REVIEW ARTICLE

IMPACT OF VITAMIN D ON PREGNANCY AND PREGNANCY OUTCOME

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ABSTRACT: Vitamin D is required throughout life. It is necessary for the formation of bone, but also likely plays an important role in several other physiological systems and it prevents several degenerative diseases and anticancer agent. Its use may well prevent several degenerative diseases, and it may also play a role as an anticancer agent. 84% of pregnant women in Northern India have suboptimal vitamin D levels. Vitamin D deficiency during pregnancy can significantly impact pregnancy and fetal outcome. A high prevalence of physiologically significant hypovitaminosis D and its magnitude are now recognized in pregnant and breast feeding women and infants. Despite abundant sunlight, UV drenched Indians remain vitamin D deficient because of highly pigmented skin and inadequate direct sunlight exposure, either due to a cultural tendency or due to liberal use of sunscreen. In India, rickets and hypocalcaemia seizures due to vitamin D deficiency in exclusively breastfed young infants have been reported. Vitamin D in breast milk relates to mothers' vitamin D intake, skin pigmentation and sunlight exposure. Vitamin D is thought to have a role in asthma exacerbations. Repletion of vitamin D through supplementation ensures adequate maternal vitamin D stores for prenatal and postnatal period and hence, helps prevent infant rickets. A maternal daily intake of vitamin D 4000 IU/day increased the antirachitic activity of milk by nearly 100 IU/L.
KEYWORDS: Vitamin D, Rickets, Osteomalacia.

INTRODUCTION: VITAMIN D METABOLISM: No one would contest that India is a country that has plenty of sunshine. But unfortunately, there is a pandemic w of vitamin D deficiency and insufficiency around the world and those of us living in sunny India are not immune to the problem! In a study conducted in India, 96% of neonates, 91 % of healthy school girls, 78% of healthy hospital staff and 84% of pregnant women have been reported to have suboptimal levels of vitamin D in their body.

Despite abundant sunlight, UV-drenched Indians remain vitamin D deficient because of highly pigmented skin and inadequate direct sunlight exposure, either due to a cultural tendency or due to liberal use of sunscreen. When exposed to factors that adversely affect vitamin D and bone mineral metabolic status, an imbalance in bone mineral metabolic homeostasis results.

Among such factors, low-calcium, high-phytate diets; soft drinks replacing milk; increasing prevalence of children and adults favoring indoor activities; pregnancy; and reduced sunlight exposure in people living among tall buildings in urban areas, working in offices and covering themselves due to religious and cultural reasons are important. This results in the up regulation of parathyroid hormone, which may promote insulin resistance, weight gain, hypertension, left ventricular hypertrophy and the acute-phase response, which in turn increase the risk for ischemic arrhythmias and cardiovascular mortality.

In the last 20 years, there has been a tremendous study in the field of vitamin D due to its important role not only in skeletal development and maintenance, but also due to its beneficial effects on extra skeletal tissues. Figure 1 shows the structure of vitamin D_3. Various reports have shown that relatively high proportions of people have inadequate levels of vitamin D.[1,2]

The circulating level of the inactive precursor 25-hydroxyvitamin D [25(OH)D] is the universally accepted indicator of vitamin D status, because it is easily measured, has the longest half-life in circulation (approximately 2 or 3 weeks) and the levels of 25(OH) D correlate with clinical disease states. The vitamin D input needed to achieve optimal serum 25(OH) D obviously depends upon both the starting value and the chosen target level.

Vitamin D deficiency/insufficiency leads to falls & fractures, infections, allergies, tumors, type-I diabetes, type-II diabetes, hypertension, stroke, heart attack, heart failure, multiple sclerosis.

A 25(OH) D continuum is said to exist to depict vitamin D status:

- Vitamin D deficiency: <10ng/mL
- Insufficiency: 20-29ng/mL
- Sufficiency: 30-100ng/mL

'Sufficiency' refers to levels of 25(OH) D corresponding to the absence of abnormalities in calcium homeostasis. Deficiency indicates 25(OH) D levels corresponding to clinically evident disease states with respect to skeletal health (i.e. osteomalacia or rickets).[3]

IMPACT OF VITAMIN D DEFICIENCY: Vitamin D deficiency during pregnancy has important implications for the newborn and infant. There are few data from India about the prevalence of hypovitaminosis The vitamin D deficiency epidemic during pregnancy is caused by a lack of adequate sunlight exposure needed to synthesize vitamin D_3 (cholecalciferol) in the skin, coupled with oral intakes that are too low to meet the increased demands of pregnancy, even with regular use of prenatal vitamins containing 400 IU vitamin D_3.

D in pregnancy and in the newborn. Vitamin D deficiency during pregnancy is linked not only to maternal skeletal preservation and fetal skeletal formation, but also is vital to the fetal 'imprinting' that may affect chronic disease susceptibility later in life as well as soon after birth. Vitamin D deficiency during pregnancy has been associated with a number of serious short and long term health problems in offspring, including impaired growth, skeletal problems, type 1 diabetes, asthma and schizophrenia.[4]

Although most of the studies involve the risk of skeletal deformities and vitamin D, recent studies have observed reduced weight gain in vitamin D-deficient pregnant women. Anorexia and malaise are often associated with vitamin D deficiency, which may explain the poor weight gain among pregnant women with vitamin D deficiency.

Another reason for low-weight gain is the anabolic effect of vitamin D, specifically 1,25 (OH)2D, and impaired maternal weight gain and fetal growth among mothers with severe deficiency.[5,6]

Pre-eclampsia is a pregnancy-specific syndrome and can be linked to vitamin D deficiency. The prevalence of preeclampsia is high in women with deep pigmented skin suggesting the role

of vitamin D. The pathogenesis of preeclampsia has been shown to involve biological processes that may be directly or indirectly affected by vitamin D, including immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation and hypertension. Vitamin D has been hypothesized to influence preeclampsia risk.[7]

Vitamin D deficiency has a deleterious impact on musculoskeletal health. The inverse relationship between serum 25(OH) D levels and PTH and direct correlations exist between vitamin D and bone mass as well as muscle mass, and the efficacy of vitamin D in reducing falls and fractures. Chronically low levels of skeletal calcium that result from vitamin D deficiency allow unmineralized osteoid tissue to accumulate, causing bone pain and fracture.[8] There is a correlation between 25(OH)D level and spine hip; forearm BMD and pain; preeclampsia and gestational diabetes.

The serum level of 25(OH) D deficiency has long been suspected as a risk factor for glucose intolerance and perhaps 1,25(OH) 2D has a role in the regulation of insulin secretion and the development of GDM. Researchers have observed a correlation between obesity and vitamin D levels. In a cross-sectional study conducted in pregnant women, the prevalence of severe vitamin D deficiency (<12.5) in GDM patients was higher than in normoglycemic pregnancies. The regression model revealed a strong correlation between the HOMA index and serum levels of vitamin P.[9,10]

Postpartum vitamin D deficiency can affect the vitamin D content of the breast milk. Since breast milk is the only food for the growing infant, this can affect the vitamin D intake of infant leading to rickets and other impact of Vitamin D Deficiency Postpartum vitamin D deficiency can affect the vitamin D content of the breast milk. Since breast milk is the only food for the growing infant, this can affect the vitamin D intake of infant leading to rickets and other manifestations of vitamin D deficiency. Low vitamin D levels can also affect the dentition of the growing infant and lead to hypocalcemia.[11]

Low vitamin D status of the mother affects the vitamin D content of breast milk leading to rickets and inadequate dentition in infants.

Vitamin D deficiency affects fetal growth by affecting maternal calcium homeostasis. Reduced growth of fetus is observed in mothers who had suboptimal levels of vitamin D. Recent findings suggest that maternal vitamin D insufficiency during pregnancy has consequences for the offspring's bone health in later life.

Children of mothers with low vitamin D status during late pregnancy had reduced whole-body BMC, bone area and areal BMD at the age of 9 years.

Maternal vitamin D status may help neonatal skeletal development and body composition in the offspring by influencing the interaction between osteoblasts and adipocytes. Low maternal S-25-(OH) D is associated with shorter duration of gestation and consequently, reduced growth of long bones in newborns.

The serum parathyroid hormone levels are elevated in vitamin D-deficient mothers probably due to increased mineral demands of growing fetus.

It has been pointed out that children of mothers, with low vitamin D status during late pregnancy had reduced whole-body bone mineral content, bone area and areal bone mineral density at the age of 9 years. The birth-weight and growth during the first year of life may also contribute to skeletal fragility later in life.[12]

Mahon et al[13] showed that lower maternal 25(OH)D is associated with greater femoral metaphyseal cross-sectional area and a higher femoral splaying index at 19 weeks' gestation [r=-0.16, 95% confidence interval (CI) -0.25 to -0.06 and r = -0.17, 95% CI-0.26 to -0.07, respectively] and at 34 weeks' gestation (r=-0.10, 95% CI-0.20 to 0.00 and r=-0.11, 95% CI-0.21 to -0.01, respectively).

The study was carried out in 424 pregnant women who were randomized into three groups based on their vitamin D levels [sufficient/borderline (>50nmol/L, 63.4%), insufficient (25-50 nmol/L, 30.7%), and deficient (≤ 25nmol/L, 5.9%)]. Across these groups, the geometric mean femoral splaying indices at 19 weeks' gestation increased from 0.074 (sufficient/ borderline) to 0.078 (insufficient) and 0.084 (deficient).

Mahon et al. pointed out that maternal vitamin D insufficiency can influence fetal femoral development as early as 19 weeks' gestation.[13]

The vitamin D status of a new-born infant during the first 6-8 weeks of life is determined by the vitamin D levels "at birth, which in turn, depends on the vitamin D status of the mother. Vitamin D deficiency with a resurgence of rickets and tetany is increasingly being reported in Indian young infants.

A study by Jain et al. determined the prevalence of vitamin D deficiency and insufficiency among healthy term breastfed 3-month-old infants and their mothers. Vitamin D deficiency was found in 66.7% of infants 81.1 % of mothers. Insufficiency was found in an additional 19.8% of infants and 11% of mothers. Infants who had a serum 25(OH) D levels <10ng/mL reported to have radiological rickets.

Vitamin D in breast milk relates to mother's vitamin D intake, skin pigmentation and sunlight exposure.

Vitamin D concentrations in breast milk have been observed to be low (≤20 IU/L) and is inadequate for the needs of the growing infant. Vitamin D in breast milk related to mothers' vitamin D intake, skin pigmentation and sunlight exposure. This implies that babies born to mothers with vitamin D deficiency are very likely to develop vitamin D deficiency unless supplemented from outside or adequately exposed to sunlight which is often not practical during early infancy.[14]

Vitamin D is thought to play a role in many chronic diseases like asthma as it may possess immunomodulatory properties. Vitamin D plays a complex role in the immune system and its regulation of various aspects of immunity has allowed speculation on its potential role in asthma. Vitamin D receptors are present in peripheral blood mononuclear cells and help to regulate the balance of several proinflammatory and anti-inflammatory responses in the immune system.

Studies have suggested that prenatal vitamin D intake has an effect on childhood wheezing and asthma. Additionally, vitamin D may play a role in asthma exacerbations, and recent evidence also suggests its importance in steroid-resistant asthma.[15]

Vitamin D Supplementation and Serum Vitamin D Levels: Delvin et al. assessed whether modification of vitamin D nutritional status during the last trimester of pregnancy influenced maternal and neonatal calcium homeostasis. Forty pregnant women were randomly assigned to two groups and blood taken to assess the basal values of Ca, Pi, Mg, iPTH, 25(OH)D, and $1,25(OH)_2D$. Vitamin D (1000 IU) was supplemented to one group. At the time of delivery,

maternal serum 25(OH) D was higher in the +D group ($p<0.0005$). Adequate maternal vitamin D stores ensured better perinatal handling of calcium which is of particular importance for populations at risk for hypovitaminosis D.[16]

It is recommended that all infants, including those who are exclusively breastfed, have a minimum intake of 200 IU of vitamin D per day beginning during the first 2 months of life. In addition, it is recommended that an intake of 200 IU of vitamin D per day be continued throughout childhood and adolescence, because adequate sunlight exposure is not easily determined for a given individual.[17]

Specker et al. determined whether amounts of vitamin D lower than recommended dose is effective in preventing rickets in China. Serum 25(OH) D concentrations were shown to be higher with an increasing supplemental dosage of vitamin D ($p<0.001$). None of the infants had rickets at 6 months of age.[18]

Administration of vitamin D in two large doses of 600,000 U each in the seventh and eighth months of pregnancy in 20 women proved more efficacious. Statistically significant improvement was observed in all the three biochemical parameters in maternal as well as cord sera. Fetal birth-weight was also significantly greater with this mode of therapy.[19]

Maternal supplementation with vitamin D has shown to result in an increase in circulating 25(OH)D concentrations among nursing infants, which leads to an elevation of the antirachitic activity of the mothers' milk. A maternal daily intake of vitamin D 4000 IU/ day increased the antirachitic activity of milk by nearly 100 IU/L. This increase in circulating 25(OH) D concentrations among the nursing infants is a direct reflection of the vitamin D_2 intake of the mothers.[20]

TREATMENT AND PREVENTION STRATEGIES:

Infants & Toddlers (0-1 years of age): 2000 IU vitamin D_2 or D_3/day or 50,000 IU vitamin D_2 or D_3 once weekly for 6 weeks to achieve blood level of 30 ng/mL followed by maintenance therapy of 400-1000 lU/day.

Children (1-8years of age): 2000 IU vitamin D_2 or D_3/ day for 6 weeks or 50,000 IU of vitamin D_2 or D_3 once a week for at least 6 weeks to achieve blood level of 30 ng/mL followed by maintenance therapy of 600-1000lU/day.

Adults: 50,000 IU vitamin D_2 or D_3 once-weekly for 8 weeks or its equivalent of 6000 IU of vitamin D_2 or D_3 daily to achieve blood level of 30 ng/mL followed by maintenance therapy of 1500-2000 lU/day.

Prevention of Rickets[3]:

- Premature infants: 400-800 IU (10-20 mg)/day from birth.
- Term infants: 400 IU (10 mg)/day vitamin D_3.
- Pregnant/lactating mothers: 1000-2000 IU (25-50 mg) of vitamin D_3 daily.

Treatment of Rickets[3]:

- **Breast fed infants:** 200,000 IU (5000 mg) vitamin D_3 every 3 months or 1000-2000 IU (25-50 mg) vitamin D_3/day along with calcium supplement or a single oral dose of 6, 00,000 IU.
- Up to 10,000 IU vitamin D_3/day is safe.

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