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Original Research Article

Vitamin D Deficiency in Pregnancy: An Independent Risk Factor for Increased Maternal and Foetal Co-Morbidities

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ABSTRACT

Background: Vitamin D deficiency is highly prevalent in all parts of the world. Pregnant women and neonates are highly vulnerable to vitamin D deficiency. **Aim:** The present study was undertaken to assess the effect of maternal 25(OH)-D status on the risk of development of preeclampsia (PE) and pre-term labour (PTL). **Materials and methods:** 165 pregnant women were followed from less than 20 weeks of gestation to delivery (2015-2016) at a prenatal clinic in a tertiary care center. Development of maternal co-morbidities like pre-term labour/pre-term birth (PTL/PTB), gestational hypertension/ pre-eclampsia (GHTN/PE) and gestational diabetes mellitus (GDM) were noted. The maternal and cord blood was taken at the time of delivery and association between vitamin D concentration and the risk of development of maternal comorbidities was analyzed. **Results:** Women whose 25(OH)-D levels were < 25nmol/L at delivery, 20.4% (16/83) had PTL and 24.1% (20/83) had GHTN/PE; whereas in those with levels > 50nmol/L, only 2.5% (1/37) had PTL and 2.7% (1/37) had GHTN/PE. Statistical analysis revealed that vitamin D levels >25nmol/L had a protective effect against the development of PTL (OR 0.05) and GHTN/PE (OR 0.13). **Conclusion:** maternal vitamin D deficiency may be an independent risk factor for PE and PTL. Vitamin D supplementation in early pregnancy should be explored for preventing PE and PTL and for promoting neonatal well-being.

Key words: vitamin D, preterm labour, preeclampsia, gestational hypertension.

INTRODUCTION

Vitamin D is not a simple vitamin but a pro-hormone, a complex molecule that plays many important roles in the body. These roles, in addition to the main function of regulating mineral salt deposition in bones, include regulation of body metabolism, mood, blood pressure and immune function.

Vitamin D is especially important during pregnancy as low maternal vitamin D stores may contribute to problems such as low birth weight and small for gestational age babies besides an increased risk of maternal comorbidities. [1]

Vitamin D deficiency is a world-wide epidemic, with a prevalence that ranges from 18% to 84% depending upon the country of residence, ethnicity and local clothing customs and dietary intake. [2,3] Maternal vitamin D deficiency during pregnancy has been documented in a

number of studies all over the world. [4,5]

Clinical studies establishing an association between vitamin D levels and adverse pregnancy outcomes such as preeclampsia, gestational diabetes, low birth, preterm labour and caesarean delivery have conflicting results. [6] This is likely due to a paucity of randomized trials, heterogenicity of population studies and low sample size with poor adjustment for confounding among observational studies.

The present study was undertaken to correlate the effect of vitamin D deficiency and the risk of development of maternal and fetal co-morbidities.

MATERIALS AND METHODS

This was a prospective cohort study conducted in the department of Obstetrics and Gynaecology along with the department of Biochemistry and Neonatal division of Paediatrics at a Tertiary Care Hospital in New Delhi, India after obtaining the required clearance from the Institutional Ethics Committee.

A sample size of 165 was calculated taking 15% as the margin of error and 95% confidence limit. Primigravidae with singleton pregnancy at 18-20 weeks, willing to comply with the study protocol were included in the study between 2015 to 2016. Pregnant women with pre-existing chronic medical diseases such as hyperparathyroidism, renal, liver dysfunction, tuberculosis were excluded from the study.

At the initial visit a detailed history including symptoms of vitamin D deficiency (generalized body ache, muscular weakness), menstrual history and obstetrical history was taken. Dietary history was taken in detail based on one week recall method. Diet software (Dietsoft Vr. 1.1.7) was used to calculate the daily intake of calorie, protein and calcium intake. Vitamin D intake was calculated approximately based on vitamin D content in different food products.

Follow up was done in all patients as per the hospital protocol. Maternal co-morbidities: preeclampsia, gestational diabetes, and preterm labor, if any were recorded.

At the time of delivery, period of gestation at delivery was recorded and a complete anthropometric assessment of the neonate including: Birth weight: was recorded on electronic beam balance to the nearest 5 gm. Length: supine length was recorded to the nearest 0.1cm. Head circumference: was measured by non-stretchable fiber glass tape to the nearest 0.1cm. If caput/ moulding were present, measurement was postponed till it regressed. Signs of vitamin D deficiency in the neonate including craniotabes, condition of the fontanelles and hypocalcemic neonatal seizures were recorded.

Maternal serum and cord blood levels of 25(OH)-D using sandwich ELISA and maternal serum and cord blood calcium, phosphorus and serum ALP levels were estimated at delivery.

Women were then classified in to three groups depending upon their serum vitamin D levels at the time of delivery as sufficient: >50nmol/L, insufficient: 25-50nmol/L and deficient:<25nmol/L.

Biochemical analysis

5ml of fresh maternal/cord blood was collected in vacutainers and were immediately transported to the laboratory on ice where centrifugation was done within one hour. If analysis was done within 24 hours of collection, serum was stored at 2-8˚C, otherwise the serum was stored at -20˚C until analyzed. Repeated freeze thaw cycles were avoided.

Statistical analysis

Statistical analysis was done using SPSS statistical package (version 17; SPSS). Normally distributed continuous variables were expressed as means and standard deviations, and nonparametric variables as medians and IQR. Proportions were compared using the chi square test. P values were expressed without a Bonferroni correction. Spearman's test was used for correlations. Two- tailed significance at $p<0.05$ was considered significant. To find

the Odd's ratio, regression analysis was done. In running data, simple regression was used and in categorical data, logistic regression was applied.

OBSERVATION AND RESULTS

Clinical profile

Maternal age, BMI, nutritional intake, and duration of sun exposure were associated with vitamin D levels at delivery in the total study population of 165 patients. There was no lost to follow up.

Age was found to have no effect on vitamin D levels in the body as there was a poor association between age and vitamin D levels ($p > 0.05$).

A very good association was seen between BMI $\geq$ 25 and low 25(OH)-D levels, $p = 0.001$.

The regression statistics showed the OR 4.2, 95% CI (90.4- 224). Though 60% of the patients having BMI < 18.5 had vitamin D deficiency, a poor association was seen between BMI < 18.5 and vitamin D deficiency ($p > 0.05$).

A higher percentage of vitamin D sufficiency was seen in those with adequate daily protein (35.6%) and vitamin D (83.3%) intake compared to those with inadequate protein (15.1%) and vitamin D (12.1%) intake.

Association between the duration of sun exposure and vitamin D levels was highly significant ($p = 0.000$). Logistic regression showed that sun exposure has a protect effect against vitamin D deficiency with an Odd's Ratio of 0.06, 95% CI (0.02-0.128).

Pregnancy complications

The relation between pregnancy complications and 25(OH)-D levels at delivery in the total study population was analyzed. It was seen that amongst the women whose 25(OH)-D levels were <25nmol/L at delivery, 20.4% (16/83) had PTL and 24.1% (20/83) had GHTN/PE; whereas in those with levels > 50nmol/L, only 2.5% (1/37) had PTL and 2.7% (1/37) had GHTN/PE. (Table-1).

Table 1: Correlation between maternal vitamin D status and pregnancy complications.

Pregnancy Complications	Levels of vitamin D (nmol/L)			OR (95%CI)
	< 25 (n=83)	25-50 (n=45)	>50 (n=37)	
Preterm Labour (n=21)	(16) 20.4%	(4) 8.8%	(1) 2.5%	0.05, (0.01-0.26)
GHTN/ Preeclampsia (n=24)	(20) 24.1%	(3) 6.7%	(1) 2.7%	0.13, (0.04-0.43)
GDM (n=2)	(1) 1.3%	(1) 2.2%	(0) 0%	--
None (n=118)	(46) 55.4%	(37) 82.2%	(35) 94.6%	

Statistical analysis revealed that vitamin D levels >25nmol/L had a protective effect against the development of PTL (OR 0.05) and GHTN/PE (OR 0.13).

There were only two cases of GDM which were both in women with 25(OH)-D levels <50nmol/L. However, there was a poor association ($p = 0.404$) between the occurrence of GDM and vitamin D deficiency.

Correlation of maternal 25(OH)-D levels with cord blood 25(OH)-D levels

77% of the mothers whose serum 25(OH)-D levels were <25nmol/L were found to have neonates whose cord blood level also showed deficiency of vitamin D. Similarly 65.8% mothers whose 25(OH)-D levels were >50nmol/L had neonates with sufficient vitamin D levels. (Table 2).

Table 2: Correlation between the maternal and cord blood vitamin D levels.

Cord Blood 25(OH)D	Maternal 25(OH)D (nmol/L)			R, p
	< 25 (n=83)	25-50 (n=45)	>50 (n=37)	
<25 (n=67) 25-50 (n=40) >50 (n=58)	(64) 77 % (12) 15% (7) 8%	(28) 60.9% (17) 36.6% (2) 2.4%	(4) 9.4% (9) 24% (24) 65.8%	R =0.915 (p=0.001)

There was a very strong positive correlation between maternal and cord 25(OH)-D levels (r = 0.915, *p*= 0.001)

Maternal vitamin D levels and neonatal outcome

25.6% of the babies born to mothers who were deficient in vitamin D were found to be small for gestational age where as only 3.4% of the babies born to mothers who had sufficient vitamin D levels were small for gestational age (r = 0.398, *p*= 0.001).(Figure 1).

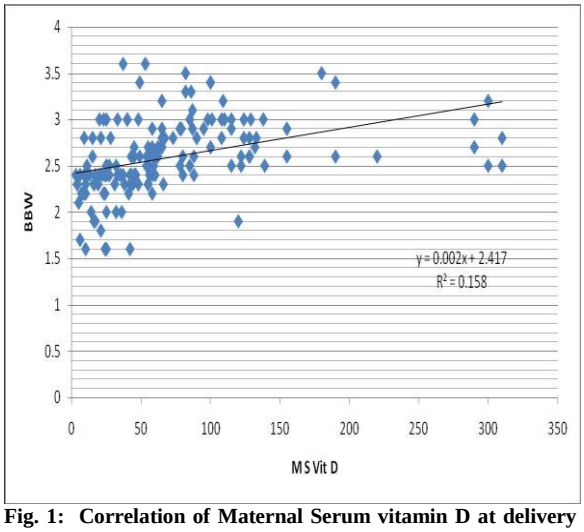

Fig. 1: Correlation of Maternal Serum vitamin D at delivery with BBW.

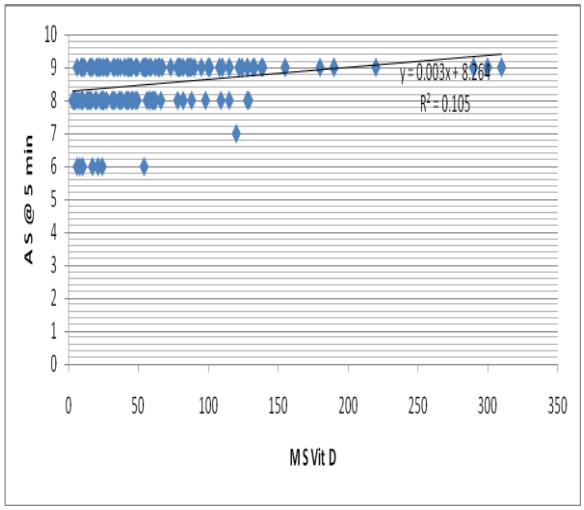

Fig. 2: Correlation of Maternal Serum vitamin D with APGAR score of babies.

Apgar level <7 was seen in 14.6% of mothers having vitamin D deficiency compared to 1.3% in those who were vitamin D sufficient at delivery (*p*= 0.000). A positive correlation was seen between the maternal vitamin D status and Apgar score (r= 0.325). (Figure 2).

DISCUSSION

Vitamin D is just not a simple vitamin, but a pro-hormone, a complex molecule that plays many important roles in the body. Vitamin D is especially important during pregnancy as low maternal vitamin D stores may contribute to problems such as low birth weight and small for gestational age babies besides an increased risk of maternal comorbidities. [1]

The mean age in the total study population in the present study was 23.48 ± 2.4 years, which was lower than the mean age (around 26 years) in a number of studies done in India and abroad. This may be because the present study included only primigravidae, while both primigravidae and multigravidae were included in other studies. [1,7,8]

On studying the total duration of the sun exposure the study subjects received and its correlation to the maternal 25 (OH)-D levels, it was found that 65.35% of the patients of the total study population were receiving less than 1 hour of sun exposure daily, irrespective of the seasonal variations throughout the year, as most of them were not allowed to work outside because of social norms and restrictions, and had clothing habits that prevented them from getting adequate sun exposure.

There was a highly significant association between the duration of sun exposure and vitamin D levels ($p < 0.05$). The quantum of UV-B rays (290 to 310 nm) received by an individual on exposed body surface determines the amount of vitamin D synthesized by the skin. There are similar reports of low 25(OH)--D from very hot countries of middle east, where women wear veils and levels were even lower in summers as women avoided the sun and heat by staying indoors. [9]

Many studies have previous concluded that circulating 25 (OH)-D

concentrations were lower in obese than lean individuals[10]. Similar results were seen in our study with level of 25(OH)-D were lower in women with BMI ≥ 25. This is postulated because Vitamin D metabolism is affected in obese individuals, as it is deposited in body fat stores, making it less bioavailable. [10]

Many clinical studies have established an association between vitamin D deficiency and higher complications during pregnancy. Vitamin D influences a number of aspects of the immune systems and may be important for infections such as bacterial vaginosis [11] which are responsible for PTL. Several studies have reported similar association between low 25(OH)-D levels and PTL [1,12] as was seen in the present study. More proportion of women with levels in deficient or insufficient range had PTL.

Vitamin D also has a role in immune modulation. Pre-eclampsia is thought to originate in early pregnancy when the maternal immune system limits placental invasion in mothers vulnerable to cardiovascular disease. Calcitriol an active metabolite of Vit D can be considered a pregnancy-supporting factor that could work through several mechanisms to reduce pre-eclampsia risk, including a direct influence of calcitriol on implantation, placental invasion and angiogenesis. [13] 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. [14]

A recent meta-analysis [14] has shown a consistent association between vitamin D and pre-eclampsia across different study types, supporting a role for vitamin D as a preventative agent against pre-eclampsia. The studies included in this review show conflicting results about the association of vitamin D levels and the risk of preeclampsia. However, in this review more than half of the studies showed a positive link between Vitamin D deficiencies and Preeclampsia. There is a clear need for further trials and other robust studies to identify the effect of Vitamin D on preeclampsia.

In the present study majority of the women who developed GHTN/PE had vitamin D levels in the deficient or insufficient range. Amongst the women whose 25(OH)-D levels were less than 25 nmol/L, 24% developed GTN/PE, while only 6.7% and 2.7% of women whose levels were 25-50nmol/L and >50 nmol/L developed GTN/PE respectively.

Vitamin D has been shown to influence insulin secretion and insulin resistance in a number of studies. [15,16] Vitamin D replenishment restores insulin secretion and sensitivity in patients with Type 2 diabetes with established Vitamin D deficiency, thus suggesting a role of Vitamin D in the pathogenesis of GDM. Maternal 25(OH)-D concentrations have been related to the risk of developing GDM in various cohorts. However, the present study did not show any significant association between vitamin D deficiency in mothers with GDM.

In addition, relation of fetal 25(OH)-D to neonatal outcome was studied by correlating cord blood levels to certain neonatal parameters. The parameters studied were birth weight, length, head circumference, APGAR score at 5 min and signs of calcium deficiency in neonate.

Vitamin D has been implicated in providing critical signals in gene regulation and expression in early placental development among placental trophoblast models. In endothelial cells, 1, 25-OH2- D3 has been demonstrated to increase expression of vascular endothelial growth factor (VEGF), through binding to vitamin D receptor and co-localization to a vitamin D responsive element in the VEGF promoter. [17] If this mechanism is also demonstrated in the placental trophoblast, it is possible that inadequate vitamin D levels may affect fetal growth through alterations in VEGF activity.

A strong correlation was noted between BBW and APGAR score with maternal vitamin D status. (fig 1 &2). A significant improvement in birth weight of infants born to vitamin D supplemented mothers has been seen in some studies [5,18] and not seen in other. [19]

Maternal vitamin D deficiency is a common, and potentially preventable, cause of neonatal hypocalcaemia. This is especially common in South Asian women but in the present study none of the babies in either group had any signs of calcium deficiency including craniotabes and hypocalcemic neonatal seizures.

CONCLUSIONS

Vitamin D deficiency is highly prevalent in all parts of the world. Pregnant women and neonates are highly vulnerable to vitamin D deficiency. Pregnant women receive very less amount of sunlight especially in parts of Southeast Asia due traditional norms and customs. Vitamin D level above 25nmol/L was found to have a protective effect against the development of PTL as well as GHTN/ PE. Also a strong positive correlation was found between maternal vitamin D levels with cord blood levels, baby's birth weight and APGAR score. Currently, there are no guidelines on vitamin D supplementation in pregnancy in India. Thus vitamin D supplementation therapy in pregnancy can help in reducing the incidence of gestational hypertension/ preeclampsia, preterm labor/births; and have a beneficial effect on the neonates.

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