

Vitamin D Efficiency in Pregnancy: An Updated Viewpoint in Indian Scenario*

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Abstract

A decade ago identified as bone-building mineral improving calcium absorption, today new research opens potentials of Vitamin D in spectrum of diseases from diabetes, hypertension to cancer including special population like pregnancy & lactation. As calcium demands increase during pregnancy, Vitamin D status becomes crucial for optimal maternal & fetal outcomes. Adverse health outcomes such as preeclampsia, low birth weight, neonatal hypocalcemia, bone fragility & increased incidence of autoimmune diseases have been linked to low Vitamin D levels during pregnancy & infancy. Vitamin D deficiency is common during pregnancy & lactation despite widespread use of prenatal vitamins, because these are inadequate to maintain normal Vitamin D levels. The current IOM (US) as well as ICMR (India) recommendations for Vitamin D supplementation is not sufficient to maintain the optimal levels of serum 25(OH) D above 30 ng/ml required during pregnancy. It may therefore be judicious to include screening of all pregnant women for Vitamin D levels as a part of routine antenatal care and supplementation should be considered if deficiency persists. Till date interventional trials in special population suggest that administration of Vitamin D during pregnancy & lactation is safe & beneficial for optimal maternal & fetal outcomes. When Vitamin D deficiency is identified during pregnancy, most experts agree that up to 2000 IU/day of Vitamin D is safe. This review elaborates Vitamin D deficiency in Indian scenario and the need for Vitamin D supplementation, expounds and exercises the facts for implementation of Vitamin D supplementation to be advised when planning for pregnancy, current recommendations and implications of Vitamin D deficiency during pregnancy and lactation.

Keywords

Vitamin D, Vitamin D Deficiency, Indian, Pregnancy, Lactation

*The paper is a representation for call on consensus for benefits of Vitamin D supplementation, adequate dose and level of Vitamin D in pregnancy and lactation particularly in Indian scenario.

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1. Introduction

As the statistics keep surfacing at the alarming pace, Vitamin D deficiency is recognized as the most un-treated nutritional deficiency currently in the world [1]-[3]. Vitamin D deficiency is a significant public health problem in both developed and developing countries including India [4]. Although India is a tropical country with abundant sunshine; still Vitamin D deficiency is very common in India in all age groups and both sexes across the country [5]. The skeletal action of Vitamin D is to maintain calcium homeostasis and bone health. In addition, it is now known to be involved in extra-skeletal functions in diverse tissues and organs, including the pancreas, heart, brain and immunomodulation [6]-[8]. Several clinical studies suggest the possible association between low Vitamin D levels and potential adverse outcomes of pregnancy [9]-[12]. The widespread Vitamin D deficiency in pregnant women and lactating mother's calls for a view to define optimum level of Vitamin D and the adequate amount of Vitamin D intake required to maintain optimum levels in these populations. The aim of the paper is to provide a comprehensive picture of Vitamin D status among pregnant women and lactating mothers countrywide. It illustrates the summation of Indian studies projecting deficiency statistics across the country firmly establishing the grave need to tackle the issue. It particularizes on the need to raise the desired Vitamin D level in pregnancy and lactation > 30 ng/mL from the conventional > 20 ng/mL as suggested by the Institute of Medicine (IOM), US. It also discusses the safe dose that can be advocated among pregnant women and lactating mothers. The review gives details of the benefits of Vitamin D supplementation in pregnancy and lactation and insights the current recommendations by different international organization for Vitamin D supplementation in pregnancy and lactation. It discusses utility of Vitamin D as preconceptional nutrition as well as the possible benefits of Vitamin D supplementation in first trimester, a section less explored. In order to ease data representation, all 25(OH) D levels in this review are interpreted in a single concentration unit—nanogram per milliliter (ng/mL) and all Vitamin D doses as interpreted in International Unit (IU). Representation in single unit is aimed to allow easy comparison among studies. This could enable physicians to optimally diagnose and treat the broader concern of Vitamin D deficiency among Indian population.

2. Need for Vitamin D Feed

Vitamin D deficiency is common in pregnant women (5% - 50%) and in breastfed infants (10% - 56%), despite the widespread use of prenatal vitamins, because these are inadequate to maintain normal Vitamin D levels (≥ 32 ng/mL) [9]. Although being a tropical country, Vitamin D deficiency is documented high in pregnant women & lactating mothers in India. **Table 1** and **Table 2** summarize studies depicting the status of Vitamin D in pregnancy and lactation among Indian population. Insufficient outdoor activity in urban areas, dark skin colour, poor dietary calcium causing secondary Vitamin D deficiency and environmental pollution could be few risk factors that account for high prevalence of Vitamin D deficiency in the country [13]-[16].

2.1. The Significance of Vitamin D in Pregnancy

During initial to mid-trimesters, the fetal organs begin to develop and there is start of skeleton formation in form of collagen matrix. The skeleton of the fetus begins to calcify in the last trimester, thereby increasing maternal demand for calcium. This demand is met by increased production of 1, 25(OH)₂D by the mother's kidneys & placenta. Circulating concentrations of 1, 25(OH)₂D gradually increase during the 1st & 2nd trimesters, owing to an increase in Vitamin D-binding protein concentrations in the maternal circulation. However, the free levels of 1, 25(OH)₂D, which are responsible for enhancing intestinal calcium absorption, are only increased during the 3rd trimester [32]. Fetal calcium levels are higher than maternal throughout gestation. There is active transport of calcium across the placenta [33]. Fetal Vitamin D concentrations are up to 20% lower than maternal as measured in cord blood. Vitamin D deficiency during pregnancy is linked with preeclampsia [34], gestational diabetes mellitus, preterm labour [35] [36] and an increased risk for caesarean section delivery [37]. The importance of Vitamin D for fetal & infant skeletal development has long been recognized. In full-term infants, impaired fetal bone ossification correlated with maternal Vitamin D deficiency [38]. Maternal Vitamin D deficiency is associated with subtle fetal bone abnormalities like shorter knee-heel length [39], low birth weight [40] & high risk of being small for gestational age (SGA) [41].

2.2. The Significance of Vitamin D in Lactation

During lactation, it is required that the mother increase the efficiency of dietary absorption of calcium to ensure

Table 1. Studies depicting Vitamin D status in pregnant women-Indian studies.

Study population & location	25(OH) D (ng/mL) mean (SD)	Vitamin D status			Reference
		% Deficient	% Insufficient	% Sufficient	
N = 139 Pregnant women, Lucknow, age 26.7 (4.1) yrs.	15.12 ± 7.92	74%	-	-	Sahu M. <i>et al.</i> [17] (2009)
N = 260 Pregnant women + girls in summer (subclass).	22.2 ± 7.92	54%	-	-	
N = 260 Pregnant women + girls in winter (subclass).	10.92 ± 4.92	93%	-	-	
N = 207 Pregnant women, Lucknow, age 24 ± 4.1 yrs.	14 ± 9.3	84.05%	-	-	Sachan A. <i>et al.</i> [18] (2005)
N = 140 Urban females (subclass).	14.0 ± 9.5	84.3%	-	-	
N = 67 Rural females (subclass).	14.1 ± 8.9	83.6%	-	-	
N = 207 Neonates/cord blood.	8.4 ± 5.7	95.7%	-	-	
N = 42 Pregnant women, Western India, age 20 - 35 yrs.	22.99 ± 10.93	50% [#]	-	-	Bhalala U. <i>et al.</i> [19] (2007)
N = 42 Cord blood/neonates.	19.36 ± 9.57	62% [#]	-	-	
N = 559 Pregnant women, Mysore, age 24 yrs.	Median 15.12 (9.6 - 23.4)	66.5%	-	-	Farrant H.J. <i>et al.</i> [20] (2009)
N = 20 Pregnant women, Delhi, age 28.05 ± 0.89 yrs.	16.24 ± 4.36	75%	10%	15%	Agarwal N. <i>et al.</i> [21] (2011)
N = 21 Cord blood.	15.28 ± 3.36	81%	9.5%	9.5%	
N = 568 Pregnant women, Mysore.	Median 15 (9.6, 23.2)	67%	-	-	Krishnaveni G.V. <i>et al.</i> [22] (2011)
N = 521 Pregnant women, Delhi, age 24.6 (2.8) yrs.	9.28 ± 4.88	96.3%	-	-	Marwaha R.K. <i>et al.</i> [23] (2011)
N = 50 Pregnant women, Guwahati, age 20 - 40 yrs.	NM	42%	14%	-	Dasgupta A. <i>et al.</i> [24] (2012)
N = 180 Pregnant women HIV-infected, Pune, age 23 (21 - 25) yrs.	Median 15.25 (10.0 - 18.25)	24%*	98%	-	Mave V. <i>et al.</i> [25] (2012)
N = 48 Pregnant women, Lucknow, age 26.3 yrs.	Median 12.68 (5.6 - 22.88)	-	-	-	Kalra P. <i>et al.</i> [26] (2012)
N = 49 Pregnant women, age 27 yrs.	Median 12.8 (5.8 - 18.28)	-	-	-	
N = 150 Pregnant women, Mumbai, age 20 - 35 yrs.	Affluent group: 11.8 (10.8, 12.9) nonaffluent: 9.8 (9.1, 10.6)	93.75% (Affluent 91.2%, nonaffluent 96.3%)	6.25 % (Affluent 8.8%, nonaffluent 3.7%)	-	Jani R. <i>et al.</i> [27] (2014)

Notes: All 25(OH) D values have been shown in nanogram/milliliter (ng/mL). To convert from nanomoles per liter to nanogram per milliliter, nanomoles per liter values were divided by 2.5. Vitamin D deficiency is defined as 25(OH) D < 20 ng/mL, insufficiency as 20 - 29 ng/mL and sufficiency as ≥30 ng/mL. *Vitamin D deficiency defined as <10 ng/ml in these studies. #Vitamin D deficiency defined as <25 ng/ml in these studies. Abbreviations: N, Number of subjects; NM, not measured; 25(OH) D, 25 Hydroxy Vitamin D; ng/mL, nanogram per milliliter.

Table 2. Studies depicting Vitamin D status in lactating women-Indian studies.

Study population & location	25(OH) D (ng/mL) mean (SD)	Vitamin D status			Reference
		% Deficient	% Insufficient	% Sufficient	
N = 35 Infants, 3 months old.	18.19 ± 9.74	80% [#]	-	-	Bhalala U. <i>et al.</i> [19] (2007)
N = 180 Healthy lactating mothers.	10.88 ± 5.8	47.8%*	-	-	Seth A. <i>et al.</i> [28] (2009)
N = 180 Exclusively breast fed infants, 2 - 24 week old.	11.6 ± 8.3	43.2%*	-	-	
N = 60 Lactating mothers, age 25.0 (2.0) yrs.	9.06 ± 4.78	98.3%	-	-	Mehrota P. <i>et al.</i> [29] (2010)
N = 60 Breastfed infants, age 3.0 (0.14) months.	9.03 ± 4.63	100%	-	-	
N = 97 Lactating mothers.	9.85 ± 6.28	-	-	-	Agarwal N. <i>et al.</i> [30] (2010)
N = 97 Exclusively breastfed infants.	12.59 ± 8.37	-	-	-	
N = 98 Lactating mothers, Delhi, age 23.3 (3.3) yrs.	Median 9.8 (5.0 - 13.8)	92.6%	-	-	Jain V. <i>et al.</i> [31] (2011)
N = 98 Breastfed Infants, 58.2% male, age 13.6 (2.2) weeks.	Median 10.1 (2.5 - 17.1)	86.5%	-	-	
N = 342 Lactating mothers, 6 - 8 weeks postpartum.	7.84 ± 3.32	99.7%	-	-	Marwaha R.K. <i>et al.</i> [23] (2011)
N = 342 Exclusively breastfed infants.	8.92 ± 4.2	98.8%	-	-	

Notes: All 25(OH) D values have been shown in nanogram/milliliter (ng/mL). To convert from nanomoles per liter to nanogram per milliliter, nanomoles per liter values were divided by 2.5. Vitamin D deficiency is defined as 25(OH) D < 20 ng/mL, insufficiency as 20 - 29 ng/mL and sufficiency as ≥30 ng/mL. *Vitamin D deficiency defined as <10 ng/ml in these studies. #Vitamin D deficiency defined as <25 ng/ml in these studies. Abbreviations: N, Number of subjects; 25(OH) D, 25 Hydroxy Vitamin D; ng/mL, nanogram per milliliter.

adequate calcium content in her milk. Breast milk Vitamin D correlates well with maternal Vitamin D concentrations so breast-fed infants are at risk of persistent Vitamin D deficiency if the mother is deficient. In the first 6 - 8 weeks of postnatal life, the Vitamin D status of a neonate is dependent largely on Vitamin D that is acquired through placental transfer in utero, as evidenced by the direct linear relationship between maternal and cord blood levels of 25(OH) D [42]. In most infants, Vitamin D stores acquired from the mother are depleted by approximately 8 weeks of age [43]. Human milk contains a very low concentration of Vitamin D (approximately 20 - 60 IU/L), which represents 1.5% - 3% of the maternal level [44]. This low concentration is not sufficient to maintain an optimal Vitamin D level in the newborns if exposure to sunlight is limited. The maternal Vitamin D status determines the breast milk Vitamin D concentration. The first step toward achieving Vitamin D sufficient breast milk must address the Vitamin D supplementation required to achieve Vitamin D sufficiency in the mother. Low Vitamin D predisposes to hypocalcaemia in the immediate postpartum period & then rickets over the next few months [39]. Symptomatic Vitamin D deficiency manifests as craniotabes, rickets rosary, swelling of the ends of long bones, frontal bossing of the skull, hypocalcaemic seizures or tetany and slow motor development. Hypocalcaemia in early infancy is commonly associated with functional or organic hypoparathyroidism [45]. Rickets during infancy has been associated with higher prevalence of lower respiratory tract infections, [46] which remain one of the largest causes of infant mortality in India.

3. Defining Vitamin D levels in Pregnancy and Lactation

Serum 25(OH) D levels is the best available biomarker for diagnosis of Vitamin D deficiency. Vitamin D researchers recommend that the serum 25(OH) D concentrations should be at least 30 ng/mL in order to provide optimal health outcomes. Serum 25(OH) D levels < 30 ng/mL may be considered insufficient/ deficient. Maintenance of adequate levels of serum 25(OH) D is essential to sustain skeletal & extra-skeletal benefits of Vita-

min D. A number of guidelines & studies suggest that in general population screening of Vitamin D levels is not required; treatment can be initiated without finding the Vitamin D levels. Vitamin D levels can be measured irrespective of fasting & non-fasting state. Various clinical studies establish the need of Vitamin D supplementation in pregnancy and lactation. As Vitamin D supplementation sets to be a routine in pregnant women and lactating mothers, there is need to define the optimum level of Vitamin D in these population. The correlation between Vitamin D levels and intestinal calcium absorption, maximal PTH suppression, bone fracture prevention, and bone turnover have been established with respect to Vitamin D levels and indicate that levels >32 ng/mL are required for sufficiency [47] [48]. These levels can also be applied in pregnancy and during lactation as the above stages correlate with maternal and fetal outcomes [49]. In mothers, Vitamin D sufficiency (32 - 100 ng/ml) is related to adequate calcium balance, parathyroid hormone levels. Severe Vitamin D deficiency (<10 ng/ml) is related to increased risk of preeclampsia, calcium malabsorption, bone loss, poor weight gain, myopathy, higher parathyroid hormone levels while Vitamin D deficiency/insufficiency (10 - 32 ng/ml) is related to bone loss and subclinical myopathy. Similarly in infants, severe Vitamin D deficiency (<10 ng/ml) is related to small for gestational age, neonatal hypocalcemia, hypocalcemic seizures, infantile heart failure, enamel defects, large fontanelle, congenital rickets, rickets of infancy if breastfed while Vitamin D deficiency/insufficiency (10 - 32 ng/ml) is related to Neonatal hypocalcemia, reduced bone mineral density, rickets of infancy if breastfed [9].

The benefits of maintaining Vitamin D levels in pregnancy is mounting with various studies documenting higher target of Vitamin D level for optimum outcomes. Two large trials, one covered by National Institute of Child Health and Human Development (NICHD), Hollis B.W *et al.* [50] and Thrasher Research, Wagner C.L *et al.* [51] suggest levels >32 ng/ml & above are safe in pregnancy. No single cases of adverse events were reported at these levels and higher Vitamin D levels were suggestive of reduction in the risk of pregnancy complications like maternal infections, preterm labor and preterm birth. In US study accessing the risk of Preeclampsia, a five-fold increased risk of pre-eclampsia was seen in pregnant women with a serum 25(OH) D concentration, <20 ng/mL compared with those with values > 30 ng/mL [52]. In another study, the prevalence of bacterial vaginosis increased 1.65-fold and 1.26-fold at serum concentrations of 8 ng/mL and 20 ng/mL, respectively compared to >30 ng/mL [53]. Also maternal serum 25(OH) D < 30 ng/mL during early pregnancy has been associated with a two-fold increased risk of periodontal disease [54]. Vitamin D status in infant cord blood has been related to the innate immune response via toll-like receptor-mediated synthesis of antimicrobial peptides like cathelicidin [55]. The risk of respiratory syncytial virus bronchiolitis in the first year of life is increased by six-fold in infants with cord blood 25(OH) D < 20 ng/mL compared with infants with 25(OH) D > 30 ng/mL. Cord blood 25(OH) D concentrations <30 ng/mL have also been linked to infantile wheezing [56] and eczema [57].

The Institute of Medicine (IOM) currently recommends a normal level of 20 ng/mL in pregnancy [58]. There is a growing consensus that the serum Vitamin D levels below 20 ng/mL represents deficiency is a practice based on skeletal actions of Vitamin D which is debated and higher target is required for extra-skeletal benefits. The Endocrine Society and the Vitamin D experts recommend a higher target of >30 ng/mL in order to achieve optimal benefits for skeletal as well as extra-skeletal benefits [32]. Literature also suggest a level > 40 ng/mL in pregnancy is safe to support 1, 25(OH)₂ D production by overcoming substrate limitation as well [59]. Given the mounting evidence of benefits of Vitamin D supplementation in pregnancy and lactation, we feel that there is substantial progress in research in this area which supports raising the optimal serum Vitamin D levels to be >30 ng/mL in pregnancy and lactation. As previously stated, with widespread deficiency statistics across the country; there is an urgent need to at least maintain all pregnant and lactating mothers under the sufficiency belt. Given the substantial scope of better outcomes with higher levels, there is need of further research to study the outcomes at these higher Vitamin D levels.

4. Vitamin D Recommendations

The Recommended Daily Allowances of Vitamin D in pregnancy and lactation has underwent a fast surging change as the data of deficiencies surface, compelling International committees to upgrade their recommendations. The Institute of Medicines (IOM) in 1997 recommended Vitamin D intake of 200 IU citing there is no additional need to increase the Vitamin D intake during pregnancy above that required for non-pregnant women. Even the recommendation during lactation were 200 IU citing that there is no evidence to indicate that lactation increases a mother's actual intake of Vitamin D [60]. The Institute of Medicines (IOM) currently recommends

daily intake of 600 IU Vitamin D in pregnancy and lactation. This recommendation is provided for achieving the recommended target serum 25(OH) D concentration of 20 ng/mL by IOM. **Table 3** describes the former and current recommended Vitamin D intakes in pregnancy and lactation by various institutions including Indian Council of Medical Research (ICMR).

There is an increasing debate among the world bodies on recommended daily allowances (RDAs) of Vitamin D. Many researchers suggest that RDA of 600 IU or less Vitamin D may not be sufficient in correcting Vitamin D deficiency. Recently, the American Congress of Obstetrics and Gynecology (ACOG) committee opined that for pregnant women thought to be at increased risk of Vitamin D deficiency, maternal serum 25-hydroxyvitamin D levels can be considered and should be interpreted in the context of the individual clinical circumstance [61]. Results of the recently conducted randomized controlled trial on Vitamin D supplementation in pregnancy suggest a safe dose of 2000 - 4000 IU/day [50] [51] [59] [62] [63] sufficient to maintain the levels above 30 ng/mL. The US Endocrine Society Guidelines, 2011 recognizes that pregnant women would require at least 1500 - 2000 IU/d of Vitamin D to maintain a blood level of 25(OH)D above 30 ng/ml (sufficient level) & lactating women may need at a minimum 1400 - 1500 IU/d. To satisfy the requirements of an infant who is fed only breast milk, the mother requires 4000 to 6000 IU/d to transfer enough Vitamin D into her milk [32]. The Canadian Pediatric Society mentions consideration should be given to administering 2000 IU of Vitamin D daily to pregnant & lactating women, especially during the winter months, to maintain Vitamin D sufficiency [64]. The American Congress of Obstetricians & Gynecologists (ACOG), 2011 Committee recognizes that use of 1000 - 2000 IU/day of Vitamin D is safe when Vitamin D deficiency is identified during pregnancy [61]. **Table 4** summarizes the Vitamin D recommendations by world committees in Pregnancy and Lactation.

Currently in India, no national guidelines recommend routine Vitamin D supplementation in pregnancy and lactation. With the growing evidence that adequate maternal Vitamin D status is essential during pregnancy, not only for maternal well-being but also for fetal development [66]-[69], clinicians should consider assessing maternal Vitamin D status during pregnancy and lactation. On an individual basis, a mother should be supplemented with adequate amounts of Vitamin D to ensure that her 25(OH) D levels are in a sufficient range (>32 ng/mL) [70]-[73]. Sufficient numbers of women of reproductive age are assumed to obtain their recommended intake of vitamins through prenatal vitamin supplementation. This is probably due to less clarity with respect to dosage, timing and route of administration during pregnancy and lactation. The knowledge that prenatal vitamins containing 400 IU of Vitamin D have little effect on circulating maternal 25(OH) D concentrations, especially during the winter months, should be imparted to all clinicians involved in the care of pregnant women and lactating mothers in India.

Table 3. Shifting opinions of Vitamin D intake in pregnancy and lactation.

Institute of Medicines (IOM)			Endocrine Society		Indian Council of Medical Research (ICMR)
RDA (1997)	RDA (2011)	UL (2011)	Daily Requirement (2011)	UL (2011)	Daily Requirement (2010)
200 IU	600 IU	4000 >19 yrs.	1500 - 2000 IU	10000 > 19 yrs.	400 IU

Abbreviations: IU, International unit; RDA, Recommended Daily Allowance; UL, Upper limit.

Table 4. Vitamin D recommendations by world committees in pregnancy and lactation.

Committees	Recommendation
National Institute for Health and Care Excellence (NICE) guidelines, UK [65]	400 IU
Institute of Medicines (IOM) [58]	600 IU
Endocrine Society [32]	1500 - 2000 IU
Canadian Pediatric Society [64]	2000 IU
American Congress of Obstetricians & Gynecologists (ACOG) [61]	1000 - 2000 IU

5. Vitamin D Supplementation before and Soon after Pregnancy?

Preconceptional counseling is different from antenatal care. In particular, it is more important than antenatal care, as 30% of pregnant women begin traditional antenatal care in the second trimester and after the period of maximal organogenesis (between 3 and 10 weeks' gestation) [74]. Preconception care refers to interventions that aim to identify and modify biomedical, behavioral and social risks to women's health or pregnancy outcome through prevention and management. A number of observational studies provide the link between low Vitamin D levels in first trimester and pregnancy outcome. Studies have shown that low 25(OH) D levels at first trimester are an independent risk factor for developing gestational diabetes mellitus and associated with insulin resistance at second trimester [75]. 50% of obese women in the first trimester had serum 25(OH) D concentrations < 20 ng/mL indicating deficiency in first trimester is a concern [76]. Among pregnant women in their first trimester, 57% women had bacterial vaginosis with Vitamin D levels < 20 ng/mL. First-trimester 25(OH) D levels of less than 15 ng/mL were related to the development of pre-eclampsia [77]. More elaborate observational studies are required to elucidate a better conclusion with respect to first trimester usage, since few trials also show no association between Vitamin D levels in first trimester and pregnancy outcomes. Interventional studies are emerging showing Vitamin D supplementation is safe and useful in overcoming deficiency in first trimester. These studies could be cornerstone for call on consensus for Vitamin D supplementation in first trimester of pregnancy. In a Qatar Study, pregnant women supplemented weekly oral dose of 50,000 IU from first trimester resulted in improvement of maternal Vitamin D levels. Newborns' Vitamin D levels could correlate with the Vitamin D level of their mothers [78]. In another Middle-east study, supplementation of oral 2000 IU/day in preconception period showed positive effect on Vitamin D levels in reproductive women [79]. Such studies should further be carried out to demonstrate the effect of safe dose of Vitamin D in the short time of preconception period which is about 2 or 3 month before being pregnant, to avoid concurrency of Vitamin D deficiency in the early stages of embryonic life and pregnancy.

6. Vitamin D Treatment Strategy in Pregnancy and Lactation

A review of randomized controlled trials of Vitamin D supplementation during pregnancy indicates that doses of 400 - 1600 IU/day were insufficient in achieving even a mean serum 25(OH) D concentration \geq 20 ng/mL [66]. However, getting 25(OH) D levels consistently above 30 ng/mL may require at least 1500 - 2000 IU/day of Vitamin D [32]. Studies have shown that Vitamin D intake of up to 10,000 IU/day for 5 months is associated with achievement of a serum 25(OH) D concentration \geq 32 ng/mL without Vitamin D toxicity [80] [81]. A number of trials have suggested that doses of 2000 IU-4000 IU would be required to maintain serum 25(OH) D \geq 32 ng/mL. In a recent trial studying the effect of two dose regimens, pregnant women with low 25(OH) D levels were randomized to 2000 IU vitamin D3/d or 400 IU/d from <20 week gestation until delivery. 25(OH)D was significantly greater in the treatment group at both 26 (41 vs. 34 ng/mL) and 36 week (46 vs. 34 ng/mL) suggesting that a daily dose of 2000 IU is effective at improving Vitamin D status in pregnant women [82]. Bruce W Hollis *et al.* [50] described a randomized, controlled trial, including 350 women with a singleton pregnancy at 12 to 16 weeks' gestation supplemented with 400 IU, 2000 IU, or 4000 IU of Vitamin D per day until delivery. Not a single adverse event was attributed to Vitamin D supplementation or circulating 25(OH) D levels. 82%, 71%, and 50%, respectively, of the mothers on 4000 IU, 2000 IU, and 400 IU of Vitamin D daily achieved a serum 25(OH) D concentration > 32 ng/mL. The authors concluded that Vitamin D supplementation of 4000 IU/day for pregnant women is safe and most effective in achieving sufficiency in all women and their neonates regardless of race. Carol L. Wagner *et al.* [51] studied safety of 2000 IU and 4000 IU Vitamin D in pregnancy & determine if maternal/fetal 25(OH) D improves in dose-dependent manner. In the study of 257 pregnant women supplemented from 12 - 16 weeks' gestation, the authors concluded that maternal supplementation with Vitamin D 2000 IU/d and 4000 IU/d during pregnancy improved maternal/neonatal Vitamin D status. Evidence of risk reduction in infection, preterm labor, and preterm birth was suggestive, requiring additional studies powered for these endpoints. The new RCT data indicate that 4000 IU/day Vitamin D during pregnancy will "normalize" Vitamin D metabolism and improve birth outcomes including primary cesarean section and comorbidities of pregnancy with no risk of side effects [74]. In a United Arab Emirates (UAE) study, oral Vitamin D₂ supplementation with 2000 IU/d or 60,000 IU/month for 3 month was safe, and it increased serum 25(OH) D concentrations significantly during lactation [83]. In another study, it was found that a maternal intake of 2000 IU/d Vitamin D would elevate circulating 25(OH) D concentrations for both mothers and nursing infants, albeit with

limited capacity, especially with respect to nursing infants. A maternal intake of 4000 IU/d could achieve substantial progress toward improving both maternal and neonatal nutritional Vitamin D status [84]. In a study from the United Arab Emirates, among pregnant Arab women with a high prevalence of Vitamin D deficiency suggested that Vitamin D supplementation of 2000 and 4000 IU/d appeared safe in pregnancy, and 4000 IU/d was most effective in optimizing serum 25(OH) D concentrations in mothers and their infants as compared to 400 IU/d [62].

7. Clinical Evidence-Indian Outlook

Although interventional trials in Indian population are scarce, as the Vitamin D deficiency awareness increases, an increasing population is being subjected to Vitamin D supplementation. Marya *et al.* [85] suggested that Vitamin D (1200 IU/day) during 32 and 36 weeks of pregnancy was associated with significant reduction systolic blood pressure (SBP) and diastolic blood pressure (DBP) than non-supplemented group. The same author had previously demonstrated that 1200 U Vitamin D/day throughout the 3rd trimester, showed significantly lower Heat-labile alkaline phosphatase (HLAP) levels and increased fetal birth weight [86].

Higher doses (*i.e.* 50,000 IU, 60,000 IU) are yet to be adapted as safe or either talked about in pregnancy. It is noteworthy that these doses are already studied among Indian population and appear to be safe in once a month dosing during second and third trimester. Marya RL *et al.* [86] suggested that administration of Vitamin D in two large doses of 60,000 IU each in the 7th and 8th months of pregnancy in 20 women was more efficacious. Jasbinder Kaur *et al.* [87] described the effect of administration of two pharmacological doses of Vitamin D (60,000 IU each) in 6th and 7th months of pregnancy. Compared to controls, the birth weight and weight of the placenta, its protein, DNA and RNA contents were significantly higher in the supplemented group. Kalra P. *et al.* [26] studied the effect of Vitamin D supplementation in two groups. Of pregnant women, one group received single oral 60,000 IU dose (second trimester) and other group received two oral doses of 120,000 IU (second and third trimester respectively) in pregnancy. Both doses improved infant anthropometry whereas the larger dose also increased maternal Vitamin D levels. Sahu *et al.* [88] reported that among 60,000 IU in fifth month and 120,000 IU in fifth and seventh month, Vitamin D in doses 120,000 IU in 5th and 7th was effective in raising the 25(OH) D levels in pregnancy. Parul Singla *et al.* [89] studied 100 pregnant women who received 60,000 IU every fortnight from 28 till 36 week of gestation. Vitamin D supplementation during the third trimester of pregnancy was found to be efficacious in reducing the risk of preeclampsia by increasing therapeutic effectiveness of calcium supplementation in pregnant women. It could be possible that higher number of Indian trials with 60,000 IU/ month usually among fifth and seventh trimester indicated better patient compliance as compared to 2000 IU/4000 IU per day doses.

With doses about 2000 IU - 4000 IU found to be safe and recommended by various committees, further randomized controlled trials among Indian population could be beneficial in defining the safe dose and duration of Vitamin D supplementation in pregnancy and lactation. There is substantial evidence that a higher dose (60,000 IU) per month does not show any clinical side effects in Vitamin D deficient pregnant women. A consensus of recommendation on higher doses is required by global committees, a fact to be discussed for inclusion in international guidelines. Further data in this perspective would be welcoming.

8. Conclusion

As calcium demands increase in pregnancy, Vitamin D status becomes crucial for optimal maternal & fetal outcomes. Low levels of Vitamin D are linked with a number of fetal health problems like small size, neonatal hypocalcaemia & seizures, impaired growth, skeletal problems including rickets & low BMD. Low levels of Vitamin D are linked with a number of maternal health problems like preeclampsia, preterm labour & an increased rate of caesarean section. The high incidences of Vitamin D deficiency in pregnancy and lactation in India call for unanimous approach to tackle this grave situation. It is also a concern that despite such high deficiency statistics, there is no national consensus statement for clarity on prevention and treatment of this deficiency. Following the evidence, there is substantial need for upgradation of target Vitamin D level to be maintained above 30 ng/mL in pregnancy and lactation. There is a need to further elaborate the effect of Vitamin D supplementation through randomized controlled trials with appropriate doses (2000 IU, 4000 IU, 60,000 IU) to further gain clarity for its beneficial clinical practice across all trimesters & beyond.

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