

Vitamin D Status in Pregnancy: Fetomaternal Outcome and Correlation with Cord Blood Vitamin D

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ABSTRACT

Introduction: Hypovitaminosis D in pregnancy has been reported to cause various maternal effects, i.e., hypocalcemia, subclinical myopathy, increased risk of preeclampsia (PE), gestational diabetes mellitus (GDM), cesarean sections, and fetal effects, i.e., neonatal tetany, hyperbilirubinemia congenital rickets, infantile rickets, etc. Only few Indian studies are available in this regard.

Objective: To estimate serum vitamin D levels in pregnant women, cord blood, and study fetomaternal outcomes.

Materials and methods: A prospective observational study was conducted on 54 consecutive pregnant women and their newborn babies. Serum 25-hydroxy vitamin D [25(OH)D] level was estimated in all women at the time of admission in labor ward. They were followed up to delivery and 48 hours postpartum. Vitamin D was also estimated in cord blood collected during delivery. All results were recorded and analyzed statistically.

Results: The mean 25(OH)D level in pregnancy was 6.81 ± 7.38 ng/mL. The mean 25(OH)D level in their babies (cord blood) was 6.34 ± 7.05 ng/mL. There was very strong positive correlation between maternal and fetal serum 25(OH)D levels (p-value 0.001, r-value 0.9). Vitamin D deficiency was strongly associated with obesity, PE, and GDM (p-value 0.001). Neonatal jaundice and tetany were also significantly associated with severe vitamin D deficiency.

Conclusion: Low levels of vitamin D have been observed in pregnant women and their newborn babies. Hypovitaminosis D has been associated with adverse fetomaternal outcomes. As there is a strong correlation of maternal and neonatal levels, supplementing vitamin D in a pregnant women might improve these adverse pregnancy outcomes.

Keywords: Cord blood vitamin D, Fetomaternal outcome, Hypovitaminosis D, Vitamin D status in pregnancy.

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INTRODUCTION

India being a tropical country, it is thought that vitamin D deficiency would not be common. Despite abundant sunshine, vitamin D deficiency has been recognized to be highly prevalent in India as reported from studies done in Delhi (28.3°N),¹ Lucknow (26.8°N)² and Tirupathi (13.4°N).¹ The high prevalence of vitamin D insufficiency during pregnancy is increasingly recognized, especially in dark women, following customs like veil, in women living in northern latitudes and during winter season.^{1,3,4} Maternal effects of hypovitaminosis D have been reported to cause calcium malabsorption, bone loss, poor weight gain, subclinical myopathy,⁵ increased preeclampsia (PE),⁶ increased gestational diabetes mellitus (GDM),⁷ increased cesarean sections.⁸ In the newborn, hypovitaminosis D has been reported to cause neonatal tetany,⁹ hyperbilirubinemia,¹⁰ large fontanelle, enamel defects, congenital rickets, and infantile rickets.¹¹ There is growing evidence that hypovitaminosis D can also have long-lasting effects on health of the offspring, i.e., impaired skeletal growth and rickets.^{5,11} In a community-based study of 901 mother and offspring pairs, researchers found that maternal vitamin D deficiency (serum 25-hydroxyvitamin D [25(OH)D] < 50 nmol/L) at 18 weeks pregnancy was associated with impaired lung development at age 6 in offspring, neurocognitive difficulties at age 10, increased risk of eating disorders in adolescence, and lower peak bone mass at 20 years of age.¹² Very few Indian studies have been done regarding vitamin D status during pregnancy, so it was considered worthwhile to study vitamin D status in pregnancy, its fetomaternal effects, and its correlation with cord blood levels.

AIMS AND OBJECTIVES

To estimate total serum vitamin D, i.e. 25(OH)D₂ + 25(OH)D₃ levels in pregnancy and find out its association with fetomaternal outcome and cord blood 25(OH)D levels.

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MATERIALS AND METHODS

This study was a prospective observational study conducted in the Department of Obstetrics and Gynecology at a tertiary hospital in Delhi, India, from March 2012 to February 2013. Approval from Institutional Ethical Committee was obtained. After informed written consent, 70 pregnant women with singleton pregnancy attending antenatal clinic in third trimester were enrolled in consecutive order and followed up till 48 hours of delivery.

Pregnant women having known liver disorders, kidney disorders, history of antitubercular and antiepileptic drugs, pregestational diabetes, and chronic hypertension were excluded from the study. Women taking vitamin D supplements were excluded from the study. All women were counseled for diet with good nutritive value as per routine for all pregnant women, including leafy vegetables, milk, curd, eggs, cheese, pulses, fruits. As a routine for antenatal women, they were advised to take ferrous sulfate 100 mg and calcium 500 mg tablets twice a day. Demographic data, detailed history, physical examination, and obstetric examination were recorded.

All women were subjected to routine antenatal investigations and other relevant investigations if required. Screening for GDM was done by estimating blood glucose levels 2 hours after 75 gm glucose intake in all women at 24 to 28 weeks. A value ≥ 140 mg% was taken as diagnosis of GDM.¹³ Any complication occurring during antenatal period was recorded. Serum calcium and serum vitamin D were estimated during admission to labor ward. Vitamin D was estimated by chemiluminescence method. All the women were followed up till delivery and 48 hours postpartum. After delivery, cord was cut and blood sample was collected from the maternal end of cord for estimation of 25(OH)D.

Fetal outcome parameters like birth weight and crown heel length were recorded. Head circumference and fontanelle size were measured after 24 hours of birth. Baby was observed for development of any neonatal jaundice, tetany, or seizure. All the observations were recorded on a predesigned proforma and analyzed.

ESTIMATION OF VITAMIN D

Vitamin D was estimated in all women using CLIA Cobas e 411 (Roche) in the Pathology Department. The most reliable marker of vitamin D status is its metabolite, 25(OH)D, which has a half-life of 3 weeks, is biologically inactive with levels approximately 1,000 times greater than its active metabolite, i.e., 1,25(OH)D.

The assay employs a vitamin D binding protein (VDBP) as a capture protein in the assay which binds to 25(OH)D. Addition of microparticles and hydroxy

vitamin D labeled with biotin causes the free sites of VDBP to become occupied. The microparticles are magnetically captured on an electrode which induces chemiluminescent emission measured by a photomultiplier. Vitamin D insufficiency was considered as levels < 20 ng/mL in our study.

Statistical Analysis

Categorical variables were expressed as number of patients, percentages and compared across the groups using Pearson's chi-square test for independence of attributes. Continuous variables were expressed as mean \pm standard deviation and compared across the groups using unpaired t-test and analysis of variance test where applicable. Statistical Package for the Social Sciences software version 16 was used for analysis. An alpha level of 0.05 was considered significant.

RESULTS

Out of 70 subjects recruited fulfilling inclusion criteria, 54 subjects could be followed up for delivery and up to 48 hours postpartum.

The mean age of women in our study was 23.89 ± 3.2 years. Most of the women belonged to the age group 21 to 25 years. The mean body mass index (BMI) of women was 24.32 ± 4.09 . Majority of women were Hindu by religion. Except for BMI the demographic distribution of women in terms of age, religion, and season was comparable in relation to vitamin D (Table 1).

The baseline investigations, i.e., mean hemoglobin, total leukocyte count (TLC), platelet counts, and serum calcium, were in the normal reference range. Mean vitamin D level was found to be low (6.81 ± 7.38 ng/dL) in our study (Table 2).

Basic parameters in terms of BMI, TLC, and serum calcium were found to be statistically significant in various subgroups of vitamin D levels. Preeclampsia and GDM were also found to be significantly more (p-values 0.023 and 0.039 respectively) in women with lower vitamin D level subgroup (Table 3).

Fetomaternal outcome and mean vitamin D was also evaluated. It was seen that mean vitamin D was significantly higher (p-value 0.001) in women who were normotensive and normoglycemic compared with those having PE and GDM. Vitamin D was found to be comparable in terms of onset of labor i.e. spontaneous or induced labor and mode of delivery i.e. vaginal or cesarean delivery. Birth weight and neonatal biometry also did not have any significant difference in terms of mean vitamin D levels. Vitamin D was significantly higher (p-value 0.001) in women whose babies did not

Table 1: Demographic distribution and vitamin D levels

Parameter	n	Mean vitamin D (ng/mL)	p-value
Age			
Mean (years)	23.89 ± 3.2	6.81 ± 7.38	
<20	9 (16.7%)	5.52 ± 6.63	0.239
21–25	31 (57.4%)	5.80 ± .66	
26–30	2 (22.2%)	9.09 ± 1.82	
>30	20 (3.7%)	14.63 ± 10.65	
BMI, kg/m²			
Mean	24.32 ± 4.09		
18.5 ≤ 25	32 (59.3%)	8.98 ± 8.92	0.001
25 ≤ 30	2 (3.7%)	7.43 ± 0.53	
> 30	20 (37.0%)	3.29 ± 1.01	
Religion			
Hindu	50 (92.6%)	6.70 ± 7.20	0.417
Muslim	4 (7.4%)	8.28 ± 10.56	
Women recruited in (n)			
Summer (March to October)	21 (38.9%)	5.78 ± 4.53	0.684
Winter (November to February)	33 (61.1%)	7.47 ± 8.73	

Table 2: Baseline lab investigations

Parameter	Mean values	Reference ranges
Hemoglobin, gm%	10.45 ± 0.81	≥11 in pregnancy 9–10.9 mild anemia in pregnancy
TLC (per cmm)	10,100 ± 2,123.08	5,000–12,000
Platelets (per cmm)	240,000 ± 52,160.8	149,000–429,000
Serum calcium, mg/dL	9.58 ± 0.74	8.2–9.7
Serum vitamin D, ng/mL	6.81 ± 7.38	>20 optimum levels <20 hypovitaminosis

Table 3: Maternal variables according to severity of hypovitaminosis D

Maternal variables	Vitamin D levels in mother				Total n = 54, 100% p-value
	<5 ng/mL n = 35 (%)	5–10 ng/mL n = 10 (%)	10–20 ng/mL n = 5 (%)	>20 ng/mL n = 4 (%)	
BMI (kg/m ²) 18.8 ≤ 25	16 (29.6%)	7 (13%)	5 (9.6%)	4 (7.4%)	32 (59.3%) 0.002
25 ≤ 30	0 (0%)	2 (3.7%)	0 (0%)	0 (0%)	2 (3.7%)
≥30	19 (35.1%)	1 (1.9%)	0 (0%)	0 (0%)	20 (37.0%)
Season – Summer	14 (26%)	4 (7.4%)	3 (5.6%)	0 (0%)	21 (38.9%) 0.320
Winter	21 (38.9%)	6 (11.1%)	2 (3.7%)	4 (7.4%)	33 (61.1%)
Hb% (gm/dL) mean	10.4 ± 0.86	10.43 ± 0.61	10.46 ± 0.69	10.95 ± 0.98	54 0.649
TLC (per cmm) mean	109,00 ± 1,718.6	9,530 ± 1,765.75	8,100 ± 1,044	6,375 ± 838.15	54 0.001
Platelets mean (per cmm)	245,000 ± 46,402.19	222,000 ± 42,450.1	224,000 ± 61,175.98	258,000 ± 105,050.78	54 0.493
Serum calcium mean (mg/dL)	9.35 ± 0.66	9.68 ± 0.59	10.2 ± 0.39	10.55 ± 0.9	54 0.001
Pregnancy outcome – PE	16	1	0	0	17
Normotensive	19	9	5	4	37 0.023
GDM present	18	3	0	0	21
GDM absent	17	7	5	4	33 0.039

p-value <0.05

have jaundice and tetany than those having neonatal jaundice and tetany (Table 4).

A strong positive correlation was found between maternal serum vitamin D and cord blood vitamin D (p-value 0.001, r-value 0.9; Table 5 and Graph 1).

DISCUSSION

The mean age in our study was 23.89 ± 3.2 years (Table 1) similar to Marwaha et al¹ and Sachan et al² in pregnant women. Age had no association with mean vitamin D levels (p-value 0.239; Table 1).

Table 4: Fetomaternal outcome and mean maternal vitamin D levels

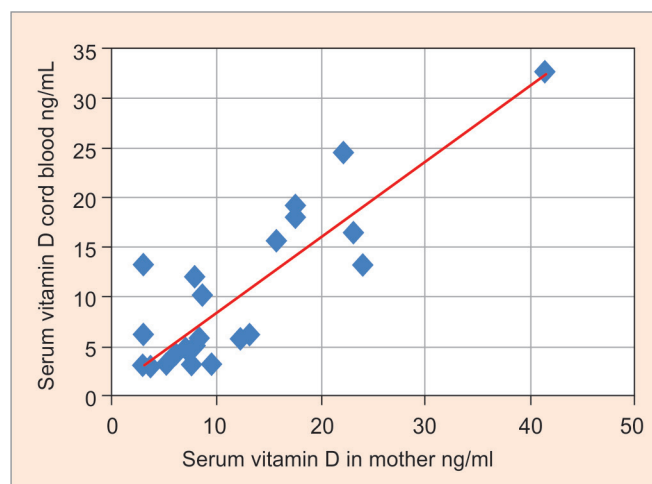
Outcome	n = 54 (%)	Mean vitamin D	p-value
PE present	17 (31.5%)	3.31 ± 0.99	0.001
PE absent	37 (68.5%)	8.43 ± 8.44	
GDM present (n = 21)	21 (38.9%)	3.69 ± 1.67	0.001
GDM absent (n = 33)	33 (61.1%)	8.80 ± 8.83	
Onset of labor – spontaneous	36 (66.7%)	7.01 ± 6.48	0.786
Induction done	18 (33.3%)	6.42 ± 9.11	
Mode of delivery – vaginal	41 (75.9%)	7.32 ± 7.72	0.326
LSCS	13 (24.1%)	4.85 ± 5.75	
Birth weight – <2,500 gm	3 (5.6%)	3.00 ± 0	0.362
>2,500 gm	51 (94.4%)	7.04 ± 7.533	
Appgar score at 1 minute – 4–6	1 (1.9%)	3	–
7–10	53 (98.1%)	6.84 ± 7.45	
Neonatal tetany – present	7 (13%)	3.0 ± 0	0.001
Absent	47 (87%)	7.339 ± 7.786	
Neonatal jaundice – present	35 (64.8%)	5.81 ± 5.38	0.001
Absent	19 (35.2%)	8.656 ± 9.998	
Crown heel length – <47 cm	3 (5.5%)	4.8 ± 3.12	0.305
47–50 cm	44 (81.5%)	7.54 ± 7.97	
> 50 cm	7 (13%)	3.11 ± 0.3	
Head circumference – < 34 cm	14 (25.9%)	4.7 ± 2.35	0.282
34–36 cm	40 (74.1%)	7.46 ± 8.4	
Fontanelle size – normal	50 (92.6%)	7.1 ± 7.6	0.313
more than normal	4 (7.4%)	3.2 ± 0.4	

LSCS: Lower segment cesarean section; p-value <0.05; APGAR: Appearance, pulse, grimace, activity and respiration

Table 5: Serum vitamin D in maternal and cord blood

Vitamin D levels (ng/mL)	Mother (n) %	Cord blood (n) %	p-value	r-value
Vitamin D levels				
<5 (severe deficiency)	35 (64.8%)	40 (74.1%)	0.001	0.9
5–10 (deficiency)	10 (18.5%)	04 (7%)		
10–20 (insufficiency)	05 (9%)	07 (13%)		
>20 (optimum)	04 (7.4%)	03 (5.5%)		
Mean vitamin D	6.81 ± 7.38	6.34 ± 7.05		

In our study, 92.6% of pregnant women were found to be having hypovitaminosis D (serum vitamin D <20 ng/mL). A high prevalence of vitamin D deficiency has been revealed in various other studies. Sachan et al² reported 84.3% urban and 83.6% rural women with vitamin D deficiency in a study in northern India. Study in second trimester of pregnancy by Sahu et al¹⁴ has shown a prevalence of vitamin D deficiency to be 74.1%. Hypovitaminosis D has been reported to be 70.7% in southern part of India¹⁵ and 93.5% in northern India.¹⁶ Dasgupta et al¹⁷ showed 56% of prevalence from northeastern part of India. A predominant nonvegetarian food habit might be the cause for lower percentage of hypovitaminosis D. Despite abundant sunshine in our country, the high prevalence of vitamin D deficiency might be due to darker skin with melanin preventing the entry of ultraviolet (UV) rays in the skin, people remaining indoors mainly, use of sunscreens, malabsorption, less

**Graph 1:** Scatter diagram showing maternal and cord blood vitamin D correlation. p-value=0.001, r-value=0.9

exposure to sunshine, a vegetarian diet, less intake of calcium in the form of milk and other dairy products being expensive, nonfortified foods, and milk.

Vitamin D insufficiency was seen in 9% (serum vitamin D 10–20 ng/mL) of women and 19% were found to be deficient (serum vitamin D 5–<10 ng/mL). Severe deficiency (serum vitamin D <5 ng/mL) was seen in 65% women. Only 7% women had optimal levels of vitamin D in our study.

In our study, the mean maternal serum 25(OH)D level was 6.81 ± 7.38 ng/mL (Table 2). A value of 14 ± 9.5 ng/

mL was reported by Sachan et al.² Harinarayan et al¹⁸ have reported mean vitamin D level of 15.5 ± 0.3 ng/mL in urban women and 19 ± 0.89 ng/mL in rural women. The lower mean maternal vitamin D level might be due to urban lifestyle of the women remaining mainly indoors, more number of obese women, and increased pollution preventing skin to exposure of UV rays.

In our study, no significant difference (p-value 0.684) in vitamin D levels in women recruited in summer (March to October) and winter (November to February) was found, though several studies showed higher prevalence of maternal vitamin D deficiency when delivered during winter and spring. Zhuang et al¹⁹ have reported lowest vitamin D level in spring, with 25(OH)D concentration <50 nmol/L in 98.6% of mothers and 99.3% of their neonates.

Obesity is a risk factor for vitamin D deficiency. There were 20 pregnant women with BMI > 30 in our study, 95% (n = 19) of them had severe vitamin D deficiency which was statistically significant (p-value 0.002; Table 3). This may be explained based on the sequestration of 25(OH)D in adipose tissue in obese women. Similar observations were made by Wortsman et al.²⁰

Vitamin D also appears to play a role in reducing inflammation. Those with adequate levels of vitamin D in their blood were less likely to develop inflammation. An inverse relation between 25(OH)D below its median and C-reactive protein (CRP) was found to be significant (geometric mean CRP change 0.11 mg/dL for each 10 ng/mL change in 25(OH)D).²¹ A significant difference in leukocyte count was observed in vitamin D-deficient women in our study (p-value 0.001; Table 2). Excess 1,25(OH)₂D is produced in an effort to upregulate the vitamin D receptor (VDR) to express antimicrobial peptides, such as cathelicidin and beta defensins which attack pathogens, and 25(OH)D is rapidly metabolized in the process, resulting in a low serum level.²²

Several studies highlighted that maternal vitamin D deficiency was an independent risk factor for PE as reported by Bodnar et al.⁶ The active form of vitamin D, 1,25(OH)₂D₃, has been shown to regulate the transcription and function of genes associated with placental invasion, normal implantation, and angiogenesis²³ supported by the known stimulatory effects of calcitriol on the expression of vascular endothelial growth factor in vascular smooth muscle cells through vitamin D response elements in the vascular endothelial growth factor promoter.²⁴ It is also believed to be important in directing immune responses by dendritic cells and macrophages at the fetal/placental interface as well as immunological adaptation by the mother to reduce the risk of infection and inflammation.²³

In our study, there were significantly more (p-value 0.023) number of women who developed PE (n = 16) in the severe deficiency group. No women had PE with vitamin D sufficiency group (vitamin D >20 ng/mL; Table 3). The mean vitamin D levels in women who developed PE were 3.31 ± 0.99 ng/mL, which was significantly low (p-value 0.001) compared with mean vitamin D (8.43 ± 8.44 ng/mL) in women who did not develop PE (Table 4). Extrapolating this observation, it can be said that supplementing vitamin D can reduce risk of PE in pregnant women and can help in reducing PE-related fetomaternal morbidity and mortality.

Vitamin D enhances expression of insulin gene, resulting in high insulin synthesis.²⁵ It also influences insulin secretion by regulating intracellular calcium levels²⁶ in insulin-sensitive tissues, such as muscle and adipose tissues. Vitamin D also improves insulin resistance by upregulating the insulin receptors.²⁷ As hypovitaminosis D by promoting inflammatory response induces insulin resistance, vitamin D by its modulating effect on the immune system²⁸ enhances insulin response. The difference in mean vitamin D level in GDM and non-GDM group (3.69 ± 1.67 and 8.80 ± 8.83 ng/mL respectively) was found to be statistically significant (p-value <0.001) in our study (Table 4). In women who developed GDM (n = 21), 85.7% (n = 18) belonged to the severe deficiency group (Table 3). Therefore, supplementing vitamin D might reduce risk of GDM in pregnant women and its associated adverse fetomaternal outcomes.

Women with cesarean deliveries had lower mean vitamin D compared with those having vaginal deliveries, though the difference was not significant in our study. Vitamin D was lower with spontaneous onset of labor compared with induction. There was no association between low vitamin D level and need of induction of labor (p-value 0.786) or mode of delivery in our study (p-value 0.326; Table 4). Merewood et al²⁹ have reported cesarean section to be four times more common in women with vitamin D levels <37.5 nmol/L. Scholl et al⁸ have found an association between vitamin D deficiency and cesarean section for prolonged labor. Poor maternal vitamin D status is associated with poor muscle tone of pelvic floor and reduced pelvic muscle strength, reducing ability to push.

Khalessi et al³⁰ found a significant difference in birth weight of babies of mothers who had higher vitamin D levels. Vitamin D has a key role in fetal growth by its interaction with parathyroid hormone and Ca²⁺ homeostasis. Mannion et al³¹ have shown that each additional cup of milk daily was associated with a 41 gm increase in birth weight (95% confidence interval

14.0–75.1 gm); each additional microgram of vitamin D, with an 11 gm increase (95% confidence interval 1.2–20.7 gm). Mothers with suboptimal vitamin D status have offspring with reduced intrauterine and postnatal skeletal development. In our study, mothers with babies having birth weight >2,500 gm had a higher mean vitamin D level (7.04 ± 7.533 ng/mL) compared with mothers whose babies had birth weight <2,500 gm, though the difference was not statistically significant (p-value 0.362). The vitamin D nuclear receptor polymorphism, *Vdr* Fok (FF/FF), is an effect modifier of birth weight with 8% lower birth weight in maternal vitamin D deficiency (<11.2 ng/mL).³² Pawley and Bishop³³ found a significant association between umbilical cord 25(OH)D concentrations and head circumference at 3 and 6 months postnatal age. Maghbooli et al³⁴ found significantly wider posterior fontanelle diameter in neonates of mothers with vitamin D deficiency (as defined by a 25(OH)D level <34.9 nmol/L or ~14 ng/mL) compared with neonates whose mothers were not deficient. However, no significant difference in crown heel length, head circumference, and anterior fontanelle size was seen in relation to mean vitamin D levels (p-value 0.305, 0.282, 0.313 respectively) in our study. Adequate nutritional vitamin D status during pregnancy is important for fetal skeletal development, bone mineralization, tooth enamel formation, and perhaps general fetal growth.

It was observed in our study that neonatal tetany was strongly associated with maternal severe vitamin D deficiency (p-value 0.001; Table 4), similar to the study by Delvin et al.³⁵

We found a strong association between severe vitamin D deficiency and neonatal jaundice (p-value <0.001; Table 3) similar to that reported by Mutlu et al.¹⁰ Although bilirubin and vitamin D metabolisms are two distinct pathways and are very different, at least one part of the synthesis takes place in a common organ, the liver. Therefore, the metabolism or synthesis of one may affect the other.¹⁰

The mean cord blood vitamin D was 6.34 ± 7.05 ng/mL. Deficiency of vitamin D (levels <10 ng/mL) was seen in 81.5% (n = 44) of babies and 83.3% (n = 45) of mothers. There was an excellent positive correlation between maternal and cord blood vitamin D levels (p-value 0.001, r-value 0.9; Table 5, Graph 1). This suggests that vitamin D status in the mother is reflected in vitamin D status in the baby. Jacquemyn et al³⁶ have reported high correlation between overall prenatal and cord blood levels (r-value 0.91). A significant (r = 0.6; p < 0.001) correlation between maternal and cord blood vitamin D levels was observed by Kumar et al¹⁵ and Sachan et al² (r = 0.79). Therefore, supplementation of vitamin D in the mother may reduce

the adverse fetal outcome and might help to improve the long-term ill-effects of hypovitaminosis D in the baby.

LIMITATIONS

Though this is definitely a venture to look into this important aspect from Indian perspective, there is need of larger randomized trials to prove the causal association between maternal vitamin D deficiency with fetomaternal outcome. The authors have also not included in their study the interventional arm to see the beneficial effects, if any, by vitamin D supplementation on fetomaternal outcome.

CONCLUSION

Prevalence of vitamin D is quite high in the population catered by our institute. Body mass index was associated with deficiency of vitamin D. Increased white blood cell and decreased serum calcium level were found to be statistically significant in women with vitamin D deficiency. Occurrence of PE and GDM was significantly more in women with hypovitaminosis D. A significantly more neonatal jaundice and tetany was seen in babies of mothers having hypovitaminosis D. There was an excellent correlation between maternal and fetal (cord blood) vitamin D status. Strategy to improve maternal status of vitamin D might help to improve neonatal status also, thereby helping to reduce the various adverse fetomaternal outcomes seen with hypovitaminosis D.

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