Maternal vitamin D deficiency and vitamin D supplementation in healthy infants

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The objective of this study was to evaluate the common effects of maternal vitamin D deficiency, various doses of vitamin D given to newborns and the effects of these on vitamin D status in early childhood.

Seventy-eight pregnant women and 65 infants who were followed up in various health centers were included in the sudy. 25-hydroxyvitamin-D (25-OHvitD), calcium (Ca), phosphorus (P) and alkaline phosphatase levels were measured in blood samples drawn from pregnant women in the last trimester. Infants born to these mothers were given 400 or 800 IU of vitamin D subsequently at the start of the second week. 25-OHvitD, Ca, P and alkaline phosphatase levels of the 65 infants who were brought in for controls (May-September 2000) were measured and hand-wrist X-rays were evaluated. We analyzed the relationship between vitamin D status of the mothers and infants and socio-economic status; mothers' dressing habits (covered vs uncovered), educational level, and number of pregnancies; and sunlight exposure of the house. Covered as a dressing habit meant covering the hair and sometimes part of the face and wearing dresses that completely cover the arms and legs. In 40 infants who were breast-fed and received the recommended doses of vitamin D on a regular basis, the relationship between serum vitamin D levels and supplementation doses given was analyzed.

Serum 25-OHvitD level of the mothers was 17.50±10.30 and 94.8% of the mothers had a 25-OHvitD level below 40 nmol/L (below 25 nmol/L in 79.5%). The risk factors associated with low maternal 25-OHvitD were low educational level ($p=0.042$), insufficient intake of vitamin D within diet ($p=0.020$) and "covered" dressing habits ($p=0.012$). 25-OHvitD level of the infants was 83.70±53.70 nmol/L, and 24.6% of the infants had 25-OHvitD levels lower than 40 nmol/L. Risk factors for low 25-OHvitD levels in infants were a) not receiving recommended doses of vitamin D regularly ($p=0.002$) and b) insufficient sunlight exposure of the house ($p=0.033$). There was a pour but significant correlation between maternal vitamin D levels and infants' 25-OHvitD levels at four months ($r=0.365$, $p<0.05$). No significant correlation was found between 25-OHvitD levels and supplementation doses of vitamin D (19 infants were supplemented with 400 IU/day and 21 with 800 IU/day of vitamin D) ($p=0.873$).

Severe maternal vitamin D deficiency remains a commonly seen problem in Turkey. However, vitamin D deficiency can be prevented by supplementation of vitamin D to newborns (at least 400 IU). Supplementation of 800 IU vitamin D in the areas of maternal vitamin D deficiency has no greater benefits for the infants.

Key words: vitamin D, pregnancy, infancy, supplementation.

Vitamin D and parathyroid hormone have important roles in calcium-phosphorus homeostasis and bone mineralization. Direct exposure to ultraviolet radiation and dietary intake are the two main sources of vitamin D. Inadequate exposure to sunlight and less dietary intake during pregnancy and lactation cause both inadequate body stores in the newborn and in breast-milk[1]. These factors impair bone growth and mineralization in early infancy and may even cause hypocalcemic convulsions[2-5].

In 1995, a series of 105 breast-fed infants presenting with hypocalcemic convulsions due to rickets were reported in Turkey[6]. In the last two years we also had four 3-6-month-old infants presenting with hypocalcemic convulsions.

Common characteristics of these four breast-fed infants were their mothers' low serum vitamin D levels due to inadequate sunlight exposure and lack of vitamin supplementation during pregnancy. The data emphasizes the significance of the maternal factors, especially in the early infancy period, in the development of rickets.

In this study we aimed to measure serum vitamin D levels of pregnant women in the last trimester, and to investigate the factors affecting serum levels, the effects of maternal vitamin D status on infants and whether a supplementation of 400-800 IU vitamin D would be sufficient.

Material and Methods

Seventy-eight pregnant women and 65 infants who were followed up in various health centers were included in the study. The pregnant women with chronic diseases or who were taking medication and those with obstetric problems such as gestational diabetes, hypertension, preeclampsia, eclampsia or premature delivery (and twin pregnancy) were excluded from the study. Infants with normal birth weight (>2500 g) were included in the study.

25-hydroxyvitamin-D (25-OHvitD), calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) levels were measured in pregnant women in the last trimester. 'Enzyme binding protein assay' (Biomedical Gruppe, Immundiagnostic, Benheim, Germany) was used for 25-OHvitD determinations, and values between 25-40 nmol/L were considered marginal and levels below 25 nmol/L as severe vitamin D deficiency.

Infants born to these mothers were given 400 or 800 IU of vitamin D subsequently at the start of the second week. 25-OHvitD, Ca, P and alkaline phosphatase levels were measured and wrist X-rays were evaluated for 65 infants who were brought in for controls (May-September 2000). We analyzed the relationship between vitamin D status of the mothers and infants and socio-economic status; mothers' dressing habits (covered vs uncovered), educational level, and number of pregnancies; and sunlight exposure of the house. Socio-economic status was determined according to house income, and vitamin D intake was calculated according to daily nutrition samples.

Covered as a dressing habit meant covering the hair and sometimes part of the face and wearing dresses that completely cover the arms and legs. In the 40 infants who were breast-fed and received the recommended doses of vitamin D on a regular basis, the infants were randomly assigned to receive either 400 IU/d or 800 IU/d of vitamin D. The relationship between serum 25-OHvitD levels and supplementation doses given was analyzed.

The study protocol was approved by the local ethics committee. Statistical analyses were performed using SPSS in Windows 6.1. version 8.0. Mann-Whitney U test, Kruskal-Wallis test and Student's t test were used for evaluation.

Results

Serum 25-OHvitD level of the mothers was 1750±10.30 and 94.8% of the mothers had a 25-OHvitD level below 40 nmol/L (below 25 nmol/L in 79.5%). The risk factors associated with low maternal 25-OHvitD were low educational level ($p=0.042$), insufficient intake of vitamin D within diet ($p=0.020$) and "covered" dressing habits ($p=0.012$). Dressing habits of women were: group I ($n=4$) covered their head and hands with black scarf, with no covering on the face; group II ($n=49$) were black scarf on their head, with no covering of hands or face; and group III ($n=25$) had no cover on the head, face or hands. Mean serum 25-OHvitD level was 10.0±4.8 nmol/L in group I, 16.8±10.1 nmol/L in group II and 20.1±10.4 nmol/L group III. Dressing habits had no correlation with Ca, P, or ALP levels. But when serum 25-OHvitD levels were evaluated, the difference was significant between groups I and III ($p=0.014$) and groups II and III ($p=0.029$), whereas no difference was found between groups I and II ($p=0.089$).

Serum 25-OHvitD levels in pregnant women in relation to maternal age, socioeconomic status, education, number of gravida, total daily vitamin D intake and daily exposure time to sunlight is presented in Table I.

25-OHvitD level of the infants was 83.70±53.70 nmol/L, and 24.6% of the infants had 25-OHvitD levels lower than 40 nmol/L. Risk factors for low 25-OHvit D levels in infants were a) not receiving recommended doses of vitamin D regularly ($p=0.002$) and b) insufficient sunlight exposure of the house ($p=0.033$). 25-OHvitD levels (86.9±49.9 nmol/L, 666±71.9 nmol/L, $p=0.033$) were compared in those infants who received daily doses of 800 and

Table I. Serum 25-HydroxyvitaminD_3 Levels in Pregnant Women in Relation to Maternal Age, Socio-economic Status, Education, Number of Gravida, Total Daily Vitamin D Intake and Daily Exposure Time to Sunlight

	n	25-OHvitD nmol/L Levels (mean±SD)	p value
All women	78	17.5±10.3	–
Age			
<25 years	39	17.1±10.4	0.651
>25 years	39	18.2±10.2	
Socio-economic status			
Low	38	17.1±10.3	0.727
Moderate	28	17.8±10.9	
Good	12	18.6±9.3	
Education			
Illiterate-elementary School graduate	46	16.4±10.4	0.042
Secondary school and graduates	32	19.3±9.9	
Numbers of gravida			
1	31	18.9±11.5	0.606
2-3	36	16.4±9.5	
≥4	11	18.1±9.3	
Total daily vitamin D intake			
<100 IU/day	33	15.4±10.1	0.020
>100 IU/day	45	19.3±10.2	
Daily exposure time to sunlight			
<1 hour/day	37	17.9±11.5	0.893
>1 hour/day	41	18.2±11.9	

400 IU vitamin D regularly, but they did not differ significantly according to different maternal dressing habits. There was poor but significant correlation between maternal vitamin D levels and infants' 25-OHvitD levels at four months ($r=0.365$, $p<0.05$).

Discussion

The vitamin D stores of the newborn depend entirely on the vitamin D stores of the mother. If the mother is vitamin D-deficient, the infant will be deficient because of decreased maternal-fetal transfer of vitamin D[7]. Infant serum 25-OHvitD concentrations correlate with those of the mother within the first eight weeks of life, but not at older ages. Although there are maternal influences on vitamin D metabolism in the neonate after the first eight weeks of life, infant vitamin D status is more affected directly by sunshine exposure than by maternal nutritional status[1,7,8]. If vitamin D deficiency of the mother continues during lactation, risk of rickets increases in breast-fed infants.

The results of several studies suggest that the bone mass of the newborn may be related to the vitamin D status of the mother[9]. A recent study conducted in China also found evidence for a possible association between maternal vitamin D deficiency and impaired fetal bone ossification[8]. Bone ossification of the fetus may be impaired and the infant may present with congenital rickets. Craniotabes, large fontanel, enamel hypoplasia of teeth, and hypocalcemic tetany may be observed[5,7,10].

Vitamin D deficiency is common in pregnant women in Turkey. In 1981, Hasanoğlu et al.[11] found low serum 25-OHvitD level in 20% of mothers who had their pregnancies in winter months, whereas mothers having their pregnancies in sunny months had normal levels. In 1989, serum 25-OHvitD levels in 55% of mothers measured just after delivery were low. In August 1998, in a study from İstanbul, Alagöl et al.[12] reported low 25-OHvitD levels in 66.6% of women of reproductive age. In a recent study from Ankara, Andiran et al.[13] also found low serum 25-OHvitD levels in mothers who delivered in October and November; 85% had 25-OHvitD levels lower than 40 nmol/L and 46% lower than 25 nmol/L. Vitamin D deficiency was even more marked in our study, with third trimester levels lower than 25 nmol/L in 94.8%

of the group. This study shows that there is a widespread vitamin D deficiency amongst pregnant women living in Turkey, indicating the need for vitamin D supplementation.

Our city, Kocaeli, has intensive industrial business and air pollution, which prevent optimal exposure to sunlight. In addition, mothers' dressing habits, low dietary vitamin D intake, lack of vitamin supplementation in pregnancy, little time spent outside the home, and air pollution contribute to vitamin D deficiency. In India, in a study enrolling 9-24 month-old infants with the same socio-economic conditions and no vitamin D supplementation, the group living in the region with intensive air pollution had lower serum 25-hydroxyvitaminD_3 levels than those living in the country with no air pollution (12.6 nmol/L versus 28.2 nmol/L)[21].

We found no significant difference in maternal serum Ca, P, ALP and 25-OHvitD levels between various socio-economic levels. But Andiran et al.[13] found vitamin D deficiency in the low socio-economic class. Similar to that study, we also found positive correlation between serum 25-OHvitD level and educational status. But in a study from Pakistan, Atiq et al.[14,15] found lower serum 25-OHvitD levels in mothers and their infants from the upper socio-economic group. The women of the upper socio-economic group, who mostly preferred to live indoors, had reduced exposure to direct sunlight. Although more vitamin consumption is expected in frequent pregnancies, we found no correlation between the number of pregnancies and vitamin D deficiency.

Dressing habits (black covering on head, face and hands) have a role in serum vitamin D levels. In the study of Alagöl et al.[12], women who dressed in black covering their hands and face had lower 25-OHvitD levels, but they found no statistical difference between women covering hands and face with those whose heads, faces and hands were uncovered. In our study the difference was also significant between the groups whose heads were covered and those with heads uncovered ($p=0.029$).

The most recent policy statement of the American Academy of Pediatrics on breast-feeding states that "vitamin D may need to be given before six months of age in selected groups of infants (for infants whose mothers are vitamin D-deficient or those infants not exposed to adequate sunlight)[16]. In a study by Rothberg et al.[17], mothers were given daily supplements of 500 IU and 1000 IU of vitamin D from delivery, and it was shown that 25-OHvitD levels of infants at six weeks were not affected, whereas daily supplements of 400 IU of vitamin D significantly increased the 25-OHvitD levels of infants at six weeks. In a study in Finland by Ala-Houhala et al.[18], it was suggested that in cases when only the mother was supplemented with 2000 IU of vitamin D, the infants had 25-OHvitD levels similar to those receiving daily supplements of 400 IU of vitamin D. These findings indicate that it is more efficient to supplement infants rather than the mothers. In a study by Pittard et al.[19], in preterm and term infants whose mothers had normal 25-OHvitD levels, supplemented daily doses of 400 and 800 IU of vitamin D were compared and it was shown that daily doses of 400 IU were sufficient to achieve normal serum 25-OHvitD levels.

In infants with subclinical vitamin D deficiency [25-OHvitD levels <30 nmol/L and PTH>60 ng/L], PTH levels remained high with a daily supplement of 500 IU of vitamin D; however, the levels decreased with daily supplementation of 1000 IU of vitamin D[20]. In a study by Specker et al.[21] in China, only breast-fed infants received daily supplements of either 100, 200 or 400 IU of vitamin D, and it was shown that daily supplements of 100 or 200 IU of vitamin D were not sufficient to maintain optimal levels of 25-OHvitD in infants living in northern parts of the country where sunlight exposure is insufficient; at least 400 IU of vitamin D was necessary to obtain normal levels of 25-OHvitD. In this study, in infants who were born to mothers whose 25-OHvitD levels were below 25 nmol/L, only the breast-fed ones were started on regular daily supplements of 400 and 800 IU of vitamin D from two weeks of age, and 25-OHvitD levels were within normal range at 16 weeks in 79.5% of the infants (76.9 ± 35.4 nmol/L, 91.8 ± 61.5 nmol/L, respectively, $p=0.873$). These findings suggest that despite the mothers' levels being very low and provided that the sunlight exposure is adequate, a daily supplement of 400 IU of vitamin D is sufficient, especially for the infants born by the end of winter. However, further studies are necessary to determine whether a daily supplement of 400 IU of vitamin D would be sufficient for the infants born by the end of summer. In this study, information obtained regarding sunlight exposure of the homes suggested that infants in houses that received limited sunlight had lower levels of 25-OHvitD (although within normal limits) compared to those whose homes were exposed to a greater amount of sunlight (86.9±49.9 nmol/L, 66.6±40.9 nmol/L, respectively p=0.033).

When we compared the infants who did not receive the recommended daily requirement of vitamin D with those who received regular doses, levels of Ca, P, and ALP did not differ significantly; however, we found that 25-OHvitD levels were considerably lower (91.3±54.8 nmol/L, 42.0±14.1 nmol/L, respectively, p=0.002). These results indicate a direct effect of supplements of vitamin D on 25-OHvitD levels and the necessity of a daily supplementation of 400 IU of vitamin D in Turkey[2,18,22,23]. Half-life of 25-OHvitD is one month and its store is used within eight weeks of birth. For this reason there is no correlation between mother and infant's 25-OHvitD levels after eight weeks of age. However, in a study conducted by Atiq et al.[14,15] it was shown that the correlation between the mother's and the infant's 25-OHvitD levels continued at 12 weeks. In this study we found a weak but significant correlation between the infant's and the mother's 25-OHvitD levels at sixteen weeks (r=0.365, p=0.05).

In conclusion, as seen in our results, studies from İstanbul and Ankara have revealed that there is serious maternal vitamin D deficiency in Turkey even in summer, and the problem gradually becomes more severe thereafter. In addition to known risk factors, including suboptimal exposure to sunlight (air pollution, spending most of the daytime at home) and low dietary vitamin D intake, mothers' dressing habit is an important factor for maternal vitamin D deficiency. 25-OHvitD level was considerably lower in the infants who did not receive the recommended daily requirement of vitamin D than in those who received regular doses (91.3±54.8 nmol/L, 42.0±14.1 nmol/L, respectively, p=0.002). These results indicate a direct effect of supplements of vitamin D on 25-OHvitD levels and the necessity of a daily supplementation of 400 IU of vitamin D in Turkey. 25-OHvitD levels in the infants and the mothers at 16 weeks were weakly but significantly correlated (r=0.365, p=0.004). There was no difference between the doses of 400 IU and 800 IU vitamin D replacement. Pregnant women should be encouraged to get direct exposure to sunlight, as well as prenatal vitamin replacement. While our study fails to provide evidence that exclusively breast-fed infants have low vitamin D levels, we believe that it is necessary for infants born to mothers with risk factors for vitamin D deficiency to receive daily supplements of at least 400 IU of vitamin D. Supplementation with 800 IU vitamin D shows no greater benefits for the infants.

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