Importance of perinatal vitamin D prophylaxis for mother and the newborn

Ali Kaya[1], Ahmet Sami Güven[1], Asım Gültekin[1], Füsun Dilara İçağasıoğlu[2], Ömer Cevit[3]

[1]*Department of Paediatrics, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*
[2]*Department of Paediatric Neurology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*
[3]*Department of Paediatric Allergy, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*

Abstract

Objective: We aimed to investigate the calcium and vitamin D metabolism in the mother and the newborn and to reveal the importance of calcium and vitamin D supplementation especially in the last trimester.

Methods: The study population included 30 pregnant women, their healthy term babies and 30 healthy controls at the same age and with similar characteristics. The serum levels of calcium, phosphor, alkaline phosphatase (ALP), parathyroid hormone, calcitonin, glucagon, and 25-hydroxy vitamin D3 [25(OH)D] obtained from the pregnant women (at 24th and 36th weeks), the newborn (at 24th and 48th hours and 15th day), the cord blood and the control group were studied.

Results: The maternal 36th week serum calcium and 25(OH)D levels were significantly lower than those of 24th week and the control group. The maternal 36th week serum glucagon and calcitonin levels were significantly higher than those of 24th week and control group. Serum calcium levels of the newborn at 24th and 48th hour were lower than those of the cord blood (p<0.05).

Conclusion: Vitamin D deficiency remains a major health problem for mothers and babies. So we suggest the families to be informed about the complications of vitamin D deficiency and risks like rickets in the early stages, and to educate the mothers for calcium-rich diets to prevent vitamin D deficiency in the babies and prophylactic vitamin D supplementation in the last trimester.

Key words: Newborn, vitamin D deficiency, 25-hydroxy vitamin D3.

Anne-bebek ikilisinde perinatal D vitamini profilaksisinin önemi

Amaç: Anne-bebek ikilisindeki kalsiyum ve D vitamini metabolizmasını araştırarak, gebelerin özellikle son trimester beslenmesinde kalsiyum ve D vitamini uygulamalarının önemini belirlemeyi amaçladık.

Yöntem: Çalışmaya 30 gebe kadın ve onların yenidoğan sağlıklı term bebekleri ile aynı yaş grubunda ve benzer özellikler taşıyan 30 sağlıklı kadın kontrol grubu olarak alındı. Gebelerden (24 ve 36. haftalarda), kord'dan, bebeklerden (24, 48. saat ile 15. günde) ve kontrol grubundan alınan serum örneklerinde; kalsiyum (Ca), fosfor, alkalen fosfataz (ALP), paratiroit hormon, glukagon, 25-hidroksi vitamin D3 [25(OH)D] ve kalsitonin düzeyleri ölçüldü.

Bulgular: Maternal 36. haftadaki serum parametreleri; kontrol grubu ve 24. gebelik haftasındaki değerlerle ayrı ayrı karşılaştırıldığında, Ca ve 25(OH)D'de saptanan düşme ile glukagon ve kalsitonin düzeylerindeki artış istatistiksel olarak anlamlıydı (p<0.05). Yenidoğanların doğumlarının 24. ve 48. saatlerindeki Ca düzeyleri, kord kanındaki Ca ile karşılaştırıldığında istatistiksel olarak daha düşük saptandı (p<0.05).

Sonuç: D vitamini yetersizliği, anne ve bebekleri için önemli bir sağlık sorunu olmaya devam etmektedir. D vitamini yetersizliği ile ilgili olarak ailelerin erken dönemlerde bilgilendirilmesi, D vitamini yetersizliğinin riketsle birlikte diğer olumsuz sonuçlarının anlatılması, bebeklerinde D vitamini yetersizliğinin önlenmesi için annelere kalsiyumdan zengin beslenme eğitimleri verilmesi ve gebeliklerinin son trimesterinde profilaktik D vitamini kullanmalarının önerilmesinin uygun olacağını düşünmekteyiz.

Anahtar sözcükler: Yenidoğan, D vitamini eksikliği, 25-hidroksi vitamin D3.

Introduction

Calcium metabolism of fetus and newborn is supported by calcium sources of mother.[1] During pregnancy, there is a rapid transition of calcium from mother to baby and placenta has an active role during transition of Ca ions to fetus. Hypercalcemia or hypocalcemia seen in mother may cause metabolic bone diseases and changes in Ca metabolisms in newborns.[2]

It is known that parathyroid hormone (PTH) has the most significant role in calcium metabolism during postpartum period. However, vitamin D and metabolites are important to adjust Ca concentrations in the body. While ionized Ca levels are normal towards the end of pregnancy, total serum Ca levels decrease.[3] Vitamin D intake and synthesis may vary according to season and geographical area lived in.[3,4] While Ca concentration and vitamin D content of mother balance Ca and phosphor (P) levels of fetus, they are also effective for adjusting PTH levels. Changes in the metabolism of Ca and vitamin D of mother during pregnancy may cause newborn to have hypercalcemia or hypocalcemia symptoms. Ca values in cord blood reflect fetal Ca concentrations.[2-5]

Vitamin D intake may vary according to socio-economical levels, nourishment habits, and ethnical, cultural and environmental differences. Although our country is rich for sunlight, vitamin D deficiency is still a major problem affecting pregnants, babies and adolescents. Recently, bone health and the importance of vitamin D supplementation are brought to agenda and it has been accepted in many countries that providing daily vitamin D supplementation to women at their last trimester and to babies would be a significant health service.[6,7] Despite the improvement in socio-economical level in our country recently, it was shown that there is no decrease in frequency and volume of maternal vitamin D deficiency.[8-10] Therefore, the Ministry of Health initiated a program of vitamin D supplementation for pregnants in order to prevent vitamin D deficiency. A single dose of 1200 IU (9 drops) vitamin D was suggested for each pregnant beginning from 12th gestational week up to postpartum 6th month.[11]

By this study, we aimed to investigate the Ca and vitamin D metabolism in the mother and the newborn and to reveal the importance of Ca and vitamin D supplementation especially in the last trimester.

Methods

Thirty pregnant women and their babies (healthy, term) were included into the study together with fully healthy 30 women in similar age group who are not pregnant as control group.

Blood samples were obtained from pregnants (at 24th and 36th weeks), the cord and newborns (at 24th and 48th hours and 15th day) in order to analyze levels of hemoglobin (Hb), hematocrit (Htc), glucagons, total Ca, P, alkaline phosphatase (ALP), calcitonin, PTH and 25-hydroxyvitamin D3 [25(OH)D]. Similarly, blood samples were also taken from individuals in the control group for the analyses of same parameters.

Serum 25(OH)D concentration was defined as normal if above 30 ng/mL, as insufficient if between 21 and 29 ng/mL and as vitamin D deficiency below 20 ng/mL. Serum 25(OH)D concentration was classified as mild if between 11 and 20 ng/mL, as mean if between 5 and 10 ng/mL and severe vitamin D deficiency if below 5 ng/mL.[12]

In the routine follow-up of pregnants, multivitamin preparations including 500-1000 IU vitamin D were used in last trimester of pregnancy.

Pregnant group taken into the study consists of healthy pregnants who were followed up in December-January in the Clinic of Obstetrics and Gynecology. Data such as pregnancy numbers of pregnants, stillbirth and miscarriage numbers were obtained. Estimated delivery dates were determined according to their last menstrual period and ultrasonographic evaluations. Examinations and regular follow-ups of all pregnants were done by same physician.

Gestational ages of babies were calculated according to Dubowitz scoring and healthy babies accepted as term were included into the study. Babies with systemic disease that may affect bone metabolism, medication and endocrine pathology were excluded from the study. Pregnants who underwent irregular follow-up during their pregnancies and those with babies who had congenital anomaly and intrauterine growth retardation were not included into the study. One of the pregnants gave birth to twins and the study continued with totally 31 babies.

Statistical evaluation of data was performed by using "SPSS for Windows 14.0". Data was presented as mean±SD. Significancy check of difference between

groups was evaluated by student's T test and Mann Whitney U test. Spearman correlation analysis was performed between serum 25(OH)D levels of mothers and babies. The value p<0.05 was considered as significant.

This study was performed by the approval of Clinical Research Ethics Board of Medicine Faculty, Cumhuriyet University in accordance with Helsinki Declaration.

Results

Of 31 babies included into the study, 19 (61.3%) babies were girl while 12 (38.7%) babies were boy. Mean birth weight of babies was 3,248.4±715.2 g, mean birth height was 48.5±3.2 cm and mean head circumference during delivery was 33.8±1.2 cm.

Mean age of mothers was 24±4.7, mean delivery number was 3±1.3, mean miscarriage was 1±1.1, mean live birth was 1.8±0.5, and mean stillbirth number was 0.1±0.04. In the control group, these parameters were 5±8.8, 3±1.1, 1±1.6, 1.6±0.4, and 0.1±0.06, respectively. In terms of age, pregnancy number, miscarriage, live birth and stillbirth numbers, statistically no significant difference was found between control group and study group (p>0.05) (**Table 1**).

In the serum samples of pregnants at 24th week, no difference was found in total Ca, P, ALP, PTH, 25(OH)D and glucagons levels compared to control group (p>0.05); however, the difference was significant between two groups in terms of calcitonin level (p<0.05).

Serum Ca and 25(OH)D levels of pregnants at 36th gestational week were significantly low when compared

Table 1. Essential demographic characteristics of pregnants and the control group (mean ±SD).

	Study group n=30	Control group n=30
Age (year)	24±10.7[a]	25±8.8
Pregnancy number	3±1.3[b]	3±1.1
Miscarriage number	1±1.1[c]	1±1.6
Live birth	1.8±0.5[d]	1.6±0.4
Stillbirth	0.1±0.04[e]	0.1±0.06

[a,b,c,d,e]p>0.05 when compared with control group.

to levels of those in control group and at 24th gestational week (p<0.05). Serum glucagons and calcitonin levels of pregnants at 36th gestational week were significantly high when compared to levels of those in control group and at 24th gestational week (p<0.05). While PTH level increased at 36th gestational week, the difference was statistically not significant when compared separately in both groups (p>0.05) (**Table 2**).

A significant decrease was found in Ca level when serum total Ca values of cord bloods of babies was compared to venous serum Ca values at 48th hour of delivery (p<0.05) (**Table 3**).

While there was statistically significant decrease in cord blood PTH values of babies compared to venous serum values at 24th hour, the value significantly increased at 48th hour and 15th day (p<0.05). Serum calcitonin values of babies at 15th day were significantly lower than the values at 24th and 48th hours (p<0.05) (**Table 3**). Insufficiency (at 36th week) was found in

Table 2. Essential demographic characteristics of pregnants and the control group (mean ±SD).

	24th gestational week n=30	36th gestational week n=30	Control group n=30
Calcium (mg/dL)	9.3±0.1	8.5±2.1[b]	9.6±0.3
Phosphor (mg/dL)	4.8±0.8	4.6±1.4	4.6±0.7
Alkaline phosphatase (IU)	221.0±81.1	331.7±99.1	121.2±71.1
Parathyroid hormone (pg/mL)	20.0±6.4	33.0±7.3	21.9±7.4
25(OH)D (ng/mL)	38.1±19.6	12.2±16.3[b]	73.2±25.5
Glucagon (ng/L)	79.9±9.3	101.1±10.1[c]	79.4±4.9
Calcitonin (pg/mL)	7.2±1.4[a]	10.2±2.2[c]	6.3±1.7

[a]p< 0.05, when compared with the control group.
[b,c]p<0.05, when compared with the control group and the values of 24th gestational week.

Table 3. Biochemical parameters of babies (mean±SD).

	Cord blood n=31	24th hour n=31	48th hour n=31	15th day n=31
Calcium (mg/dL)	11.3±6.1[a]	7.6±2.1	7.0±1.1	9.0±2.1
Phosphor (mg/dL)	4.9±1.4	4.4±1.4	4.3±1.1	4.8±1.0
Alkaline phosphatase (IU)	386.7±78.2	480.1±63.1	333.1±42.2	343.7±31.1
Parathyroid hormone (pg/mL)	21.1±6.1[b,d]	15.6±4.1[c]	26.8±7.6	30.8±8.2
25(OH)D (ng/mL)	9.2±4.4	58.1±12.8	62.0±14.4	75.2±10.7
Glucagon (ng/L)	89.1±4.6	85.3±4.1	64.4±11.1	58.4±1.8
Calcitonin (pg/mL)	29.2±5.1	28.2±6.6	29.1±2.6	17.0±3.8[e]

[a]$p<0.05$, when compared with the value at 48th hour.
[b]$p<0.05$, when compared with the parathyroid hormone value at 24th hour.
[c,d]$p<0.05$, when compared with the parathyroid hormone value at 48th hour and 15th day.
[e]$p<0.05$, when cord blood is compared with 24th and 48th hours.

serum 25(OH)D level in 10% of the pregnants we followed up while there was deficiency in 70% of them. Similarly, 25(OH)D level in cord blood of 16.1% of babies was insufficient and it was deficient in 61.2%

Table 4. 25 hydroxy vitamin D3 [25(OH)D] status of pregnants and babies.

25(OH)D Status	*Mother, n (%) n=30	†Baby, n (%) n=30
Normal (≥30 ng/mL)	6 (20%)	7 (22.5%)
Insufficient (21-29 ng/mL)	3 (10%)	5 (16.1%)
Missing (≤20 ng/mL)	21 (70%)	19 (61.2%)
Severe (≤5 ng/mL)	2 (9.6%)	3 (15.8%)
Intermediate (5-10 ng/mL)	8 (38.1%)	10 (52.6%)
Mild (11-20 ng/mL)	11 (52.3%)	6 (31.6%)

*According to the values at 36th gestational week,
†According to the values in cord blood.

(**Table 4**).

A strong positive correlation was found between 36th week pregnant serum and cord blood 25(OH)D ($r2=0.557$, $p<0.05$). According to this, 25(OH)D level in cord blood increases as vitamin 25(OH)D level increases in pregnant serum at 36th week (**Fig. 1**).

Discussion

During the period up to the formation of clinical and radiological findings associated with vitamin D deficiency, hypo/normo calcemia, hypo/normo phos-phatemia, high ALP and PTH levels, low 25(OH)D level, and normal, high and low levels of calcitriol may exist. Therefore, it is recently emphasized that subclinical vitamin D deficiency has become important. Vitamin D has significant functions especially in bone mineralization. Also it is suggested that it has a regulatory role in cell differentiation and protein induction such as skeletal muscle, immune system, "nerve growth factor", that it acts like a neurotransmitter in central nervous system and that vitamin D deficiency and vitamin D receptor polymorphism may be a preparatory risk factor for diseases like, particularly rickets, diabetes, coronary heart disease, psoriasis, multiple sclerosis and tuberculosis.[8-11] Therefore, bone health and importance of vitamin D support programs have been brought into agenda again in developed countries recently, and the necessity of giving vitamin D especially in last trimester of pregnancy has been emphasized in many developed countries.[13,14]

In most of the pregnants and babies we followed up, we found that 25(OH)D levels were insufficient. Especially the mean 25(OH)D levels in cord bloods of babies were found below 10 ng/mL. Similarly, there was a strong positive correlation in the literature between maternal serum and 25(OH)D levels of umbilical cord blood.[15,16] These findings show that vitamin D deficiency is still at a high rate among pregnants and their children. The reason may be that pregnancies of these women may be during spring and winter months in which there are mostly limited number of sunny days, and that cloth styles and insufficient
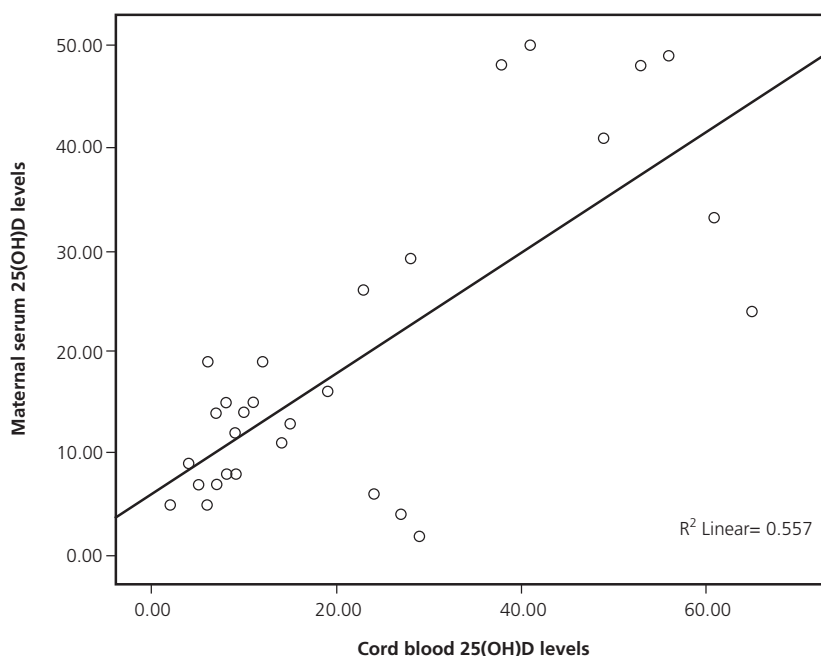
Fig. 1. Correlation between maternal serum and cord blood 25-hydroxyvitamin D3 [25(OH)D] levels (ng/mL).

vitamin D intake. However, our findings need to be supported by different studies with bigger case series. Among the reasons of early neonatal hypocalcemia, findings such as Ca deficiency and maternal hyperparathyroidism are reported.[7] Hsieh et al. detected that there were asymptomatic hyperparathyroidism in mothers of three cases with early neonatal hypocalcemia and by showing that these mothers had parathyroid adenoma, they emphasized that there might be asymptomatic hyperparathyroidism during pregnancy and that it is important to follow up biochemical profile of mothers.[17] No hyperparathyroidism was observed in the mothers included into our study.

Main role of glucagon is to provide glucose need of tissues by increasing fasting blood glucose.[18] Parathyroid hormone and calcitonin display similarity with glucagon receptors. It is reported that glucagon causes hypocalcemia in two different ways. First one is the inhibition of bone resorption and the second one is to increase calcitonin level.[19,20] We could not detect a finding that can explain the pathogenesis of the increase that we found on maternal glucagon level. However, we think that glucagon levels higher than control group may cause early neonatal hypocalcemia

by increasing cord blood calcitonin. However, we believe that detailed studies should be performed on a large scale.

It is thought that calcitonin has a notable role for the development of prenatal skeleton and for the protection of maternal skeletal integrity during pregnancy. Calcitonin levels of newborns are high, and it is higher in preterms and those with asphyxia. Generally, no direct relationship is found between high calcitonin levels and hypocalcemia. Some studies highlight that high calcitonin levels seen in diabetic mothers may cause hypocalcemia in babies.[21]

Venkataraman et al. showed that high level of maternal serum calcitonin caused early neonatal hypocalcemia in babies.[20] In our study, we observed that there is a significant relationship between high calcitonin levels found in maternal and cord bloods and early neonatal hypocalcemia.

Conclusion

Although a significant step is taken by the vitamin D supplementation program carried by the Ministry of Health in our country, our study performed on limited

number of cases in our clinic (even though it does not reflect the whole country) showed that vitamin D deficiency remains a major health problem for mothers and babies. So we suggest the families to be informed about the complications of vitamin D deficiency and risks like rickets in the early stages, and to educate the mothers for calcium-rich diets to prevent vitamin D deficiency in the babies and prophylactic vitamin D supplementation in the last trimester.

Conflicts of Interest: No conflicts declared.

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