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Effects of Vitamin D in Neonates and Young Infants

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Abstract

Vitamin D is active in the regulation of calcium and phosphorus which supports cellular processes, bone mineralization and neuromuscular function. Evidence has shown that adequate levels of vitamin D may prevent multiple bone disorders such as rickets in children; and osteoporosis in adults. Vitamin D deficiency is thought to be a widespread public health problem globally; being more prevalent in places with limited sun exposure. About 90 % of vitamin D needs are met with adequate sun exposure while dietary sources contribute only to the remaining 10 % of daily requirement. Vitamin D deficiency during childhood is associated with an increased risk of skeletal disorders and vascular abnormalities. Respiratory distress syndrome is more common in severely vitamin D deficient preterm and supplementation with vitamin D to the mothers reduces respiratory distress syndrome in neonates. The aim of this study is to review the effects of vitamin D in neonates.

***Key Words*:** Effects, Infants, Neonate, Vitamin D.

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1- INTRODUCTION

The main source of vitamin D is vitamin D3, which is synthesized in the skin through exposure to ultraviolet B radiation. Ultraviolet B initiates the synthesis of vitamin D3 by converting 7-dehydrocholesterol into pre-vitamin D3, which is converted to vitamin D3. Vitamin D3 binds to vitamin D-binding protein and is transported to the liver for 25-hydroxylation to 25-hydroxyvitamin D (25-hydroxy-vitamin D); Calcitriol. Calcidiol undergoes further hydroxylation in the kidney and other tissues to calcitriol (1,25-dihydrovitamin D), the active form of vitamin D. Calcitriol stimulates the intestinal absorption of calcium and phosphorous, renal reabsorption of filtered calcium and mobilization of calcium and phosphorous from bone (1). Vitamin D plays a critically important role in the development, growth, and mineralization of the skeleton during its formative years, and performs an equally essential role in maintaining a healthy mineralization skeleton for adults of all ages (2). Vitamin D is also essential for intestinal calcium absorption and plays a central role in maintaining calcium homeostasis and skeletal integrity (3).

In addition, both micronutrients have important roles in non-skeletal-related physiological processes. Of concern, is the fact that a significant proportion of some population groups fail to achieve the recommended calcium intakes in a number of western countries. There is an increased reliance on dietary sources during winter months to help maintain adequate vitamin D status. Since vitamin D is found naturally only in a limited number of foods, the usual dietary vitamin D intake by many European populations is not sufficient to maintain adequate vitamin D status. The Committee on Nutrition of the American Academy of Pediatrics recommends 200 IU per day vitamin D for all infants and children (4). Hypovitaminosis D is a candidate risk-modifying factor for a diverse range of disorders apart from rickets and osteoporosis. Based on epidemiology, and on in vitro fertilization and animal experiments, vitamin D has been linked to multiple sclerosis, certain cancers (prostate, breast and colorectal), insulin-dependent diabetes mellitus and schizophrenia. McGrath (5) hypothesized that low pre- and perinatal vitamin D levels imprint on the functional characteristics of various tissues throughout the body, leaving the affected individual at increased risk of developing a range of adult-onset disorders.

Vitamin D is metabolized by successive hydroxylation to 25-hydroxyvitamin D and then, to 1,25 dihydroxyvitamin D, the most potent known metabolite of the vitamin D (6). The formations of 25-hydroxylatevitamin D and 1,25-Dihydroxyvitamin D are catalyzed by CYP24A1 (7). During pregnancy, the concentration of 25-hydroxyvitamin D in maternal serum increases in parallel with the increased need to absorb dietary calcium. 1,25-Dihydroxyvitamin D is produced in the feto-placental unit as well as in the placenta suggesting that the placenta may be a target for vitamin D action (2).

2-MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, Google scholar and Pubmed. Key references from extracted papers were also hand-searched. These searches focused upon papers published between November 2000 and 2015.

2-2. Search Terms

Combinations of search terms from three categories ("Neonetes" keywords AND "Vitamin D" keywords AND "Effects"

keywords) were used to search for the relevant literature. In addition, the book NEOFAX by Young and Mangum (1) was consulted.

3- RESULTS

Yang et al. (8) conducted a meta-analysis to review the effects of vitamin D supplementation during pregnancy on neonatal 25-hydroxyvitamin D and calcium concentrations. Cord blood 25-hydroxyvitamin D concentration was significantly increased by maternal vitamin D supplementation (mean difference, 22.48 nmol/L). Vitamin D supplementation during pregnancy can improve cord blood 25-hydroxyvitamin D concentration, but does not affect calcium cord blood concentration. Pérez-López et al. (9) assessed the effects of vitamin D supplementation during pregnancy on birth variables. Birth weight and birth length were significantly greater for neonates in the vitamin D group; mean differences were 107.6 grams and 0.3 cm, respectively.

Alizadeh Taheri et al. (10) compared the prophylactic effects of 200 and 400 IU per day vitamin D on the clinical, biochemical and radiological indices of the rickets of prematurity. Thirty newborns received 200 IU per day of vitamin D and other 30 newborns received 400 IU per day of vitamin D. On the 6th to 8th weeks of life, serum calcium, phosphate, alkaline phosphates, and 25-hydroxyvitamin D were measured and X-rays of left wrist and physical examination were performed. Both groups had no differences in biochemical, radiological or clinical presentation of rickets. Low dose vitamin D (200 IU per day) is sufficient for prevention of osteopenia.

Harrington et al. (11) performed a double-blinded, placebo-controlled trial in Bangladesh, 160 pregnant women were randomized to oral vitamin D3 (35,000 IU per week) or placebo from 26 to 29 weeks of gestation. Total serum calcium was higher in cord blood of those supplemented versus placebo (2.66$\pm$0.1 versus 2.61$\pm$0.2 mmol/L; P=0.04). Change in calcium concentration from birth to day 3 of life was attenuated by vitamin D (-0.10$\pm$0.17 mmoL/) compared with placebo (-22$\pm$0.18 mmol/L; P=0.02). Maternal serum 25-hydroxyvitamin D (P=0.04) and cord serum 25-hydroxyvitamin D (P<0.01) were associated with day 3 infant calcium, suggesting that the effect of supplementation was mediated by change in maternal-infant vitamin D status.

Ziegler et al. (12) performed a double blind trial evaluating four different doses of vitamin D. Breastfed infants (n=213) were randomized at 1 month to one of four doses of vitamin D, which they received through 9 months while receiving no formula. The supplements provided daily were 200 IU, 400 IU, 600 IU, or 800 IU of vitamin D. Most infants had low 25-hydroxyvitamin D levels (<50 nmol/L) at 1 month, but with supplementation levels rose. Overall, levels of 25-hydroxyvitamin D differed significantly in proportion of vitamin D. The four doses of vitamin D produced different plasma levels of 25-hydroxyvitamin D. The higher doses were somewhat more efficacious in maintaining vitamin D sufficiently in breastfed infants. These findings support the recommended dose of 400 IU per day and stress the need to start supplementation at birth.

Roth et al. (13) estimated the effects of prenatal vitamin D supplementation on infant growth. Longitudinal follow-up infants born at term or late- preterm ($\geq$34 weeks) to participants in a randomized double-blind trial of maternal third-trimester vitamin D3 (35 000 IU per week) versus placebo. Length-for-age z-score based on World Health Organization (WHO) standards was similar between groups at birth, but 0.44 higher in vitamin D versus placebo at 1 year, corresponding

to a sex-adjusted increase of 1.1 cm. Mean change in length-for-age z-score from birth to 1 month was significantly greater in vitamin D (0.53 cm per month) versus placebo (0.19 cm per month; P=0.004). In longitudinal analysis average length-for-age z-score during infancy was 0.41 cm higher in vitamin D versus placebo (P=0.001).

Atopic dermatitis is a highly prevalent allergic skin disease that affects children worldwide. Epidemiologic, clinical and basic immunological studies have suggested an association between vitamin D deficiency and the development of atopic dermatitis. Low levels of vitamin D, a pleiotropic hormone that has widespread effects on the immune system and skin integrity, appear to be inversely correlated with vitamin D severity, and vitamin D deficiency at birth is associated with higher risk of developing atopic dermatitis (14). Monangi et al. (15) evaluated vitamin D status in early preterm infants at birth and during birth hospitalization on current vitamin D intake. Serum 25-hydroxyvitamin D concentrations, vitamin D intake and risk factors for low vitamin D status were assessed in 120 infants born at ≤32 weeks of gestation. Mean±SD (standard deviation) serum 25-hydroxyvitamin D at birth was 46.2±14.0 nmol/L with lower concentrations in infants born <28 weeks than 28-32 weeks gestation (P=0.02). Serum 25-hydroxyvitamin D was <50 nmol/L in 63% of mothers, 64% of infants at birth and 35% of infants at discharge. Serum 25-hydroxyvitamin D concentration <50 nmol/L was widespread in parturient women and in early preterm infants at birth and at discharge.

Vitamin D deficiency has been suggested as a potential risk factor for the development of preeclampsia, and vitamin D deficiency during childhood is associated with an increase risk for numerous skeletal disorders as immunological and vascular abnormalities (16). Vitamin D deficiency can occur through multiple mechanisms including the consumption of diets low in this vitamin and inadequate exposure to environmental ultraviolet B rays.

A total of 51 healthy pregnant women were recruited (17). Of these, 34 were randomized to receive either 50,000 IU (group A) or 100,000 IU (group B) of vitamin D3 per month from the second trimester of pregnancy. The remaining 17 pregnant women, who formed the third group (group C) were found to have vitamin D deficiency, were initially treated with 200,000 IU of vitamin D3, following which the dose was adjusted to 50,000 IU per month. All the pregnant women had a serum vitamin D level < 30 ng/ml at the beginning of the second trimester. The neonates of 76% of women from group A had sufficient levels of 25-hydroxyvitamin D. All the neonates born to women in group B and C had 25-hydroxyvitamin D levels >20 ng/ml. A vitamin D3 dose >50,000 IU per month is required during the second trimester of pregnancy for vitamin D deficient pregnant women in order for their neonates to achieve serum 25-hydroxyvitamin D levels >20 ng/ml. Supplementation with <50,000 IU per month is insufficient to ensure a vitamin D level >20 ng/ml in all neonates born to vitamin D deficient pregnant women.

Vitamin D deficiency is common among otherwise healthy pregnant women and may have consequences for them as well as the early development and long-term health of their children. Jacobsen et al. (18) examined the importance of exposure to vitamin D early in life for development of fractures of the wrist, arm and clavicle, obesity and type 1diabetes during child and adulthood.

Hashemipour et al. (19) performed a randomized clinical trial to investigate the effect of vitamin D administration on

maternal and fetal calcium and vitamin D status. The trial was carried out on 160 pregnant women. 25-Hydroxyvitamin D < 30 ng/ml pregnant women were recruited at 26-28 weeks of pregnancy. In the control group, a 400 IU vitamin D3 per day was given. Patients in the treatment group were treated with 50,000 IU vitamin D3 weekly for a total duration of 8 weeks. At delivery, maternal and fetal calcium and 25-hydroxyvitamin D levels in both groups were compared. In total, 81% of pregnant women were vitamin D deficient. At the time of delivery, calcium and vitamin D levels were higher in the treatment group compared with the control group (92±3 vs. 85±4 ng/L, respectively (P=0.001) for serum calcium and 47.8±11.1 vs. 15.9±6.6 ng/ml, respectively, (P<0.001) for vitamin D. At the time of delivery, 32.7% of women in the control group had hypocalcaemia, while no hypocalcaemia case was detected in the vitamin D treated group. Mean serum neonatal 25-hydroxyvitamin D concentration was higher in the treatment group compared with the control group (27.7±5.2 vs. 10.9±4.4 ng/ml), respectively (P<0.01). The neonatal calcium in the treatment group was significantly higher than that of the control group (99±3 vs. 91±3 mg/L), respectively (P<0.001). The administration of vitamin D to pregnant women with vitamin D deficiency improves both maternal and neonatal calcium levels.

Ataseven et al. (20) investigated if 25-hydroxyvitamin D deficiency is a risk factor for respiratory distress syndrome. One hundred fifty-two preterm newborns, born at 29-35 weeks of gestational age, were included in the study. In 64% of preterm infants, 25-hydroxyvitamin D levels were compatible with severe deficiency (≤10, 33% with moderate deficiency 10-20, and 3% with mild deficiency 20-30). In none of the infants were observed normal 25-hydroxyvitamin D levels. Respiratory distress syndrome was common in preterm infants with severe (28%) compared to mild-moderate 25-hydroxyvitamin D deficiency (14%) (P <0.05). Supplementation of vitamin D to the mothers might be a valuable strategy to reduce respiratory distress syndrome.

Song et al. (21) evaluated the prevalence of vitamin D deficiency in pregnant women and their newborn infants. Severe vitamin D deficiency <25 nmol/L was detected in 54.5% of mothers and 46.6% of newborns. Neither mothers nor newborns had serum 25-hydroxyvitamin D concentrations that reached the normal levels (>75 nmol/L). The concentration of 25-hydroxyvitamin D in mothers was positively correlated with that in cord blood (r=0.89, P<0.001). Newborns of mothers with severe vitamin D deficiency had lower birth length and birth weight than infants with normal levels of vitamin D. The head circumference was lower in vitamin D deficiency newborns. Neonatal 25-hydroxyvitamin D concentrations are dependently related to maternal 25-hydroxyvitamin D levels. Maternal and neonatal vitamin D status influences newborn size.

Holmlund-Suila et al. (22) conducted a randomized double-blind study. Cord blood was obtained at birth for the determination of serum 25-hydroxyvitamin D. One hundred and thirteen infants were randomized to receive vitamin D 10, 30, or 40 µg per day from age 2 weeks to 3 months. Serum 25-hydroxyvitamin D, calcium homeostasis, and skeletal characteristics were evaluated with peripheral quantitative computed tomography at age of 3 months. Baseline serum 25-hydroxyvitamin D concentration was similar in all three groups (median 53 nmol/L). At 3 months, the mean serum 25-hydroxyvitamin D values were 88, 124, and 153 nmol/L, and the minimum values were 46, 57, and 86 nmol/L in the groups receiving 10, 30, and 40 µg, respectively

(ANOVA; P<0.001). The 40 µg dose vitamin D maintained 25-hydroxyvitamin D above 80 nmol/L in all infants.

Abrams et al. (23) evaluated the effects on serum 25-hydroxyvitamin D and bone mineralization of supplementation of breast-fed Hispanic and non-Hispanic Caucasian infants with vitamin D in infants. Cord serum 25-hydroxyvitamin D was significantly lower in Hispanic than non-Hispanic Caucasian infants (16±6.5, n=27, vs. 22.3±9.4, n=22, P=0.013). Among 38 infants who completed a 3 months vitamin D supplementation, provision of 400 IU per day of vitamin D increased final 25-hydroxyvitamin D to higher levels in non-Hispanic Caucasian compared to Hispanic infants. Daily vitamin D intake of 400 IU during the first months of life appears adequate to increase serum 25-hydroxyvitamin D and support bone mineral content increases despite low initial 25-hydroxyvitamin D levels in some infants.

Specker (24) observed that increased calcium absorption may be more dependent on estrogen's up-regulation of calcium transport genes than on vitamin D status. Severe vitamin D deficiency with secondary hyperparathyroidism during pregnancy leads to abnormal calcium homoeostasis in the neonate. Maternal vitamin D supplementation during pregnancy yields a greater birth weight among infants of mothers with adequate vitamin D status.

Pregnant women with gestational diabetes, intrahepatic cholestasis of pregnancy, and periodontal disease had lower vitamin D status at mid-gestational or delivery compared with controls (25). Maternal vitamin D status early in pregnancy was associated with risk of low birth weight and small-for-gestational age infants. Polymorphisms in vitamin D receptor gene may contribute to vitamin D-related disparities in fetal growth. Cord blood vitamin D status was associated with tolerogenic immune regulation and fewer respiratory infections in the newborn.

Circulating maternal concentrations of hormonally active calcitriol rise early in the first trimester, doubling by the end of the third trimester (26). The early rise is believed to be necessary for enabling the immunological adaptation by the mother required for the maintenance of a normal pregnancy. There is accumulating evidence that vitamin D supplementation may be able to prevent the immune maladaptation and loss of tolerance that occurs in preeclampsia, with evidence for an association obtained from various types of observational studies and clinical trials. There is also evidence from observational studies for potential long-term programming effects of vitamin D supplementation on immunological diseases (such as type 1 diabetes and allergic diseases), with evidence supporting the role of active vitamin D as a potent immunomodulator.

Walker et al. (27) assessed cord blood vitamin D concentrations from healthy term newborns, ascertained whether cord blood vitamin D insufficiency precludes optimal induction of the Toll-like receptor antimicrobial pathway in monocytes, and determined whether in vitro fertilization supplementation with 25-hydroxyvitamin D3 and/or 1,25-dihydroxyvitamin D3 restores Toll-like receptor-induced antimicrobial responses. Cord blood 25-hydroxyvitamin D and 1,25-hydroxyvitamin D2 were measured from cord blood of 23 newborns. Cord blood 25-hydroxyvitamin D and 1,25-hydroxyvitamin D2 concentrations were positively correlated (r=0.78; P<0.05). Compared with those conditioned in vitamin D-sufficient plasma 25-hydroxyvitamin D > 75 nmol/L, monocytes cultured in severely vitamin D-deficient plasma 25-hydroxyvitamin D < 30 nmol/L exhibited decreased Toll-like

receptor induces cathelicidin expression (P<0.05). Human milk has little vitamin D, and supplementation vitamin D must be given to all infants via drops or as contained in infant formula of foods. The calcium and phosphorus in human milk are adequate for infants in the first six months of life, with supplemental minerals coming from weaning foods after six months (28).

In humans, there are physiologic mechanisms that support the necessary calcium fluxes across the placenta and mammary gland and that are unresponsive to increases in calcium intake (29). This applies across the range of dietary calcium intakes recorded in healthy individuals. In contrast, although there is unlikely to be additional requirement for vitamin D during pregnancy and lactation, many women have poor vitamin D status. This places them at risk of osteomalacia and their infants at risk of rickets, osteomalacia, compromised skeletal growth and other outcomes.

Savino et al. (30) assessed the bone status using quantitative ultrasound applied to the second metacarpus and evaluated the influence of vitamin D supplementation on bone mineralization in exclusively breast-fed infants. Measures of speed of sound and quantitative ultrasound were significantly lower in the group of breast-fed infants without vitamin D supplementation (respectively, P=0.001 and P=0.015). A statistically significant difference was also observed between the two groups for z-scores of quantitative ultrasound parameters for age and length, with lower levels in infants not supplemented with vitamin D. Both measures of speed of sound and bone transmission time decline during the first year of life. These data support the importance of vitamin D supplementation in breast-fed infants in the first period of life to provide an adequate bone development.

Eighty-seven children were followed from birth to 14 months. At 14 months bone variables were measured with peripheral computed tomography from the left tibia (31). Serum 25-hydroxyvitamin D and bone turnover markers were determined. The children were divided in two groups based on vitamin D status during pregnancy. Despite discrepant serum 25-hydroxyvitamin D at baseline (median 36.3 vs. 52.5 nmol/L, P<0.05), the values at 14 months were similar (63 vs. 66 nmol/L) in low vitamin D and high vitamin D. Serum 25-hydroxyvitamin D increased more in low vitamin D (P<0.001) despite similar total intake of vitamin D (mean 12.3 µg per day). In low vitamin D, tibial bone mineral content was lower at birth but bone mineral content gain was greater (multivariate analysis of variance ANOVA; P=0.032) resulting in similar bone mineral content at 14 months in the two groups. In high vitamin D, tibial total bone cross-sectional area was higher at baseline; the difference persisted at 14 months (ANOVA; P=0.032).

Human milk reflects the vitamin D status of the mother and often contains inadequate levels of 25-hydroxyvitamin D for infant nutrition (32). The Committee on Nutrition of the American Academy of Pediatrics recommends 200 IU of vitamin D supplementation of all infants. Many breast-feeding advocates believe that the Committee on Nutrition of the American Academy of Pediatrics recommendations undermine breast-feeding, implying that human milk is inadequate for infant nutrition. Past experience with routine provision of 10 µg per day (400 IU per day) of vitamin D to all pregnant mothers suggests that this dose is sufficient to prevent overt neonatal complications of vitamin D deficiency (33). Recent data suggest that supplementation with dosages above 10 µg per day of vitamin D may be required for optimal health in the mother and child.

Human disease associations and basic physiological studies suggest that vitamin D deficiency is plausibly implicated in adverse health outcomes including mortality, malignancy, cardiovascular disease, immune functioning and glucose metabolism (34). Vitamin D deficiency during pregnancy has been linked with a number of maternal problems including infertility, preeclampsia, gestational diabetes and increased rate of cesarean section. Likewise, for the child, there is an association with small size, impaired growth and skeletal problems in infancy, neonatal hypocalcaemia and seizures, and an increased risk of HIV transmission. Other childhood disease associations include type 1 diabetes and effects on immune tolerance.

Acting through the vitamin D receptor, vitamin D can produce a wide array of favorable biological effects via genomic, and non-genomic or intracrine mechanisms and, therefore, contributes to the improvement of human health. Lapillonne (35) hypothesizes that some of the effects may be even more critical during pregnancy. It appears that vitamin D insufficiency during pregnancy is potentially associated with increased risk of preeclampsia, insulin resistance and gestational diabetes mellitus. Furthermore, experimental data also anticipate that vitamin D sufficiency is critical for fetal development, and especially for fetal brain development and immunological functions.

Yu et al. (36) determined the vitamin D status in pregnancy and evaluated the effects of daily and of single-dose vitamin D supplementation. A total of 180 women were recruited at 27 weeks gestation and randomized into three treatment groups: a single oral dose of 200,000 IU vitamin D, a daily supplement of 800 IU vitamin D from 27 weeks until delivery and no treatment group. Vitamin D and calcium levels in mothers at 27 weeks and at delivery and cord 25-hydroxyvitamin D and calcium levels were measured. The final maternal 25-hydroxyvitamin D levels were significantly higher in the supplemented group (daily dose, median 42 nmol/L, stat dose (median) 34 nmol/L vs. median 27 nmol/L in the no treatment; P=0.001). Cord 25-hydroxyvitamin D levels were significantly higher with supplementation daily dose (median 26 nmol/L, stat dose 25 nmol/L vs. median 17 nmol/L in no treatment (P=0.001). Single or daily dose improved 25-hydroxyvitamin D levels significantly. However, even with supplementation, only a small percentage of women and infants were vitamin D sufficient.

Current vitamin D guidelines for the neonatal period, 5-10 µg (200-400 IU) per day, prevent rickets at the typical calcium intakes in developed countries. The annual incidence of vitamin D-deficiency rickets in developed countries ranges between 2.9 and 7.5 cases per 100,000 children (37). The 25-hydroxyvitamin D deficiency at the third-trimester is associated with fetal bone mineral accrual that may affect prepubertal bone mass accumulation. Five µg (200 IU) per day of vitamin D has little effect on vitamin status as measured by the serum 25-hydroxyvitamin D concentration.

Vitamin D insufficiency and deficiency during pregnancy are reflected in lower maternal weight gain and biochemical evidence of disturbed skeletal homeostasis in infants, with, in extreme situations, reduced bone mineralization, radiological evident rickets, and fractures (38). In the short term, lack of vitamin D supplementation in infancy leads to biochemical disturbances, reduced bone mineralization, slower growth, and eventual alteration in bone shape and increased risk of fracture, the hallmarks of rickets. In long term, lack of vitamin D supplementation may result in reduced bone size and mass during childhood and an increase risk of type 1 diabetes mellitus.

Nishimura et al. (39) measured the serum 25-hydroxyvitamin D levels in pregnant women, as well as measuring 25-hydroxyvitamin D levels in cord blood and breast milk in pregnant women hospitalized for longer than 1 month. Maternal serum 25-hydroxyvitamin D levels were decreased at delivery compared with those in control subjects (10.9±26 ng/L vs. 19.5±4.9; P<0.01). The levels of 25-hydroxyvitamin D in the cord blood were not significantly different between the long-term hospitalization and control pregnant women (9.36±1.7 ng/L vs. 11.1±3.0 ng/L). The 25-hydroxyvitamin D concentrations in the cord blood were significantly lower than the maternal levels in both groups; the ratios of the levels in cord to maternal blood in the long-term hospitalized women and control subjects were 82.1% and 60.3%, respectively. Long maternal hospitalization does not always cause neonatal vitamin D deficiency.

In post-neonatal infants, vitamin D metabolism shows seasonal variation. Namgung et al. (40) hypothesized that in winter-born infants, the bone mineral content is low and serum osteocalcin is high, related to increased bone turnover and high serum 1,25-dihydroxyvitamin D. These authors studied 246 healthy, term appropriate-for-gestation infants in winter (January through March 140 children) and summer (July through September, 106 children). The bone-mineral content of the one-third distal radius was measured before 3 days of age by photon absorptiometry. Significant seasonal differences were found: summer-born infants had significantly lower bone-mineral content, higher serum osteocalcin and 1,25-dihydroxyvitamin D, and lower serum calcium than winter-born infants. Seasonal effects on fetal bone operate especially in early pregnancy approximately 6 months before birth.

In a double-blind trial of supplementary vitamin D (1,000 IU daily) administered in the last trimester of pregnancy to Asian women living in London, supplemented mothers gained weight faster (63.3 grams per day) than those in the control group (46.6 grams per day), and at term had significantly higher plasma levels of retinol binding protein and thyroid binding prealbumin indicated better protein-calorie nutrition (41). Almost twice as many infants in the unsupplemented group weighed under 2,500 grams at birth, and had significantly lower retinol binding protein levels than infants of supplemented mothers. The nutritional benefits of supplementation provide further support for the routine administration of vitamin D to all British Asians during pregnancy.

In a double-blind trial of vitamin D supplements in pregnant Asian women ergocalciferol (1,000 IU per day) was administered to 59 women and placebo to 67 control women during the last trimester (42). At entry to the trial maternal serum 25-hydroxyvitamin D concentrations were low in both treatment and control groups and significantly lower in vegetarians than non-vegetarians. Mothers in the treatment group gained weight faster in the last trimester than those in the control group, and at term they and their infants all had adequate plasma 25-hydroxyvitamin D concentrations. Mothers and infants in the control group, however, had low plasma of 25-hydroxyvitamin D and calcium and raised plasma alkaline phosphate activity. Five of these infants developed symptomatic hypocalcaemia. Almost twice as many infants in the control group were small for gestational age (29% vs. 15%), but there were no significant differences between the two groups of infants in anthropometric measurements. Infants in the control group, however, had larger fontanelles, suggesting impaired ossification of the skull.

4-DISCUSSION

Vitamin D is essential for the development and mineralization of the skeletal (2). The mineralization of the skeletal is due to the calcium which is absorbed from the intestine (3). The vitamin D is found naturally only in a limited number of foods and supplementation with exogenous vitamin D is required. The dose of exogenous vitamin D is 200 or 400 IU per day to achieve a normal level of 25-hydroxyvitamin D >75 nmol/L. Sunlight increases the vitamin D levels but adequate sunlight exposure is difficult to determine for each subject.

Hypovitaminosis D is a factor for different disorders like sclerosis and prostate, breast and colorectal cancers. These disorders may be due to prenatal deficiency of vitamin D (5). Vitamin D supplementation during pregnancy has been associated with increased circulation of 25-hydroxyvitamin D concentration in cord blood. Neonates to mothers supplemented with vitamin D have greater weight and length than the neonates from mothers not supplemented with vitamin D (9). Total serum calcium is higher in the cord blood of the mothers supplemented with vitamin D than in the cord blood of neonates born to mothers not supplemented with vitamin D (11). A dose of 35,000 IU per week of vitamin D3 during the third trimester of pregnancy increases the length of neonates compared with the infants born to mothers not supplemented with vitamin D3.

Vitamin D deficiency in pregnant women may have consequences for them and for early development and long-term health of their children (18). Skeletal disorders and immunological and vascular abnormalities during childhood are associated with deficiency of vitamin D. Deficiency of vitamin D can cause development of fractures of the wrist, arm and clavicle, obesity and type 1 diabetes during child and adulthood. The administration of vitamin D to pregnant women with vitamin D deficiency improves both maternal and neonatal calcium levels (19).

Respiratory distress syndrome was more common in severely lacking vitamin D preterm. Supplementation of vitamin D to mothers reduces the distress syndrome. The concentration of 25-hydroxyvitamin D in mothers was positively correlated with that in cord blood. Maternal and neonatal vitamin D status influences newborn size. Neonates to mothers with severe vitamin D deficiency had lower birth length and birth weight than infants born to mothers with normal levels of vitamin D. The head circumference was lower in vitamin D deficiency newborns (21). Vitamin D3 supplementation with 40 µg dose per day from age 2 weeks to 3 months, maintained 25-hydroxyvitamin D above 80 nmol/L in all infants (22).

Human milk reflects the vitamin D status of the mother and often contains inadequate levels of 25-hydroxyvitamin D for infant nutrition (32). The Committee on Nutrition of the American Academy of Pediatrics recommends 200 IU of vitamin D supplementation of all infants. Hypponen and Boucher (33) state that 10 µg per day (400 IU per day) of vitamin D to all pregnant mothers may be required for optimal health in the mother and child. Vitamin D deficiency during pregnancy has been linked with maternal infertility, preeclampsia, gestational diabetes and increased rate of cesarean section. In infants with deficiency of vitamin D, there is an association with small size, impaired growth and skeletal problems. The annual incidence of vitamin D-deficiency rickets in developed countries ranges between 2.9 and 7.5 cases per 100,000 children (37). Vitamin D (200-400 IU) per day prevents rickets at the typical calcium intakes. Five µg (200 IU) per day of vitamin D has little effect on vitamin D status as measured by the serum 25-hydroxyvitamin D

concentration. Populations at risk for vitamin D are those for which, for environmental, cultural, or medical reasons, exposure to sunlight is poor and dietary intake of vitamin D is low. In post-neonatal infants, vitamin D metabolism shows seasonal variation. Summer-born infants have significantly lower bone-mineral content, higher serum osteocalcin and 1,25-dihydroxyvitamin D, and lower serum calcium than winter-born infants (40). Supplementation of vitamin D (1,000 IU daily) administered in the last trimester of pregnancy yields weight increase faster than those in the control group. Maternal weight correlates with postpartum levels of both retinol binding protein and thyroid binding prealbumin. Several infants born to unsupplemented mothers weighed under 2,500 grams at birth and had significantly lower retinol binding protein levels than infants born to supplemented mothers (41).

Ergaciferol (1,000 IU) administered daily in the third trimester of pregnancy yields weight increase faster than in the control group, and at term they and their infants all had adequate plasma levels of 25-hydroxyvitamin D concentrations. Infants in the control group had larger fontanelles, suggesting impaired ossification of the skull. This body of knowledge is consistent with the view that vitamin D exerts several beneficial effects in the infants. Vitamin D is important in the development, growth, and mineralization of the skeletal. This is due to the intestinal calcium absorption. Vitamin D is metabolized to 25-hydroxyvitamin D and the concentration of this metabolite is often low in the serum of mothers and infants. The supplementation of vitamin D in pregnant women increases the cord concentration of 25-hydroxyvitamin D. The concentration of this metabolite correlates in the serum of mothers and infants. 25-Hydroxyvitamin D is metabolized to 1,25-dihydroxyvitamin D, the latter is produced in the feto-placental unit as well as in the placenta. Thus, the placenta may be a target for vitamin D action.

5- CONCLUSION

Vitamin D is important for the development, growth and mineralization of the skeletal in neonates and children. Vitamin D is essential for intestinal absorption of calcium. Vitamin D is metabolized to 25-hydroxyvitamin D and then to 1,25-dihydroxyvitamin D. Pregnant women in developed countries often have insufficient serum concentrations of 25-hydroxyvitamin D and a supplementation of vitamin D is necessary, usually a daily dose of 400 IU of vitamin D is sufficient to increase the serum level of 25-hydroxyvitamin D to normal value of >75 nmol/L. Supplementation of vitamin D increases birth weight and birth length compared to newborn infants born to unsupplemented pregnant women.

6-CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

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