.88	0.24
Alkaline Phosphatase	497.95±195.07	476.87±204.89	0.61
Parathyroid Hormone	43.93±20.48	41.07±23.61	0.53
25(OH)D	16.34±6.81	20.18±8.43	0.01



(r=0.789, *P*=0.000)

Figure 1. Correlation between level of vitamin D in sample mothers and neonates of this study.

Table 2. Comparison of paraclinics value between two genders.

	Boys	Girls	*P*. value
	Mean±SD	Mean±SD	
Calcium	6.48±0.78	6.50±0.58	0.88
Phosphorus	5.93±2.09	6.08±1.84	0.70
Alkaline Phosphatase	512.26±213.40	469.741±80.02	0.28
Parathyroid Hormone	41.00±17.93	44.98±24.56	0.35
25(OH)D	17.88±8.66	17.88±6.36	0.72

Discussion

Results of this study indicated high prevalence of hypocalcaemia (100%) and hypovitaminosis D (85%) in neonates as well as high prevalence of hypovitaminosis D in mothers (74%). These results are compatible with/similar to findings of previous studies in India (6) and Turkey (7) in which prevalence of hypovitaminosis D in neonates has been 90% and79.5% respectively. These figures show higher prevalence of hypovitaminosis D in comparison with other studies in the Netherlands (63.3%) (8), Pakistan (52%) (9) and the previous study in Iran (68.2%) (5). It is noteworthy that despite several studies carried out in other countries, some very limited numbers of studies have been published in Iran (5,10), and specific study or investigation on delayed hypocalcaemia has not been seriously taken into consideration. Findings of this study, similar to most of the previous ones, (6,7) have shown a strongly positive correlation between level of 25(OH) D in mothers and neonates.

In a study conducted in India(6), serum 25(OH)D concentration in mothers was 17.50±10.30 and 79.5% of mothers had less than 25nmol/L serum concentration which is similar to the results of this study (in which mean of serum 25(OH)D concentration is 19.87±7.74 and 74% of mothers have less than 25nmol/L serum concentration).

The reason why prevalence of hypovitaminosis D is higher in this study in comparison to previous ones in Iran (5) is that this study is carried out in a sub-specialty and referral center.

Calcium supply is provided via placenta during the embryonic period and breast feeding after birth. During pregnancy active transmission of calcium takes place via placenta reaching its maximum level of 10mg/kg/day within the last three months of pregnancy which is mainly due to rapid skeletal growth(5). However, hypocalcaemia is prevalent in the neonatal period (1). Of course, most of the time temporary hypocalcaemia occurs which can lead to some symptoms and complications such as apnea, seizure, muscle tremor and others (5).

Furthermore, vitamin D reserves in neonates are directly related to maternal vitamin D supply. As a consequence, if mother suffers from vitamin D deficiency, the neonate encounters this deficiency due to reduced placental vitamin D transmission (7) and in case of extended maternal vitamin D deficiency during breast feeding, the neonate will be at risk of rickets which was strongly confirmed in this study too. Previous studies have highlighted the most significant relationship between maternal and neonatal vitamin D in the first eight weeks of birth (7) which is a remarkable issue in this study too. Women's clothing style besides their diet is one of the most important reasons for high prevalence of hypocalcaemia and hypovitaminosis D which has been highlighted in several studies (6-11). As it can be seen, prevalence of hypovitaminosis D is higher in Islamic countries (8,7), and South Asia (6) in which women have a quite completely covered clothing style and also in other studies carried out in The European countries(9,11,12) prevalence of hypovitaminosis D is higher among the black and Asian population. Accordingly, more preventative measures should be taken into serious consideration in Muslim countries, especially in Iran.

At present, supplementary vitamin D therapy initiates from the second week of birth in Iran, but due to the high prevalence of hypocalcaemia and hypovitaminosis D it seems that implementing preventative strategies especially during pregnancy should be considered seriously. Hence, due to low level of vitamin D in women, it seems that early initiation of supplementary vitamin D in neonates is of great importance. According to the guide lines on prevention of rickets and vitamin D deficiency published by the American academy of pediatrics in 2008, initiation of supplementary vitamin D therapy 400U/Day from birth is recommended (13). Therefore, further studies are

required to consider possible changes of protocol in Iran.

Several factors affect prevalence of delayed hypocalcaemia. In this study gender had no effect on the prevalence of delayed hypocalcaemia which is similar to findings of the previous studies (5,7).

Another influential factor in incidence of hypocalcaemia and hypovitaminosis D having been highlighted in previous studies is women's socio-economic status (7,8). Unfortunately, due to weak cooperation and unreliable responses possibility of studying the relationship between women's socio-economic status and incidence of hypocalcaemia and hypovitaminosis D has not been provided yet, which on its own can be considered as a limitation in this study.

It seems that lack of exposure to sunlight due to the clothing style in our country is the most important predisposing factor for hypovitaminosis and hypocalcaemia in women and consequently in neonates. In a study carried out in Pakistan, women belonging to lower socio-economic status benefit from higher concentration of vitamin D in comparison with the ones categorized in higher economic levels of society which,according to the author, is due to spending more time out of home which naturally results in more exposure to sunlight (8).with regard to results of previous studies and the current one, expansion of public education on vitamin D deficiency and taking preventative measures to modify eating habits as well as initiating supplementary vitamin D therapy during pregnancy are remarkably important issues.

In this study, mean concentration of alkaline phosphates was high in neonates and mothers which can be indicative of increased bone turnover. This finding is compatible with results of previous studies (9).

PTH hormone is a sensitive indicator for sub-clinical vitamin D deficiency (8). In this study increased PTH (above than60pg/ml) was seen in 8% of neonates with vitamin D deficiency which was less than the figure in the study conducted in Pakistan (30%) (8).

In general, results of this study were indicative of high prevalence of neonatal vitamin D deficiency and its strong relationship with level of vitamin D in mother. Due to the present socio-cultural status of the country besides women's clothing style and nutritional deficiencies before and during pregnancy, health authorities and policymakers have to consider serious measures regarding hypocalcaemia and hypovitaminosis D in neonates. Also, given the recent changes in clinical guides (13), changing protocol of supplementary therapy in pregnant women and neonates should be taken into account subsequently. In conclusion, results of this study are indicative of high prevalence of neonatal vitamin D deficiency and its strong relationship to maternal vitamin D deficiency. With regard to the socio-cultural status in Iran besides women's clothing style and nutritional deficiencies before and during pregnancy, health authorities and policy makers are responsible to focus their serious attention on hypocalcaemia and hypovitaminosis D in neonates. Hence, some changes should be made in therapy protocols on pregnant women and neonates.

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