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Original Research Article

A study to evaluate serum 25-hydroxy vitamin D3 and calcium levels in maternal and cord blood and their effect on pregnancy outcome

Radha B. P. Thangappah[1]*, Ursula Sampson[2], Amrin Azad[1], Rathna Arumugam[1], Smriti Anand[1], Ponnalagan Karuakaran[2]

[1]Department of Obstetrics and Gynecology, [2]Department of Biochemistry, Meenakshi Medical College and Research Institute, Kancheepuram, Tamil Nadu, India

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***Correspondence:**
Dr. Radha B. P. Thangappah,
E-mail: radhaprabhu54@ymail.com

ABSTRACT

Background: To determine the prevalence of vitamin D deficiency among pregnant mothers and their neonates and to study the effect of vitamin D deficiency on maternal and perinatal outcome.
Methods: This prospective cohort study conducted in a teaching hospital included 223 pregnant mothers and their offspring born in 2017. Detailed history was taken to ascertain the causes of vitamin D deficiency. vitamin D3 and calcium levels were estimated in maternal and cord blood samples. To study the association between the vitamin D status and the various maternal and neonatal parameters.
Results: 91.9 % of women were house wives involved in indoor activities. Pre-eclampsia and GDM were seen in 4.5% of cases each. 5.41% were obese and 84% were of medium complexion, and 8% were dark. 93.7% were non-vegetarians, and fish, egg and milk consumption was adequate in 61.3% , 64% and 71% respectively. Only 5.40% of women had adequate exposure to sunlight. The mean birth weight was 3.08± 0.36 Kg. and 14 babies were admitted to NICU for neonatal asphyxia.77.40% had deficient levels of vitamin D <20 ng/ml. Only four pregnant mothers (1.8%) had sufficient levels vitamin D. There was no statistically significant association between vitamin D deficiency and various maternal and neonatal parameters.
Conclusions: This study has shown that the prevalence of vitamin D deficiency among south Indian pregnant mothers and their newborn is very high and the ways to improve the vitamin D status among pregnant mothers should be looked at.

Keywords: Calcium, Maternal and perinatal outcome, Vitamin D deficiency

INTRODUCTION

Vitamin D is a key modulator of calcium metabolism and is essential for a number of physiological processes. In spite of the natural source of vitamin D from sun light, the prevalence of vitamin D deficiency is high throughout the world. Though the dietary contribution is small, poor availability of vitamin D containing food sources may also contribute to the vitamin D deficiency.[1,2] Vitamin D deficiency is common in northern Europe due to the limited availability of sunlight.[3] In India sunlight is available in plenty, but the exposure is limited. Studies have shown a high prevalence of vitamin D3 deficiency among Indian pregnant women.[4]

Observational studies have shown that pregnant women with insufficient levels of vitamin D3 may be at increased risk of gestational diabetes (GDM), pre-eclampsia, and having infants small for their gestational age and is a major cause of hypocalcaemic seizures in the neonates.[5,6] The objectives of the study was to determine the prevalence of vitamin D deficiency among pregnant mothers and their neonates; to study the effect of vitamin

D deficiency on maternal and perinatal outcome and to examine the factors associated with vitamin D deficiency.

METHODS

This was a prospective cohort study conducted at Meenakshi Medical College and Research Institute, Kancheepuram, in 2017. The study included 223 pregnant mothers and their newborns. Consent from each participant was taken and Ethical Committee approval was obtained.

Inclusion criteria

- Pregnant mothers with more than 34 weeks of gestation with singleton pregnancies.

Exclusion criteria

- Those mothers who were on therapeutic or prophylactic doses of vitamin D3, those with chronic liver and renal disease.

Using a general questionnaire, demographic detail, obstetric history and medical history were collected. Medication history was taken with regards to calcium and other micronutrient intake. Using a structured food-frequency questionnaire (FFQ), detailed dietary history was taken. In collaboration with a dietician, the FFQ tool was modified and validated to suit present study. Details of intake of fish, egg, milk etc and their frequency and adequacy were noted.

Consuming fish at least once a week, taking 3 eggs a week and drinking 2 glasses of milk everyday was considered adequate.

They were enquired about the nature of their job, and the duration of exposure to sunlight. Sunlight exposure was considered adequate if their face, arms and hands were exposed to the sun light for at least for 30 minutes a day, between 10 am to 4 pm. BMI was calculated for all patients. The skin colour was reported as fair/ medium brown/ dark brown or black. Features of osteomalacia such as proximal muscle weakness, and bone tenderness were looked for.

In all patients, 5 ml. of venous blood sample was taken to measure the vitamin D3 and calcium levels. After delivery, the delivery details were noted, and cord blood samples were collected. Both maternal and cord blood samples were processed and stored at -70 to -80oC until further analysis.

In the newborns anthropometric measurements were noted. Newborns were assessed by the Paediatrician for evidence of distress, jitteriness, intra-uterine growth restriction (IUGR). The babies were also monitored in the postnatal period for evidence of hypocalcaemia.

Biochemical analysis

25(OH) vitamin D3 level was measured using enzyme linked immuosorbent assay. Serum levels <20ng/ml. was considered deficient, levels between 20-29ng /ml was insufficient and levels of 30-32 ng/ml. was sufficient.[7] For both maternal serum and cord blood same reference range was used. The calcium level in the maternal serum and cord blood was measured by photometric test. The normal reference range of calcium for maternal serum was 8.9-10.1mg/dl and for the cord blood was 10-11mg/dl.

Statistical analysis

For statistical analysis, IBM SPSS version 22 was used. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Independent sample t-test /ANOVA and Chi square test were used to assess the statistical significance. Association between maternal vitamin D and quantitative variable was assessed by pearson correlation coefficient and the data was represented in a scatter diagram.

RESULTS

The mean age of the study population was 26.1±3.6 years, 92% were Hindus, 2.7% were Christians and 4.5% were Muslims. 91.9 % of women were house wives, 3.6% worked as teacher, technician and security and 4.5% worked in the paddy fields.

The mean gestational age was 38.49 ± 1.01 weeks, pre-eclampsia and GDM were seen in 10 patients each and anaemia was seen in 6 patients. In 6 mothers IUGR was diagnosed and 8 babies delivered preterm. 39.64% of mothers were overweight and 5.41% were obese. 84% were of medium complexion, 8% were dark and another 8% were fair (Table 1).

93% of women were on prophylactic calcium tablets (1000mg/day). On analysing the food habits, 93.7% were non-vegetarians and adequate intake of fish, eggs and milk was seen in 61.3%, 64%, 71% respectively.

Only 5.40% had adequate exposure to sunlight with exposure more than 3 hours per week, 13.50% had moderate exposure of 1-2 hours a week, 61.30% had exposure < 1 hour a week and 19.80% had no exposure to sun light at all. Among those who had good exposure to sun light, ten of them worked in the paddy fields, and two worked as securities. (Table 2).

Four women reported backache and eight reported muscle weakness. 64% delivered by caesarean section and 36% delivered by the vaginal route. 62.2% were male and 37.8% were female babies. The mean birth weight, length and head circumference were 3.08±0.36kg, 59.91±5.14cm, 36.15±1.43cm respectively (Table 3).

Fourteen babies were admitted to NICU for neonatal asphyxia.

One baby was diagnosed with talipes and another with Hirsch sprung disease and four babies (3.60%) had wide anterior fontanelles. Only four pregnant mothers (1.8%) had sufficient levels vitamin D. 20.7 % had insufficient levels, 44.10% had deficient levels between 10-20ng/ml and 33.30% had severe deficiency with levels <10ng/ml. The mean maternal D and calcium levels were 14.77±7.68 and 7.07±1.95 respectively. In the cord blood, the mean vitamin D level and calcium were 14.05±7.09 and 6.66±1.69 respectively (Table 4). In 52.7% of cord samples the calcium level was <8mg/dl indicating hypocalcaemia in the neonate.

The association between vitamin D levels and various maternal parameters was analysed. There was no statistically significant difference in the vitamin D levels between the primigravida and multigravid women and whether they were involved in indoor or outdoor activities.

Table 1: Descriptive analysis of maternal characteristics (N=223).

Parameters	No.	Percentage
Age distribution in years		
< 19 years	4	1.80
20-24 years	78	35.1
25-29 years	101	45.00
30-34 years	34	15.30
35 years and more	6	2.70
Religion		
Hindu	207	92.8
Christian	6	2.70
Muslim	10	4.50
Occupation		
House wife	205	91.90
Assistant Professor	02	0.90
Lab Technician	02	0.90
Teacher	02	0.90
Security	02	0.90
farming	10	4.50
Gravidity		
Primigravida	72	32.40
Multigravida	151	67.60
Gestational age		
34-37 weeks	8	3.60
38 weeks and more	215	96.39
Antenatal problems		
Pre-eclampsia	10	4.50
GDM	10	4.50
Type I DM	2	0.90
Anaemia	6	2.70
Hypothyroidism	4	1.80
None	191	85.6
Fetal problems		
IUGR	6	2.70
Pre term birth	8	3.60
BMI		
Normal	123	54.95
Over weight	88	39.64
Obese	12	05.41
Complexion		
Dark	18	8.10
Brown	187	83.80
Fair	18	8.10

Table 2: Descriptive analysis of vitamin D and calcium sources (food habits and sun light exposure).

Parameters	No.	Percentage
Food habit		
Non-vegetarian	209	93.7
Vegetarian	14	6.30
Fish intake		
Adequate	137	61.30
Inadequate	60	27.00
No intake	26	11.70
Egg intake		
Adequate	143	64.00
Inadequate	68	30.60
No intake	12	05.40
Milk intake		
Adequate	159	71.20
Inadequate	64	28.80
Sun light exposure		
Adequate exposure	12	05.40
Moderate exposure	137	61.30
Minimal exposure	30	13.50
No exposure	44	19.80

Analysis of food habits also did not show statistically significant difference if they had taken adequate dietary sources of vitamin D or not. With regards to sunlight exposure, irrespective of the duration of exposure, 77.4% had deficient levels of vitamin D.

The mean difference in maternal vitamin D levels among women with normal weight, over weight and obesity was statistically not significant. There was no association between the sex of the baby, birth weight and vitamin D status of the mother. The mean vitamin D level in women with or without pre-eclampsia was 16.78±8.62 and 14.66±7.6 respectively. There was no statistical difference in vitamin D levels in women with or without pre-eclampsia and GDM. There was also no significant association between vitamin D deficiency and IUGR and preterm delivery (Table 5).

On analysing the correlation between the maternal and cord blood vitamin D levels, there was a moderate positive correlation between maternal and cord blood vitamin D levels (Figure 1).

There was also a weak positive correlation between maternal vitamin D and cord blood calcium levels (Figure 2). There was a weak negative correlation between the birth weight, length and head circumference of the neonate and the maternal vitamin D levels.

Table 3: Descriptive analysis of neonatal characteristics

Parameter	Mean ±SD	Median	Min	Max	95% C.I.	
					Lower	Upper
Birth weight (Kg)	3.08±0.36	3.10	2.37	4.60	3.01	3.14
Birth length (in cm)	59.91±5.14	60.00	45.00	70.00	58.92	60.89
Head circumference (cm)	36.15±1.43	36.30	32.00	39.00	35.88	36.43

Table 4: Descriptive analysis for vitamin D and calcium levels in maternal serum and cord blood.

Parameter	Mean ±SD	Median	Min	Max	95%C.I.	
					Lower	Upper
Maternal Vitamin D	14.77±7.68	13.50	2.20	38.50	13.29	16.24
Maternal Calcium	7.07±1.95	7.40	2.00	16.60	6.70	7.44
Cord Blood Vitamin D	14.05±7.09	13.70	2.00	29.20	12.69	15.41
Cord Blood Calcium	6.66±1.69	6.70	2.00	11.00	6.33	6.98

Table 5: Association of maternal vitamin D levels with various maternal and neonatal parameters.

Gravidity	Maternal vitamin D Mean± SD		Mean difference	95% CI		P value
				Lower	Upper	
Primi gravida	15.57±7.66		1.20	-1.87	4.27	0.440
Multi gravida	14.37±7.62					
Occupation						
House wife	14.84±7.63		2.94	-5.92	11.80	0.512
Out door	11.9±8.06					
Food habit						
Non-vegetarian	14.78±7.77		0.35	-5.57	6.27	0.906
Vegetarian	14.43±5.24					
Fish intake						
Adequate (Base line)	15.4±8.19					
Inadequate	14.11±7.37		1.29	-2.03	4.60	0.443
None	12.89±4.36		2.52	-2.06	7.10	0.279
Egg intake						
Adequate	13.75±6.82					
Inadequate	16.74±9.21		2.99	-0.14	6.11	0.061
None	15.45±4.92		1.70	-4.67	8.07	0.598
Milk intake						
Adequate	14.88±7.57		0.44	-2.74	3.61	0.785
Inadequate	14.45±7.84					
Sun light						
Good exposure (Base line)	11.08±7.36					
Minimal exposure	14.43±7.6		3.35	-3.10	9.79	0.305
Moderate exposure	16.38±8.21		5.30	-2.01	12.61	0.154
No exposure	15.66±7.39		4.58	-2.39	11.55	0.195
BMI category						
Normal (Base line)	14.45±7.53					
overweight	14.83±7.72		-0.38	-3.39	2.62	0.801
obese	17.33±8.65		-2.88	-9.38	3.61	0.381
Gender (New born outcome)						
Male	14.57±7.91		0.49	-3.46	2.47	0.743
Female	15.06±7.18					
Birth weight category						
Up to 2.5kg (Base line)	17.87±8.07					
2.6 to 3kg	14.7±7.72	3.17	-2.97	9.30		0.309
3.1 to 3.5kg	14.04±7.73	3.83	-2.28	9.94		0.217
3.6 and above	17.14±5.62	0.73	-7.37	8.82		0.859
Pre-eclampsia						
Yes	16.78±8.62	2.12	-4.81	9.04		0.546
No	14.66±7.6					
GDM						
Yes	20.76±6.82	6.28	-0.55	13.12		0.071
No	14.48±7.56					
IUGR						
Present	19.67±9.4	5.04	-3.78	13.87		0.260
Absent	14.62±7.57					
Preterm birth						
Present	11.33±7.29	3.56	-4.13	11.26		0.361
Absent	14.89±7.63					

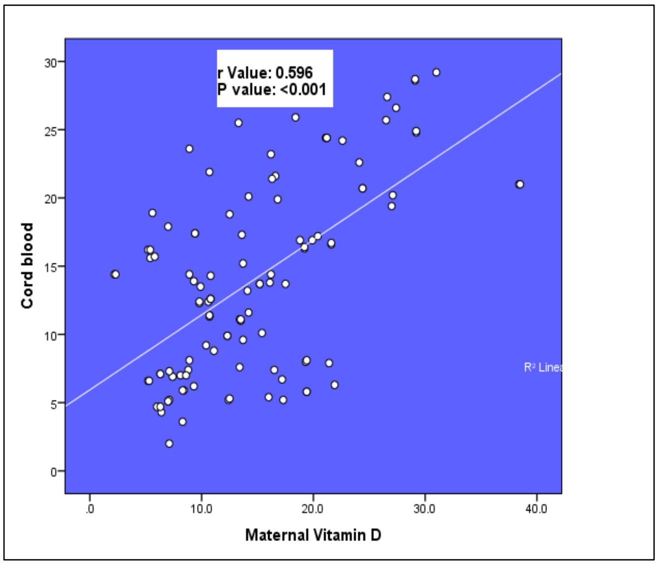

Figure 1: Correlation between maternal and cord blood vitamin D levels.

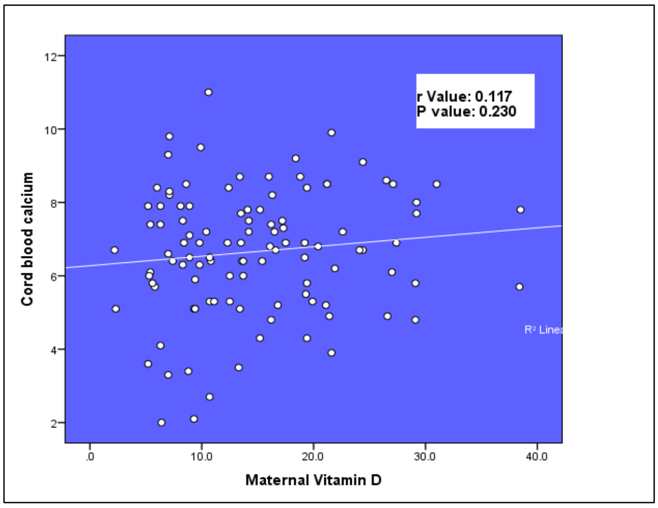

Figure 2: Correlation between maternal vitamin D and cord blood calcium levels.

DISCUSSION

Vitamin D deficiency is reported worldwide in all age groups. Recent studies suggest that vitamin D deficiency is common during pregnancy.[8] In India, in spite of plenty of natural source of vitamin D, a high proportion of general population as well as pregnant women are vitamin D Deficient. In present study, only 2% of pregnant mothers had sufficient levels vitamin D. A total of 77.4% were vitamin D deficient, with severe deficiency seen in 33.30% of cases. Similar to present study, a high prevalence of severe vitamin D deficiency was reported in 42.5% of pregnant mothers by Alok Sachan et al. from north India.[4] Even developed nations have reported a high prevalence of vitamin D deficiency in pregnancy. In a study from Netherlands vitamin D deficiency was seen in 44.6% of pregnant mothers, with severe deficiency seen in 12.1% of cases.[8] In a London antenatal population, a vitamin D level of < 25 nmol/l was found in 47% of Indian Asian women, 64% of Middle Eastern women, 58% of black women and 13% of Caucasian women.[3] Risk factors for maternal vitamin D deficiency include: dark skinned women, indoor occupation, women who 'cover up' , cold climate, etc. More than 90% of the vitamin D requirement comes from exposure to sunlight. A Cochrane review has suggested that, in summer, people with fair skin generally require about 5 minutes exposure per day.[9] Because it efficiently absorbs UVB photons, people with increased skin melanin pigmentation require longer exposures to sunlight to make the same amount of vitamin D3, compared with light-skinned people.[10] Ritu et al has suggested that for the Indian complexion, a minimum of 45 minutes of exposure is required to get the adequate quantity of vitamin D.[7] In this study, 91.9 % of women remained indoors as they were house wives, and 3.6% were involved in indoor occupation. Not only their sunlight exposure was limited, 92% of women were either brown or dark in complexion, which explains the high prevalence of vitamin D deficiency in this study. Most of the dietary sources of vitamin D are of animal origin such as fish , egg and milk. In this study, fish, egg and milk intake were adequate in majority of women , however, the mean vitamin D levels were < 20 ng/ml indicating that the contribution of dietary sources to vitamin D status is probably very minimal. Studies have shown that pre-pregnancy obesity has been associated with lower levels of vitamin D in both pregnant women and their neonates.[11] In present study, only 5.5% of women were obese and there was no statistically significant difference in the levels of vitamin D between normal weight and obese women. There have been evidence through studies that vitamin D deficiency is associated with an increased risk of pre-eclampsia and small for gestational age (SGA) infants.[5,12,13]

Baker et al have shown a five-fold increased risk of severe pre-eclampsia with vitamin D levels less than 50 nmol/l.[14] Early onset severe pre-eclampsia has been shown to be associated with reduced levels of vitamin D compared to control women.[15] However, present study failed to show any association between vitamin D levels and the development of pre-eclampsia. Similar to present study, many studies have also shown a weak or no relationship between vitamin D and hypertensive disorders in pregnancy. Shand et al have shown that a low level of vitamin D during the first half of pregnancy was not associated with the subsequent development of pre-eclampsia, adverse pregnancy outcomes or gestational hypertension, in women at high risk of pre-eclampsia.[16] A similar study from the USA also failed to demonstrate an association between maternal vitamin D levels and the subsequent development of pre-eclampsia.[17] Evidence suggests that vitamin D improves insulin sensitivity by enhancing insulin responsiveness to glucose transport.[18] The association between low vitamin D levels and gestational diabetes mellitus (GDM) is also conflicting. A meta-analysis demonstrated that vitamin D insufficiency was associated with a higher risk of GDM.[5] However, some studies have found no association between maternal 25(OH)D levels and the development of GDM.[19] Present study also did not find significant association between low vitamin D levels and GDM. Farrant et al have shown that Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size.[20] There are conflicting reports on vitamin D deficiency and neonatal birth weight. Some studies have shown that maternal vitamin D deficiency is associated with increased risk of having a SGA baby and reduced intrauterine long bone growth.[21,22,23] However, Khalessi et al found no independent relation between maternal vitamin D levels and any of the neonatal anthropometric measures.[24] Rodriguez et al did not find any association between vitamin D status in pregnancy and GDM, preterm delivery, FGR, SGA and anthropometric birth outcomes.[25] Present study also did not find significant association between vitamin D status and various maternal and neonatal parameters . Maternal vitamin D deficiency increases the risk of neonatal vitamin D deficiency . Mehrotra et al have demonstrated a strong positive correlation of 25 (OH) D levels between mothers and their infants, ($P<0.001$).[6] In our study, there was a moderate positive correlation between maternal and cord blood vitamin D levels (r Value: 0.596, P value: <0.001) . There was also a weak positive correlation between maternal vitamin D and cord blood calcium levels indicating that maternal vitamin D deficiency can lead to neonatal hypocalcaemia. Vitamin D deficiency is a major cause of hypocalcaemic seizures in neonates and infants. A serum calcium level of < 8mg/dl for term and <7mg/dl for preterm babies is called neonatal hypocalcaemia. Early neonatal hypocalcaemia is usually asymptomatic and is incidentally detected. If symptomatic they present with features of neuromuscular irritability. In present study, 52.7% of babies had serum calcium levels < 8 mg/dl. However, none of the babies presented with features of neuromuscular irritability before discharge from the hospital. Vitamin D deficiency is one of the causes of late onset neonatal hypocalcaemia.[26] One limitation of this study was that follow – up of infants after discharge was not done. Babies of mothers with vitamin D deficiency in pregnancy should be supplemented with vitamin D and calcium.[27] As a high number of Indian pregnant mothers are vitamin D deficient, routine screening of all pregnant mothers for vitamin D deficiency may not be cost effective. On the other hand, universal supplementation with vitamin D may be a better option in terms of health benefits to both mother and the baby. National organizations have recommended 600 international units of vitamin D per day during pregnancy and lactation.[28]

CONCLUSION

The prevalence of vitamin D deficiency among south Indian pregnant mothers and their newborn is very high. Though this study has not demonstrated significant short term adverse maternal and perinatal outcome due to vitamin D deficiency, the long term skeletal and extra skeletal effect on the child is not known. In order to improve the vitamin D status among our pregnant mothers, the tenable solution could be increasing the awareness on the importance of sunlight exposure, fortifying food products and supplementing vitamin D during pregnancy.

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