Editorial

Vitamin D supplementation in pregnancy

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Obstetric endocrinology is a field characterized by opportunity, challenges and caution. Opportunity, because the antenatal period presents a window during which endocrine and metabolic manipulation can impact not only maternal and fetal health, but also long-term outcomes in offspring. Caution is necessary, too, because the same therapy may lead to unwanted adverse effects in the innocent fetus, and have (as yet unknown) long-term complications. Challenges in obstetric endocrinology are unique, too, as ethical and practical issues make it difficult to conduct randomized placebo controlled trials as many situations. The rapidly increasing incidence of endocrine dysfunction in obstetrics, and the public health importance of these conditions, therefore, require closer attention and debate.

Issues relates to obstetric thyroidology and gestational diabetes mellitus[1,2] have been discussed in the pages of IJEM earlier. The editorial focuses on another controversial field of obstetric metabolism: Vitamin D and pregnancy.

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.[3-5]

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)$_2$D 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]

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.139204

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 offspring[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

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maternal vitamin D deficiency with asthma and impaired lung function in offspring.[19]

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 Cesarian 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. Yet another study from New Zealand has proven the safety and utility of supplementing 2000 IU/day of vitamin D from 27 weeks onwards, and continuing 800 IU/day supplementation in infants till 6 months of age.[22]

These studies have not been included in the most recent (2012) Cochrane review on vitamin D supplementation for women during pregnancy. This may be reason for the Cochrane authors to conclude that there is a requirement for "further rigorous randomized trials" to evaluate this subject.[23]

Targets and Strategies

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 nonpregnant 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 nonpregnant adults. The added dimensions of fetal health, and later health of offspring, however, complicate the issue. Data regarding the effect of increasing vitamin D levels on birth weight, neonatal health, later health, and maternal outcomes is scarce.

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 nonpregnant 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".

Given the lack of solid, consistent outcome data with higher levels of 25(OH)D, we feel that a minimum level of 20 ng/ml would be desirable in pregnancy. This still leaves scope for better outcomes with higher levels, and further data is awaited.

Recommended Daily Dose

The recommended daily intake of vitamin D ranges from 400 to 600 IU (by the IOM),[26] 400 IU (by the National Institute for Health and Clinical Excellence, United Kingdom),[27] and to 1500-2000 IU (by the Endocrine Society),[28] and 2000 IU (by the Canadian Society).[29] Results of the recently conducted randomized controlled trial on vitamin D supplementation in pregnancy suggest a safe dose of 2000-4000 IU/day.[14,20-22] The daily upper safe limit for vitamin D has been set at 4000 IU by IOM and 10,000 IU by the Endocrine Society.[26,28]

Indian Evidence

While discussing the dose of vitamin D in pregnancy, one most remember the extremely low levels of vitamin D seen in South Asian women. Three decades ago, Marya *et al.* from Rohtak used surrogate markers such as serum calcium and heat-labile alkaline phosphatase to demonstrate the benefits of 1200 IU/day of vitamin D on fetal and maternal outcomes.[29,30] More recently, Kalra *et al.* described the results of vitamin D supplementation in doses as low

as a single 1500 mcg second trimester dose, and two 3000 mcg doses (one each in second and third trimester). Both does improved infant anthropometry, whereas the larger dose also increased maternal vitamin D levels.[31] Sahu *et al.*, from the same institute,[32] reported that cholecalciferol in doses of 120,000 U each in fifth and seventh gestational months was effective in raising 25OHD at delivery, though end of study levels were barely in the normal range.

Conclusion

As we mentioned initially, obstetric endocrinology is a field marked by both opportunity and caution. With the available evidence regarding vitamin D supplementation, and the conflicting interpretations of whatever has been published, it becomes challenging to issue evidence-based guidelines. However, the benefit of vitamin D supplementation in pregnancy is potentially even greater than in the nonpregnant state. Yet, we continue to prescribe lower doses to pregnant women than to their nonpregnant peers, perhaps because of an unfounded fear of side effects.

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. In routine practice, however, this investigation is not necessary. In resource constrained settings, patients on vitamin D therapy can be screened for hypercalcemia by checking for calcium crystalluria.

As in other fields of obstetric endocrinology, 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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Cite this article as: Mithal A, Kalra S. Vitamin D supplementation in pregnancy. Indian J Endocr Metab 2014;18:593-6.
Source of Support: Nil, **Conflict of Interest:** None declared.