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Review Article

Hypovitaminosis D in Pregnancy: A Review

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ABSTRACT

Vitamin D is required to maintain proper levels of calcium and phosphorous, so inadequate Vitamin D in pregnancy may lead to abnormal bone growth, fractures or rickets in newborns. Deficiency of Vitamin D has been linked with higher risk of pregnancy complications such as pre-eclampsia, preterm birth, low birth weight and gestational diabetes. However, some studies have found no association between Vitamin D and pregnancy outcome. The Aim of this study is to review the current information about deficiency of Vitamin D and adverse pregnancy outcomes.

Key words: Vitamin D, pregnancy

INTRODUCTION

Deficiency of vitamin D is wide spread in individuals irrespective of their age, gender, race and geography, as it plays an essential role in health at all stages of life. Vitamin D is produced in the skin after exposure to sunlight or to artificial UV light, so deficiency of vitamin D is not expected in a tropical country like India, where abundant sunshine is present for most or all of the year however deficiency of vitamin D may result from limited exposure to sunlight (due to increasing urbanization), long term wearing of covering clothes (Traditional Indian households), uses of sunscreen, age as well as low consumption of food containing vitamin D_2 (ergocalciferol) and malabsorption syndrome. [1,2] Along with these factors sunlight is less effective in producing vitamin D in persons with darker skin because UV light is absorbed by the skin pigment. [3,4] The recognition that ultraviolet light produces skin cancer, and the public health campaigns directed against excessive exposure to ultraviolet light has resulted in the appearance of Vitamin D deficiency. Main function of Vitamin D is maintaining serum calcium and phosphorus concentrations within normal range by enhancing the efficiency of the small intestine to absorb these minerals form the diet. [5]

Human disease associations and basic physiological studies suggest that Vitamin D deficiency is plausibly implicated in adverse health outcomes including mortality, malignancy, cardio vascular disease, immune functioning and glucose metabolism. Deficiency of Vitamin D in children results in inadequate mineralization of the skeleton causing rickets and in adult osteomalacia. Vitamin D is also required for growth and development including regulation of cellular differentiation and apoptosis, immune system development and brain development which has led to increased interest in the role of this vitamin during pregnancy too. [6-8]

There is considerable evidence that low maternal level of 25-hydroxy vitamin D are associated with adverse outcomes for

both mother and fetus in pregnancy, as human fetus is entirely dependent on the maternal pool of Vitamin D.

Deficiency of Vitamin D during pregnancy has been linked with a number of maternal problems including infertility, preeclampsia, gestational diabetes and an increased rate of caesarean section. Likewise for the child there is an association with small size, neonatal hypocalcemia and seizures and an increase risk of HIV transmission. Other childhood disease associations include type I diabetes and effects on immune tolerance. So, hypovitaminosis during gestation may have impact on the offspring in utero, infancy, and later in life.

Overview of the role of Vitamin D:

Vitamin D, a secosteroid, can either be made in the skin form a cholesterol like precursor (7-dehydrocholesterol) by exposure to sunlight or can be provided pre-formed in the diet. [9] Vitamin D which is made in the skin is referred to as vitamin D_3 (cholecalciferol) whereas the dietary form can be Vitamin D_3 or a closely related molecule of plant origin known as Vitamin D_2 (ergocalciferol), Because Vitamin D can be made in the skin so some nutritional text refer to the substance as a prohormone and to the two forms as cholecalciferol (vitamin D_3) or ergocalciferol (vitamin D_2). It is now established that Vitamin D_3 is metabolized first in the liver to 25-hydroxyvitamin D (Calcidiol) [10] and subsequently to the kidneys to 1, 25-$(OH)_2D$ to produce a biologically active hormone, which stimulates intestinal absorption of calcium and phosphate and mobilizes calcium and phosphate by stimulating bone resorption. [5]

It is also discovered that 1-$25(OH)_2D$ induces fusion and differentiation of macrophages and suppresses interleukin-2 production in T lymphocytes, [11] an effect which suggest that hormones might play a role in immunomodulation in vivo. In calcium homeostasis 1, $25(OH)_2D$ works in conjunction with parathyroid hormone (PTH) to produce its beneficial effects on the plasma levels of ionized calcium and phosphate.

Vitamin D in pregnancy:

Vitamin D and calcium supplementation of the pregnant mothers is associated with increased skeletal growth and bone mass in the offspring. [12] So, maternal vitamin D requirements can increase up to four to five fold to facilitate the availability of extra calcium required for fetal skeletal growth. [13] Mothers with suboptimal Vitamin D status have offspring with reduced intrauterine and postnatal skeletal development. [14,15] Therefore maintaining optimum Vitamin D nutrition during pregnancy is essential for prevention of hypovitaminosis D in the fetus and vitamin D deficiency at birth and in early infancy.

The fetus requires about 30 g of calcium during development, the majority in the third trimester. It is evident from animal studies and correlations between cord and maternal blood concentrations of 25(OH)D in humans, that 25(OH)D readily crosses the human placenta and vitamin D pool of the fetus is entirely dependent on that of the mother. Physiologically active form $1,25(OH)_2D$ does not readily cross the placenta. [16] Parathyroid hormone-related protein (PTH-P) increases during pregnancy, which is expressed in the fetal parathyroid glands, myometrium, and in the placenta and other fetal membranes and increases 1-α-hydroxylase activity in the kidney and placenta, resulting in an increase in the production of 1,25-$(OH)_2D$. Local production of $1,25(OH)_2D$ may be important for its increased concentration in the early stage of pregnancy, which has been suggested to influence implantation, partly through the immunomodulatory effect and partly by regulation of the target genes associated with implantation. [17]

In normal pregnancy, maternal 1,25-$(OH)_2D$ increases progressively form the first trimester to a peak of twice the non-pregnancy level in the third trimester, which almost doubles the intestinal absorption of calcium. An increased efficiency of

maternal calcium absorption from approximately 35% in the non-pregnant state to approximately 60% during the third trimester of pregnancy appears to be the primary mechanism to support fetal calcium accretion. [18] The elevation of $1,25(OH)_2D$ in the early stage of pregnancy could reflect its role in implantation, as demands to meet increased calcium requirements for the fetal skeletal development come later in pregnancy. [19] Vitamin D might also be important for the maintenance of normal pregnancy through its impact on the maternal immune response to the fetus. [17,20]

It also has been hypothesized that prolactin and placental lactogen stimulate intestinal calcium absorption independently of $1,25(OH)_2D$ during pregnancy. [21] In a population that already has a high prevalence of Vitamin D deficiency and poor dietary calcium intake, the problem is likely to worsen during pregnancy because of the active transplacental transport of calcium and vitamin D to the developing fetus.

The vitamin D status in adults, including pregnant women, is based currently on measurement of serum 25(OH)D concentrations, but what constitutes the "normal" or "optimal" level is controversial. The institute of medicine in the US in its recent report recommended that the serum 25(OH)D concentration of 50nmol/L (20ng/mL) is adequate for calcium absorption and bone health in adults, including pregnant women, in the US and Canada. [22] However, new clinical guidelines from the endocrine society recommend maintaining a serum 25(OH)D concentration >75nmol/L (30ng/mL) in order to maximize calcium absorption and bone health, and for potential extraskeletal benefits noted in observational studies. [23] The accepted biochemical indicator of vitamin D status is serum 25(OH)D concentration. The assays currently available include competitive protein-binding assays; radio-immunoassays (RAI) and direct detection measures include gas chromatography/mass spectrometry (GC/MS), high performance liquid chromatography (HPLC), and liquid chromatography tandem mass spectroscopy (LC-MS/MS). [24,25]

The normal range in pregnancy and lactation is likewise uncertain. The maternal and infant complications associated with vitamin D deficiency occur more often with a vitamin D level below 50nmol/L. Deficiency of vitamin D is more common in women in pregnancy throughout different ethnic and socio-economic groups. Those groups with increased skin pigmentation or customs of dress or behavior that reduces sunlight exposure are at increased risk.

Effect of Hypovitaminosis on pregnancy and fetus birth weight:

Deficiency of vitamin D during pregnancy has been linked with a number of maternal and fetal health problems. These include potentially increased risk of fetal growth restriction, a higher rate of cesarean section, increased risk of pre-eclampsia, gestational diabetes, bacterial vaginosis, HIV transmission and higher risk of lower respiratory tract infection, wheezing and eczema in infants.

Maternal complications:

Different studies have reported an association between maternal vitamin D during pregnancy and development of pre-eclampsia. Pre-eclampsia is a common complication of pregnancy affecting 3%-10% of pregnancies worldwide. Since pre-eclampsia is characterized by reduced perfusion of the placenta, oxidative stress and endothelial dysfunction, numerous nutritional targets for intervention have been suggested. [26] $1,25(OH)_2D$ may play a key role in maintaining immunologic tolerance in pregnancy, and adequate vitamin D may help in the prevention and management of pre-eclampsia. [19]

It has been reported that the serum concentration of 25(OH)D in early pregnancy is reduced in woman who subsequently develop pre-eclampsia. [27] Baker et al. [28] found in a study a five-fold increased risk of preeclampsia in pregnant

women with a serum 25(OH)D concentration <50nmol/L compared with those with values >75 nmol/L (adjusted odds ratio 5.41;Cl 2.02-14.52).

Pregnancy is an insulin resistant state during which improved ß-cell function and proliferation normally occur to meet increased secretory demands. [29] As evidence suggests that vitamin D contributes to insulin sensitivity or ß-cell function and insulin secretion, [30] deficiency may contribute to impaired glucose tolerance during pregnancy. Maternal diabetes in pregnancy increases the risk of obesity and diabetes in the offspring. Cho et al. [31] found in a study that 27.5% of normal pregnant women and 85% of women with GDM had Vitamin D deficiency, with serum 25(OH)D levels <20 ng/ml. They found serum level of 25(OH)D were lower in women with GDM than normal pregnant women (P<0.1).

Bacterial vaginosis (BV), a vaginal infection that affects nearly 1 in 3 reproductive aged women, is a syndrome characterized by the loss of normal vaginal flora, predominantly hydrogen peroxide producing lactobacillus species, and an increased prevalence of anaerobic bacteria. [32] BV is more prevalent in black women, who typically have lower serum 25(OH)D concentrations and have a six fold higher chance of vitamin D deficiency, compared with white women. [33] Black women carry the burden of Vitamin D deficiency, because their dark skin pigmentation prevents adequate cutaneous synthesis of cholecalciferol from casual exposure to sunlight. [34] Vitamin D has effects on the immune system, cytokines and antibacterial peptides that are likely to regulate the bacterial flora. Nutritional Vitamin D status has recently been linked to the human innate immune system and its ability to contain mycobacterium tuberculosis.

1,25-dihydroxyvitamin D, the hormonally active form of vitamin D, is important in regulating the production and function of innate antimicrobial defense molecules, such as cathelicidin which is a neutrophils degranulation product that protects against invasive bacterial infection. [35] In a study among African American women (tested at <16 weeks gestation), an inverse dose-response relation was observed between serum 25(OH)D and prevalence of bacterial vaginosis (adjusted prevalence ratio 0.82 per 15nmol/L increase in serum 25(OH)D (95% CI 0.68-0.99). [36]

A study conducted in Boston, USA, between 2005 and 2007; Vitamin D status was associated with risk of primary cesarean section. It was found in study that women with 25(OH)D concentrations <37.5 nmol/L were nearly four times more likely to have a cesarean delivery than women with 25(OH)D concentrations ≥ 37.5 nmol/L (adjusted OR 3.84, 95% CI-1.71-8.62). [37] Low levels of Vitamin D are also associated to several other maternal adverse effects, such as bone resorption, myopathy and inadequate calcium homeostasis. Mild insufficiency (11-32 ng/ml) would be enough to determine bone loss and subclinical myopathy. [38]

Effect of hypovitaminosis on fetus, newborn and the infant

Hypovitaminosis D in the mother during pregnancy has long been associated to impaired bone metabolism and development in the fetus. The association between birth weight and maternal vitamin D status is controversial. In some studies it is found positively correlated, as in a large study of 1013 white and black mother infant pairs from Boston, second trimester serum 25(OH)D levels <25nmol/L were associated with an increased risk for delivery of a small-for-gestational age infant. [39] However other studies demonstrated no relationship between maternal Vitamin D levels in the first trimester and birth weight but did demonstrate that low vitamin D levels in late pregnancy were associated with reduced intrauterine long bone growth and lower gestational age at delivery. [40]

High resolution 3D ultrasound (3DUS) analysis of the pregnant women showed that suboptimal vitamin D status is associated with increased femur

metaphyseal cross-sectional area and femur splaying index at 19 and 34 weeks of gestation. These changes contrasted with the measurement of femur length, which showed no variability across the different categories of vitamin D status. This study is the first of its kind to describe changes in skeletal morphology in utero that are related to maternal vitamin D status. The splaying and associated metaphyseal widening documented in this study are analogous to the radiographic characteristic of the femoral and tibial bowing that occurs with rickets. The authors have shown previously that children born to mothers with vitamin D deficiency (<25nM 25-OHD) or insufficiency (<50 nM 25-OHD) during pregnancy exhibit deficits in bone mineral content at 9 year of age. [41]

Hypponen E (2011) has demonstrated that vitamin D status during pregnancy impacts the immune response of the offspring. Vitamin D status in infant cord blood has been related to the innate immune response via toll like receptor-mediated synthesis of antimicrobial peptides. Immunomodulatory effects of vitamin D during pregnancy have been claimed to have a long term effect on child health. Vitamin D during pregnancy would contribute to establish and maintain fetal T-cell repertoine and would affect lymphocyte Th1-Th2 balance, affecting the pattern of the immune responses of the child later in life. [42]

Some observational studies suggested a role for Vitamin D in the immune response against respiratory tract infections. Belderbos et al. [43] in a longitudinal study showed that vitamin D deficiency (<20ng/ml) at birth is associated to a higher risk of lower respiratory tract infections (LRTI) by respiratory syncytial virus. A recent cohort study by Morales et al. [44] in more than 1700 mother-children pairs showed an inverse association between maternal vitamin D levels during pregnancy and the risk of respiratory tract infections in the child during the first year of life. Cord blood 25(OH)D concentrations <75nmol/L have also been linked to infantile wheezing [45] and eczema, [46] possibly due to adverse consequences on the early immune development of the fetus.

Vitamin D deficiency is also & major cause of hypocalcemic seizures in neonates and infants, which is a potentially severe problem. Mother of babies who suffer hypocalcemic seizures is more likely to be vitamin D deficient (85%) than mother of babies who do not (50%). [47]

A recent work by Sorensen et al. [48] found that the risk of developing Type 1 diabetes mellitus is twofold higher in children born from mothers with low vitamin D levels during pregnancy, compared to mothers with high levels.

Vitamin D has shown its involvement in several biological pathways, such as synaptic, plasticity and neurotransmission. [49] Whitehouse et al. (2012) found an association between maternal 25(OH)D levels <18 ng/mL during pregnancy and language difficulties in children of five and ten years of age. Hypovitaminosis D has been claimed to play a role in few neurological and psychiatric pathologies since fetal life. Schizophrenia and multiple sclerosis have also been considered.

Management of hypovitaminosis D in pregnancy:

As of now there are no data to support routine screening for hypovitaminosis D in pregnancy in term of health benefits. It is suggested that on the basis of skin colour, obesity, risk of preeclampsia or diabetic conditions pregnant women should undergo for screening of vitamin D deficiency. At present there are no data to support a strategy of measurement followed by treatment in the pregnant population. [50] Measurement of vitamin D in a hypocalcemic woman as part of their management continues to be applicable. Pregnant women with a low calcium concentration, bone pain, alcohol abuse or a previous child with rickets should go for screening of vitamin D deficiency.

Screening of vitamin D in all pregnant women is not cost-effective as test is expensive so universal supplementation is offered on safer side. Daily vitamin D supplementation with oral cholecalciferol or ergocalciferol is safe in pregnancy. The 2012 recommendation from UK chief medical officers and NICE guidance [51,52] state that all pregnant and breastfeeding women should be informed about the importance of vitamin D and should take 10 micrograms (400 units) of vitamin D supplements daily. High risk women are advised to take at least 1000 units a day (women with increased skin pigmentation, reduced exposure to sunlight, obese). Women at high risk of pre-eclampsia are advised to take at least 800 units a day combined with calcium. [53]

For the majority of women who are deficient in vitamin D, treatment for 4-6 weeks, either with cholecalciferol 20000 iu a week or ergocalciferol 10000 iu twice a week, followed by standard supplementation, is a appropriate. [54,55] In adults, very high doses of Vitamin D (300000-500000 iu intramuscular [IM] bolus) may be associated with an increased risk of fractures and such high doses are not recommended in pregnancy. A study demonstrated that supplemental doses of 4000 iu cholecalciferol a day were safe in pregnant women and most effective compared to the lower doses. [56] Different studies on recommended intake of vitamin D shows an urgent need to optimize vitamin D status in pregnancy and its related complications.

CONCLUSION

It is evident that deficiency of vitamin D is associated with worse outcomes for both mother and fetus in pregnancy and for the neonate. Along with pregnancy complications testing and supplementation of vitamin D in normal pregnancy should also be considered. So, more research is required to assess the recommended daily allowance with measurement of 25 hydroxy vitamin D to determine the baseline status in case of pregnancy complications as well as in normal pregnant population in Indian climate.

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