



# The Effect of Vitamin D during Pregnancy and on Neonate

Dr. Owais Nazir Qanoongo, D Ortho<sup>1</sup>, Dr. Sheeba Farooq<sup>2</sup>, Dr. Faheem Nazir Qanoongo<sup>3</sup>

Government Medical College Jammu, India<sup>1</sup>

MD/MS Gynae and OBS Government Medical College Srinagar, India<sup>2</sup>

Senior Resident Medicine KD Medical College Mathura, India<sup>3</sup>

## Abstract:

**Objective:** Vitamin D deficiency is a serious health problem despite a general improvement in socio-economic status In jammu& Kashmir. The aim of this study was to evaluate maternal vitamin D status and its effect on neonatal vitamin D concentrations after a support programme for pregnant women was introduced.

## I. INTRODUCTION

Vitamin D (vitD) inadequacy among pregnant women is prevalent worldwide, and has been associated with adverse pregnancy outcomes [1–10]. Developmental origins of disease have gained increasing attention, and maternal hypovitaminosis D during fetal life is one of the factors suggested to be of significance for future disease, including osteoporosis and cardiovascular disease [11–13]. Ultraviolet-B (UVB) radiation of the skin is considered to be the major determinant of vitD levels [3, 8, 14]. However, due to latitude, cutaneous synthesis of vitD occurs less than six months of the year in the Nordic countries, and dietary content is also limited [9, 14–17]. 25-hydroxyvitamin D (25(OH)D) is metabolized in the kidneys by 1-alpha-hydroxylase to the active form, 1,25-dihydroxyvitamin D (1,25(OH)2D) [3, 4, 18]. Through the vitamin D receptor, regulates 1,25(OH)2D hundreds of genes in a variety of body tissues [6, 14, 19, 20]. A major proportion of 25(OH)D and 1,25(OH)2D binds to vitamin D-binding protein (DBP) or albumin (>99%) [21, 22]. Free and bioavailable fractions seem to be more strongly correlated to the biological activity [14, 22–24]. Serum levels of 25(OH)D are used for evaluation of vitD status [3, 14, 15, 21]. The optimal levels of 25(OH)D and 1,25(OH)2D during pregnancy are, however, not settled, and recommendations concerning vitD intake are diverging [4–6, 14, 17, 25]. In pregnancy, the calcium requirement of the fetus results in profound changes in maternal calcium homeostasis [4, 26]. Whereas parathyroid hormone (PTH) plays a major role in calcium and bone metabolism in the non-pregnant state, vitD appears to be a prominent regulator during pregnancy [8, 27]. This is reflected in a two- to threefold rise in 1,25(OH)2D levels to increase intestinal calcium absorption, and ensure mineralization of the fetal skeleton [4, 26, 27]. This rise is dependent on sufficient 25(OH)D [28]. The relationship between 25(OH)D and 1,25(OH)2D during pregnancy remains, however, unclear [18, 23, 26]. There are many determinants of 25(OH)D contributing to the diverse prevalence rates reported during pregnancy [3, 5, 9, 16, 29, 30]. A large variation in 1,25(OH)2D levels in third trimester has also been observed [18]. Larger longitudinal studies concerning 1,25(OH)2D, free and bioavailable vitamin D in pregnancy are scarce [18, 21, 23]. Vitamin D Deficiency in Pregnancy: Vitamin D deficiency and insufficiency are common across the globe. Large

epidemiological studies reveal the high prevalence of vitamin D in women, including antenatal and lactating mothers.[3,4,5] Vitamin D requirements are probably greater in pregnancy, as evidenced by physiologically higher 1,25-dehydroxy vitamin D levels seen in the second and third trimesters. While 1,25(OH)2D levels do not correlate directly with 25 hydroxy vitamin D concentrations, the physiological rise in the active metabolite, the enhanced intestinal calcium absorption, and enhanced fetal requirement of calcium (250 mg/day in the third trimester) all point to the importance of vitamin D biology in pregnancy. [6].The musculoskeletal manifestations of vitamin D deficiency are well known: Rickets and osteomalacia have been linked with the condition for nearly a century now. Myriad metabolic, nonskeletal associations of vitamin D deficiency are now being unraveled as well. Various authors report links between low vitamin D levels and various elements of the metabolic syndrome. Yet others describe the immunomodulatory, anabolic, anti-infective and anti-tumoral potential of vitamin D. Maternal secondary hyperparathyroidism and osteomalacia, neonatal hypocalcemia and tetany, delayed ossification of the cranial vertex, enlarged size of cranial, fontanelles, and impaired fetal bone ossification has been reported by various authors, and reviewed in detail by others.[6] The relationship between low vitamin D and adverse maternal outcomes such as pregnancy – induced hypertension,[7] high blood pressure in diabetic pregnancy,[8] gestational diabetes mellitus,[9] recurrent pregnancy loss,[10] preterm delivery,[11] primary Caesarian section,[12] and postpartum depression[13] has been documented in recent years. Evidence has also accumulated regarding the impact of maternal vitamin D levels on long-term health of off spring[6,14] Data related to effects of maternal vitamin D on skeletal integrity in childhood is conflicting. One study which assessed bone mass at 9 years of age, found a positive correlation with high maternal vitamin D,[15] whereas another analysis of the same longitudinal study could not detect any relevant association.[16] Nested case control studies have shown a high risk of type 1 diabetes in offspring of women with low levels of vitamin D during pregnancy,[17] though vitamin D intake from either food or supplements has not been shown to increase this risk in a population based cohort infants at genetic risk of type 1 diabetes.[18] Other authors have described the association of maternal vitamin D deficiency with asthma and impaired lung function in offspring.[19]

## II. VITAMIN D SUPPLEMENTATION

Randomized controlled trials are available to support the need for, and benefits of, vitamin D supplementation in pregnancy. While older studies were relatively smaller, and limited to 3-4 months duration,[14] newer data proves the safety and efficacy of 4000 IU vitamin D, administered daily over 6 months of pregnancy.[20] This study by Holles et al. demonstrates a significant decrease in complications of pregnancy including primary Cesarean section, hypertensive disorders of pregnancy, and comorbidities of pregnancy.[20] It has not however, found any correlation between maternal vitamin D and birth weight. Simultaneously, no adverse event due to vitamin D was documented in any subject. The study conducted by Holles et al. is significant, because of the duration of the study (from 12 weeks gestation onwards), the dose used (400, 2000, and 4000 IU daily), the ethical decision to have a control group supplemented with 400 IU/day the large subject size, the need to take an investigational new drug approval from the US Food and Drug Administration, and the fact that it is the first study to address this question in nearly three decades. Similar results were found by Dawodu et al., who supplemented vitamin D in doses of 2000 and 4000 IU/day, from 12 to 16 weeks gestation onwards, to antenatal Arab women from vitamin D deficient regions.[21] Thus, the results of both studies can be extrapolated to other heliophobic, vitamin D deficient countries such as India.

## III. TARGETS AND STRAGIES:

While there is general consensus regarding the need for vitamin D supplementation in pregnancy, there is confusion regarding optimal target levels, and the dose required to achieve them. The optimal level of vitamin D in no pregnant adults is defined as levels of 25(OH) D which are required to maintain serum parathormone levels and prevent secondary hyperparathyroidism. Following this line of thought, normal levels in pregnancy should be the same as those in no pregnant adults. The added dimensions of fetal health, and later health of offspring, however, complicate the issue.

### Normal Vitamin D Levels in Pregnancy:

There is little consensus on what constitutes a 'normal' 25(OH)D level in pregnancy. The Institute of Medicine recommendations suggest a normal level of 20 ng/ml in pregnancy, while the Endocrine Society recommends 30 ng/ml or more.[24,25] However, using mathematical models, Holles et al. suggest that pregnant women should have a circulating vitamin D >40 ng/ml, irrespective of how it is achieved.[14] They quote data from Luxwolda who states that pregnant tribal African women achieve levels of 60 ng/ml, when compared to their no pregnant peers, who enjoy mean vitamin D concentrations of 46 ng/ml. The minimum normal level of 40 ng/ml in pregnancy that Holles et al. suggest for optimizing, vitamin D health is meant to support 1,25(OH) 2D production by overcoming "substrate limitation".

### Recommended Daily Dose:

The recommended target range for nonpregnant adults is 32–100 ng/mL (80–250 nmol/L), which appears to be a safe range during pregnancy. In the United States, the current recommendation for vitamin D intake during pregnancy is 200–400 IU/d.

However, a previous study has shown that prenatal supplements that contain 400 IU of vitamin D are not adequate to achieve normal vitamin D levels in pregnant women or their infants.[112] Even more concerning, studies of supplementation with 800–1600 IU vitamin D per day during the last trimester of pregnancy in women with 25(OH)D levels <15 ng/mL showed that vitamin D levels increased from 5.8 ng/mL to a mere 11 ng/mL.[74,113,114] Therefore, supplemental vitamin D in doses that exceed 1000 IU per day (2000–10,000 IU/d) may be required to achieve a normal concentration of circulating vitamin D in severely deficient patients. Studies with  $\geq 2000$ –4000 IU daily of vitamin D supplementation in nonpregnant women have shown these amounts to be safe and effective at achieving normal vitamin D levels.[115] Studies in pregnant women are underway in the United States that use vitamin D at doses of 2000 IU and 4000 IU daily to establish vitamin D recommendations during pregnancy.

## IV. CONCLUSION

At no other time during the lifespan is vitamin D status more important than during pregnancy, affecting not only the mother but also her growing fetus, and later, her growing infant. While there has been considerable controversy surrounding the daily requirement of vitamin D and what constitutes sufficiency during these critical periods, there is mounting evidence of the importance of vitamin D supplementation during pregnancy to achieve a total circulating 25(OH)D concentration of at least 40 ng·mL<sup>-1</sup>, the point at which the conversion of 25(OH)D to 1,25(OH)2D is optimized and associated with a lower risk of comorbidities of pregnancy and better outcomes. Past data suggesting that vitamin D is a teratogenic compound is completely unfounded at the physiological doses reviewed in this chapter. As has been shown, significant amounts of vitamin D—whether their source is sunlight or supplement—are required during pregnancy to protect the mother and fetus and impart genomic imprinting on the fetus to ensure long term health. With enhanced knowledge about vitamin D's role as a preprohormone, it is clear that recommendations about supplementation must mirror what is clinically relevant and evidence-based. Future research that focuses on the critical period(s) leading up to conception and during pregnancy to correct deficiency or maintain optimal vitamin D status remains to be studied. In addition, what effects vitamin D has on genetic signatures that minimize the risk to the mother and developing fetus have not been elucidated. Clearly, while there is much more research that needs to be performed, our understanding of vitamin D requirements during pregnancy has advanced significantly during the past few decades. Symptomatic or documented vitamin D deficiency in pregnant women should be treated in the same manner as in nonpregnant individuals. Daily doses of 4000 units/day are recommended for treatment in pregnancy. The use of lower doses of vitamin D, as contained in most prenatal calcium preparations (100-800 IU) cannot be condoned in symptomatic patients, or in those with documented low levels. In healthy, asymptomatic antenatal women, 1000-2000 IU can be supplemented daily in the second and third trimesters, without fear of vitamin D toxicity or teratogenicity. No safety data, however, is available for the first trimester with this dose, either. Serum alkaline phosphate, a surrogate marker of vitamin D deficiency, cannot be used as such in pregnancy, because of

the placental secretion of this enzyme. 25 hydroxy vitamin D levels may be measured in each trimester, if easily affordable. there is an urgent need for greater research in vitamin D therapeutics in pregnancy. While we wait for more robust data, we should continue to supplement this nutrient in all pregnant women from the 12th week of gestation onwards. Daily doses of 1000-2000 IU can be recommended in all antenatal women in South Asia, without estimating serum 25(OH) D levels. Higher doses can be used in symptomatic antenatal women, and in those with documented severe deficiency. Recent studies suggest that higher doses, as used in non pregnant women, are safe and effective, and as more data become available, one may recommend standard weekly regimens. However at present it may be safest to adhere to 4000 IU/day as a standard practice in India.

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