REVIEW ARTICLE

Vitamin D in pregnancy - an overview

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ABSTRACT

Vitamin D is a pleiotropic secosteroid hormone important for health and disease prevention. The actions of vitamin D are mediated by the vitamin D receptor that binds the active form of vitamin D [1, 25(OH) $_2$ D] to induce both transcriptional and non-genomic responses. Vitamin D has well known classical functions in calcium uptake and bone metabolism, but more recent work highlights the importance of the nonclassical actions of vitamin D in a variety of cell types. Vitamin D deficiency among pregnant women is frequent in many populations over the world. Research indicates that adequate vitamin D intake in pregnancy is optimal for maternal, fetal and child health. Adverse health outcomes during pregnancy are preeclampsia, gestational diabetes mellitus and caesarean section. Vitamin D deficiency in pregnancy result in low birth weight in infant, neonatal rickets, a risk of neonatal hypocalcaemia, asthma and/or type1 diabetes. Therefore, prevention of vitamin D deficiency among pregnant women is essential. This review article highlighted the metabolism of vitamin D, source of vitamin D, role of vitamin D in pregnant women, testing and treatment for vitamin D deficiency.

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Vitamin D has been a hot topic in the medical world for the past 10 years. Concerns about vitamin D have resurfaced in medical and scientific literature owing to its multiple effects on human health. Vitamin D deficiency is an unrecognized epidemic which is common among children, adults and pregnant women throughout the world, across ethnicity and season. There are increasing studies worldwide reporting poor vitamin D status, including those in tropical countries.

India is a vast tropical country extending from 8.4º N latitude to 37.6° N latitude. Majority of its population lives in areas receiving ample sunlight throughout the year and hence there was disbelief that vitamin D (Vit D) deficiency is uncommon in India [1]. However from the data available in the published literature, Vit D deficiency is very common in India in all the age groups and both sexes across the country [2]. It has been estimated that 1 billion people worldwide have Vit D deficiency or insufficiency [3]. The prevalence of

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vitamin D deficiency has been reported to range from 15% to 80% [4, 5]. There are few data from India about the prevalence of hypovitaminosis D in pregnancy. The increasing prevalence of disorders linked to vitamin D deficiency is reflected in the several hundred children with rickets treated each year. However, these children represent a small proportion of the individuals with a suboptimal vitamin D status in the population. Research suggests that some of the damage done by vitamin D deficiency is done in-utero, while the fetus is developing. Much of that damage may be permanent, that is, it cannot be fully reversed by taking vitamin D after birth.

Vitamin D

Vitamin D itself is devoid of any biological activity, but enzymatic conversion to 1, 25‑dihydroxyvitamin D [1, 25$(OH)_2$ D] generates the hormonal form with diverse biological activities. The active form of vitamin D (1, 25‑dihydroxyvitamin D_3, 1,25$[OH]_2$ D_3) has well‑established effects on bone metabolism and mineral homeostasis which is known as classical response. Recent data indicate vitamin D functions in nonclassical ways as well. Over 30 human tissues express the vitamin D receptor and are thus equipped to respond to 1,25$(OH)_2$D . Vitamin D and the VDR play a role in immune function, cell proliferation, cellular differentiation and hormone secretion. Important changes occur in the maternal concentration of vitamin D and in calcium metabolism to provide the calcium needed for fetal bone mineral accretion during pregnancy. Calcium is transported from the mother to the fetus through the placenta. Approximately 25‑30 g of calcium are transferred to the fetal skeleton by the end of pregnancy, most of which is transferred during the last trimester. The requirement for vitamin D in maintaining normal calcium metabolism throughout pregnancy and lactation in mothers, fetuses and newborn infants is still controversial. It is clear, however, that vitamin D requirements are increased in mothers during pregnancy and lactation. Established as the chorioallantoic placenta at the end of the first trimester, villous tissues secrete multiple hormones that maintain pregnancy and regulate placental physiology [6]. The synthesis, metabolism and function of vitamin D compounds during pregnancy are complex. The human endometrial decidua makes 1,25$(OH)_2$D and 24,25$(OH)_2$D and the placenta synthesizes only 24,25$(OH)_2$D. Data suggest that 1,25$(OH)_2$D aids implantation and maintains normal pregnancy, supports fetal growth through delivery of calcium, controls secretion of multiple placental hormones, and limits production of proinflammatory cytokines. Notably, the 24,25$(OH)_2$D synthesized by the placenta accumulates in bone and may be involved in ossification of the fetal skeleton [7].

Sources of vitamin D

The most important source of vitamin D is the skin's synthesis of the vitamin from sunlight. This vitamin is photosynthesized by ultraviolet‑B radiation in the epidermis. Use of sun blocks, increased coverage of clothing and time spent indoors increase the risk of vitamin D deficiency [8, 9]. It has been estimated that exposure to sunlight for usually no more than 5‑15 min/day between 10 AM and 3 PM, in the spring, summer, and fall at latitudes above and below 35° (and all year near the equator) to exposed parts of the body involving "arms, legs and face "provides the body with its required 1000 IU of cholecalciferol.

Vitamin D is present in a small number of foods, although, for an average person food will only supply about 10% of the amount needed. Dietary sources of vitamin D include: fatty fish species, such as catfish, salmon, mackerel, tuna etc., egg, beef and fish liver oils. Although liver and cod liver oil contain vitamin D, they are not recommended in pregnancy as they also contain too much vitamin A [7].

Role of vitamin D in pregnant women

Adequate vitamin D intake is essential for maternal and fetal health during pregnancy, and prevention of adverse outcomes. Recent work emphasizes the importance of nonclassical roles of vitamin D in pregnancy. Vitamin D deficiency

during pregnancy is associated with the nonclassical actions of this hormone, being linked with preeclampsia, insulin resistance, gestational diabetes mellitus [10], bacterial vaginosis, and an increased risk for caesarean section delivery.

A new study finds that women who develop severe preeclampsia tend to have lower blood levels of vitamin D than healthy pregnant women raising the possibility that the vitamin plays a role in the complication. Preeclampsia rates are elevated during winter months, when sunlight dependent 25(OH) D productions are reduced. Vitamin D supplementation reduces preeclampsia risk, compared to unsupplemented controls [11]. Preeclampsia is associated with low circulating levels of IGF‑I and $1,25(OH)_2D$ and in vitro, IGF‑1 increases $1,25(OH)_2D$ production by primary human syncytiotrophoblasts from placenta in normal pregnancies but not in preeclamptic pregnancies. Studies by other groups have reported abnormal expression of 1α‑hydroxylase, a vitamin D - activating enzyme in preeclamptic pregnancies, revealing a potential role for $1,25(OH)_2D_3$ as a regulator of placentation. Induction of the 1α‑hydroxylase in early gestation might provide a mechanism by which environmental or dietary vitamin D can influence fetal‑placental development. Two clinical trials support a potential role of vitamin D in the prevention of preeclampsia, although neither of these treated with vitamin D supplements alone. In an uncontrolled trial, supplementation with a multivitamin/mineral supplement and halibut liver oil (containing 900 IU/d vitamin D) provided at 20 wk gestation reduced the odds of preeclampsia by 32% (95% CI, 11‑47%) [12]. Vitamin D supplementation in early pregnancy should be explored for preventing preeclampsia and promoting neonatal well‑being. Vitamin D is known to influence insulin secretion. $1,25(OH)_2D$ regulates insulin secretion by pancreatic β‑cell and thereby affects circulating glucose levels [13]. As expected, low concentration of 25(OH) D is a risk factor for insulin resistance, glucose intolerance, and features of metabolic syndrome in normoglycemic subjects. Vitamin D deficiency during early pregnancy significantly increases the risk for gestational diabetes in later pregnancy [14].

Vitamin D may influence the course of infectious diseases during pregnancy. Low 25(OH) D levels are correlated with increased bacterial vaginosis in the first trimester. Bacterial vaginosis 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. Vitamin D has effects on the immune system, cytokines, and antibacterial peptides that are likely to regulate the bacterial flora.

Importantly, when the 3A trophoblast cell line was exposed to E. coli, vitamin D treatment resulted in a lower rate of infection and reduced cell death, likely because of the increased CAMP levels. This finding suggests vitamin D supplementation may reduce infection during pregnancy [15].

Nutritional vitamin D status has very recently been linked to the human innate immune system and its ability to contain Mycobacterium tuberculosis. Serum 25(OH) D levels are inversely related to primary cesarean section in nulliparous women, an unexpected and unexplained maternal outcome recently identified. The risk was four‑fold higher in women with serum 25(OH) D levels below 37.5 nmol/L (15ng/mL) controlling for multiple confounding factors [16]. VDR and $1,25(OH)_2D$ normally increase skeletal muscle function. Conversely, vitamin D deficiency results in proximal muscle weakness and decreased lower extremity muscle function perhaps contributing to the risk for cesarean section. The cochrane library issued a review of vitamin D supplementation during pregnancy and identified 7 relevant studies. The cochrane review concluded that there is not enough evidence to evaluate the requirements and effects of vitamin D supplementation during pregnancy. Data from three trials involving 463 women show a trend for women who receive vitamin D supplementation during pregnancy to more frequently have a baby with a birth weight

below 2500 grams than those women receiving no treatment or placebo, although the statistical significance was borderline. Animal models of vitamin D deficiency have shown just how important adequate nutritional intakes of vitamin D are to skeletal, cardiovascular, and neurologic development in experimental animals [17].

Vitamin D appears to have a protective effect against multiple sclerosis (MS). Research has found direct connections between vitamin D and the genes known to be involved in MS, but exact pathology and whether vitamin D supplements during pregnancy or childhood can lessen the likelihood of the child developing MS later in life is not known. While there is interest in the role of vitamin D in the prevention of multiple sclerosis, following epidemiological studies demonstrating an association between vitamin D supplementation and reduced prevalence of the disease, future research, including randomized controlled trials in pregnant or nonpregnant individuals, is awaited to confirm or refute such benefit. Because the poor vitamin D stores of the mother may impair vitamin D state in the infant, it is important to know whether rickets can be prevented in breast fed infants by supplementation of the mother [18]. The Canadian pediatric society recommended 2000 IU of vitamin D_3 for pregnant and lactating mothers with periodic blood tests to check levels of 25(OH) D and calcium [19]. The American academy of pediatrics recommendations focus on supplementing the infant and make no specific recommendations about universally supplementing breastfeeding mothers.

A sufficient supply of vitamin D to the breast fed infant is achieved only by increasing the maternal supplementation up to 2000 IU/day. As such a dose is far higher than the daily dietary allowance recommended for lactating mothers its safety over prolonged periods is not known and should be examined. Other suggests vitamin D supplementation of 400 IU/day to breast fed infants is the most secure way of preventing rickets in infants.

Role of vitamin D in newborn and infant

Adequate maternal vitamin D levels are also important for fetal and child health. Fetal vitamin D concentrations are mainly dependent on maternal concentration, and maternal deficiency may lead to adverse outcomes in offspring. Vitamin D deficiency in mothers has significantly increased risk of infantile rickets due to inadequate maternal–fetal transfer of 25‐hydroxyvitamin D [20]. Recent retrospective studies found a significant and previously undetected association of maternal vitamin D deficiency with rickets associated infant heart failure and with acute lower respiratory tract infection [21], a serious complication often associated with sepsis without clinical signs of rickets. While vitamin D supplementation in pregnancy has previously been associated with reduced risk of wheezing and type 1 diabetes [22]. A few studies have observed that maternal vitamin D concentrations are related to offspring birth weight and growth during the postnatal years. Lower maternal vitamin D status was associated with lower bone mineral concentration and impaired glucose homeostasis in newborn infants [23]. Maternal vitamin D deficiency also has been associated with craniotabes [23], a softening of skull bones that is one of the earliest signs of vitamin D deficiency, in a case study with neonatal seizures of a hypocalcemic infant and with impaired skeletal development in utero. Interestingly, vitamin D deficiency during pregnancy is also associated with risks of health problems later in childhood, including improper bone development at 9 yrs of age, asthma, dental cavities, schizophrenia, and type I diabetes [24 -26]. The concept that maternal nutritional status influences the risk of chronic disorders in the offspring has attracted interest over the past 2 decades. However, very few studies have been in position to examine this association directly in animals. Women of Indian origin, especially pregnant women are known to have a high prevalence of vitamin D deficiency.

In Indian women calcium intakes are low and the demands are high because of repeated cycles of pregnancy and lactation. A study in pregnant women in South India assessed maternal vitamin D

status by measuring serum 25‑hydroxyvitamin D in stored serum samples [27]. More than 60% of the women of the women had low 25(OH) D concentration (≤50 nmol/L) at 30‑week gestation. Although there was no association between maternal vitamin D status and offspring birth size. At present, vitamin D supplementation is not a part of antenatal care programs in India.

Testing and treatment for vitamin D deficiency

Women of reproductive age are assumed to be able to obtain the recommended intake for almost all vitamins without the use of supplements, and no national organization recommends routine vitamin D supplementation during pregnancy unless a woman is at nutritional risk. The US Preventive Services Task Force does not comment for or against routine screening for vitamin D deficiency in pregnant women. One approach is to consider serum testing in patients at high risk for vitamin D deficiency but treating without testing those at lower risk. The basis for these recommendations was made before it was possible to measure the circulating concentration of 25‑hydroxyvitamin D [25(OH) D], the indicator of nutritional vitamin D status [28, 29]. Endocrine Society issues practice guideline on vitamin D and the guideline recommend that clinicians screen for vitamin D deficiency in people at risk for deficiency, including obese individuals, blacks, pregnant and lactating women, and patients with malabsorption syndromes [30]. If electing to test vitamin D status, serum 25‑hydroxyvitamin D is the accepted biomarker to be offered early in pregnancy [31]. Although $1,25(OH)_2D$ is the active circulating form of vitamin D, measuring this level is not helpful because it is quickly and tightly regulated by the kidney. True deficiency would be evident only by measuring 25(OH) D. Of note, questions have been raised regarding the need for standardization of assays. A large laboratory (Quest Diagnostics) recently reported the possibility of thousands of incorrect vitamin D level results. Sunlight exposure questionnaires are imprecise and are not currently recommended. There is no consensus about the optimal 25(OH) D level, but many experts accept a range 75nmol/L (≥30 ng/mL) as optimal [31]. Controversy exists regarding the optimum concentration of serum 25‑hydroxyvitamin D for defining vitamin D deficiency, especially in pregnancy. Most experts agree that serum vitamin D levels below 50 nmol/L (20 ng/mL) represent deficiency. However this current practice is based on the skeletal actions of the vitamin and may not be applicable for its nonclassic actions. As was recently pointed out in a cochrane review, the topic of maternal vitamin D requirements during pregnancy has been poorly studied. The reality is that the actual vitamin D requirement during pregnancy is not known. For that matter, the requirement for the general population is not known either. There is no dietary recommended intake (DRI) for vitamin D. What is known today is that for a pregnant woman, the adequate intake for vitamin D is 200 IU per day. However this recommended level, which was largely arbitrarily set, seems to be less helpful to improve the nutritional vitamin D status of pregnant women. National Osteoporosis Foundation's (NOF) recommends 400‑800IU vitamin D for pregnant women. A recent systematic review concluded that antenatal vitamin D supplementation is effective in improving the vitamin D status of Asian and white women, improves growth in the first year of life in South Asian babies and therefore may contribute to reducing the incidence of rickets in this latter group, without evidence of harm [32]. The NICE guidelines for antenatal care were therefore updated in 2008. Current NICE guidance states clearly that pregnant women should inform at their first antenatal booking of the importance of adequate vitamin D during pregnancy and then after to maintain their own and their baby's health. These women are advised to take 10 micrograms per day in the form of a multivitamin supplement. It is crucial to ensure the risk women about the awareness of this need. Those identified as at risk include: women from black and ethnic minorities who are socially excluded, women with limited

exposure to sunlight, especially those who are housebound and obese women with pre pregnancy BMI > 30. Current U.S. guidelines call for pregnant women to get 400‑600 IU. However, research in recent years has been challenging those ideas on what is enough, and what is too much. The U.S. guidelines are currently under review. For now, though, 600 IU in prenatal vitamins remains the recommended daily intake for pregnant women. However, getting 25(OH) D levels consistently above 75 nmol/L (30ng/mL) may require at least 1500‑2000 IU/day of vitamin D. If a mother is vitamin D deficient, breast milk is not a good source of vitamin D, so infants need to be given vitamin D supplementation until they are weaned. Also women are encouraged to continue to take vitamin D supplements after pregnancy to help protect against health problems such as osteoporosis. It was recently shown that a maternal supplementation of 2100 IU vitamin D/day was needed, when administered during the period of lactation, in order to observe an increase in serum levels of 25(OH)D in the breastfed infants comparable to that observed in children given 400 IU/day.

Conclusion

Vitamin D has emerged as something of a wonder supplement, according to the claims of dozens of studies published in the past few years. The current lack of evidence of benefit for women at lower risk of vitamin D deficiency points to the need for further research into vitamin D supplementation in pregnant women. There is a similar gap in the knowledge base for optimal dosing, as there is little empirical robust evidence to support 600 IU/day. What is clear is that adequate vitamin D intake in pregnancy is optimal for maternal, fetal and child health. However, vitamin D deficiency is prevalent and this potentially has negative consequences for both mother and child. Clearly, further investigation into the effects of vitamin D, of vitamin D supplementation, and of vitamin D analogs will contribute to an improvement in human health generally and mothers and children specifically.

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