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Original Research Article

Effect of Vitamin D Deficiency on the Outcome of Pregnancy

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Abstract: Vitamin D deficiency based on low circulating 25(OH)D concentration is now a world wide phenomenon. Non-classical actions of this hormone is now the main focus of interest for researchers. This prospective cohort study was conducted among pregnant women visiting antenatal OPD of Gauhati Medical College & Hospital, to see whether the Vitamin D status of pregnant women has any effect on the development of preeclampsia and other adverse pregnancy outcomes.25(OH)D estimation was done on VitrosECiQ Immunodiagnostic System . Statistical analysis was done using GraphPadInstat Version 3 and Med Calc statistical software. Vitamin D deficiency and insufficiency was found in a higher percentage of pregnant women in this study. 44.81% of pregnant women with deficient vitamin D level presented with adverse pregnancy outcome in comparison to 32.93% with normal level. Significant difference in the vitamin D level was found between women who did not present with any adverse outcome and those who presented with preeclampsia. (23.16ng/ml ± 8.3ng/ml vs 21.46 ng/ml ± 7.2 ng/ml, p=.0235). Difference in the rates of Low Birth Weight(LBW), Intrauterine Death(IUD), and Primary Caeserian Section by vitamin D concentration was also observed. It can thus be concluded that vitamin D deficiency during pregnancy has an adverse effect on the outcome of pregnancy.
Keywords: Caeserian section Pre-eclampsia, preterm birth, pregnancy, vitamin D.

INTRODUCTION:

Vitamin D is part of a complex steroid hormone system, long known to be involved in bone metabolism. Recently however it has been found that vitamin D has a role in other physiologic processes as diverse as vascular health, immune function, metabolism and placental function. There are two forms of the vitamin. Vitamin D3(Cholecalciferol),produced from the conversion of 7-dehydrocholesterol in the skin and Vitamin D2, produced in mushrooms and yeast. The active form is 1,25 (OH)2D which is formed subsequent to two hydroxylations of the molecule, first in the liver followed by hydroxylation in the kidney. Although 25(OH)D has low biologic activity, it is the major form of circulating vitamin D and its concentration in blood is generally thought to reflect the nutritional status.

During pregnancy there is increased synthesis of $1,25(OH)_2D$ in kidney [1] and serum levels of 1,25(OH)2D increases upto two fold starting at 10-12 weeks of gestation , reaching a maximum in the third trimester [2]. An increase in the levels of the active form of the vitamin during the second and third trimester clearly suggest a role of the vitamin in obstetric wellbeing. Recent studies have emphasized on the non-classical roles of vitamin D during pregnancy and have tried to correlate vitamin D with adverse pregnancy outcomes like pre-eclampsia, bacterial vaginosis, increased frequency of caeserian delivery [3].

Vitamin D deficiency has been identified as a public health problem in many countries affecting children, adults, pregnant women across ethnicity and season [2,4]. Vitamin D deficiency during pregnancy is associated with the non-classical actions of this hormone and new researches in this field have found that women who develop pre eclampsia, the most studied pregnancy outcome , have low levels of vitamin D [5,6]. Also reduced risks of complications including pre eclampsia, preterm birth, infection have been found in women who received high doses of vitamin D supplementation during pregnancy [7,8].But there are

other studies which have failed to establish any such relationship between low vitamin D level during pregnancy and adverse pregnancy outcome [8,9]. Due to these conflicting results there exists no consensus as regards to the optimum vitamin D levels in pregnancy or its role in the outcome of pregnancy. Very few studies have been conducted in India to evaluate the vitamin D status in pregnant women [10].

This study has been planned with an aim to:

1. Study the vitamin D status of pregnant women attending a tertiary care hospital in North eastern part of India.
2. Correlate the vitamin D status with adverse outcome of pregnancy.

MATERIALS & METHODS :

This study was designed as a prospective cohort study .It was conducted among 500 pregnant women visiting ante-natal OPD Clinic of Gauhati Medical College & Hospital. Ethical approval was obtained from the Institutional Ethical Committee of Gauhati Medical College. Informed consent was taken from each of the study participant. Pregnant ladies visiting Antenatal OPD irrespective of age, gravida, parity and duration of pregnancy were included in the study. Pregnant ladies with Type1 Diabetes Mellitus, Chronic kidney disease, autoimmune disease, Pregnancy Induced Hypertension, Gestational Diabetes Mellitus or other severe chronic disease were excluded from the study.

The study was conducted from September 2014 to January 2016.Pregnant women visiting GMCH antenatal clinic were recruited for the study after taking informed consent. Data on maternal characteristics like age, gravid, parity, diet history, sun exposure, weight, height etc was collected and noted down in a questionnaire at the time of recruitment. A venous blood sample was collected at the same time for vitamin D estimation. The samples were promptly centrifuged and serum stored at -20° C until analysis.

Serum 25(OH)D was estimated using the Vitros 25(OH)D total reagent pack on the VitrosECiQ Immunodiagnostic System.A competitive immunoassay technique is used which involves the release of the 25(OH)D in the sample from the binding protein using a low ph denaturant and the subsequent competition of the free 25(OH)D with HRP labelled 25(OH)D reagent for the monoclonal anti-vitamin D bound to the wells. Calibration of the reagent was done every 28 days and one level of control was run with each batch of assay.

Information on the outcome of pregnancy like preeclampsia, mode of delivery,birth weight of the baby, preterm birth and other details of delivery was collected from hospital records and recorded in the "delivery details" section of the questionnaire. The study participants were also given a card containing the contact nos of the investigators for easy follow up of the cases.

Subjects were classified into three categories based on the vitamin D level.

i) Vitamin D deficient – 25(OH)D< 20 ng/ml.
ii) Vitamin D insufficient – 25(OH)D – 20-<30 ng/ml.
iii) Vitamin D normal – 25(OH)D- 30-100 ng/ml.

Pre-eclampsia was defined as new onset hypertension after 20 weeks of gestation with proteinuria.Low birth weight was defined as babies born with birth weight less than 2.5 Kg. Preterm birth was defined as babies born before 37 completed weeks of gestation.

The data was expressed as mean ± SD and number, n(%). Statistical analysis was carried out by unpaired t test by using software "GraphPadInstat version 3". P-value<0.05 was considered to be statistically significant. Odds Ratio and 95% CI was calculated using Med Calc statistical software.

RESULTS & OBSERVATIONS:

A total number of 500 antenatal women were recruited for the study. All necessary details were noted down in a proforma and 25(OH)D estimation done. But follow-up information regarding outcome of pregnancy was available for 483 women. In this study as shown in table 1, 37.89% of antenatal women were found to be vitamin D deficient, 45.13% vitamin D insufficient and only 16.98% had normal vitamin D levels.

Table 2 shows the mean vitamin D concentration in relation to pregnancy outcome. Significant difference in vitamin D level has been observed between the groups who had no adverse pregnancy outcome and who presented with adverse maternal and neonatal outcome (23.16ng/ml ±8.3,20.8±7.06,pvalue=.0017).

Also mean vitamin D level differed significantly between antenatal women without any adverse pregnancy outcome and those presenting with pre-eclampsia(p value =.0239). 6 cases presented with IUD and among them 3 women had 25(OH)D below the

reportable range i.e<8 ng/ml. Women who gave birth to babies weighing less than 2.5 kg also had significantly low vitamin D level (20.32ng/ml±8.14)as compared to those who had no adverse outcome including low birth weight(23.16ng/ml ±8.3,p=.0059).

Fig 2 and fig 3 shows the percentage of adverse pregnancy observed according to the vitamin D status of the studied group. 44.81% of antenatal women with deficient vitamin D level presented with adverse outcome on follow-up in comparison to 32.93% of antenatal women with normal vitamin D level. Preeclampsia, one of the major adverse outcome which was noted down on follow up was found to be presented mostly by antenatal women who had deficient vitamin D level. 40.98% of antenatal women with deficient vitamin D level suffered from preeclampsia as compared to 20.73% of women with normal level. Preterm birth however showed no such variation with vitamin D status . It was found to be highest in the normal group with 31.71% of antenatal women with normal vitamin D level delivering before 37 completed weeks of gestation.

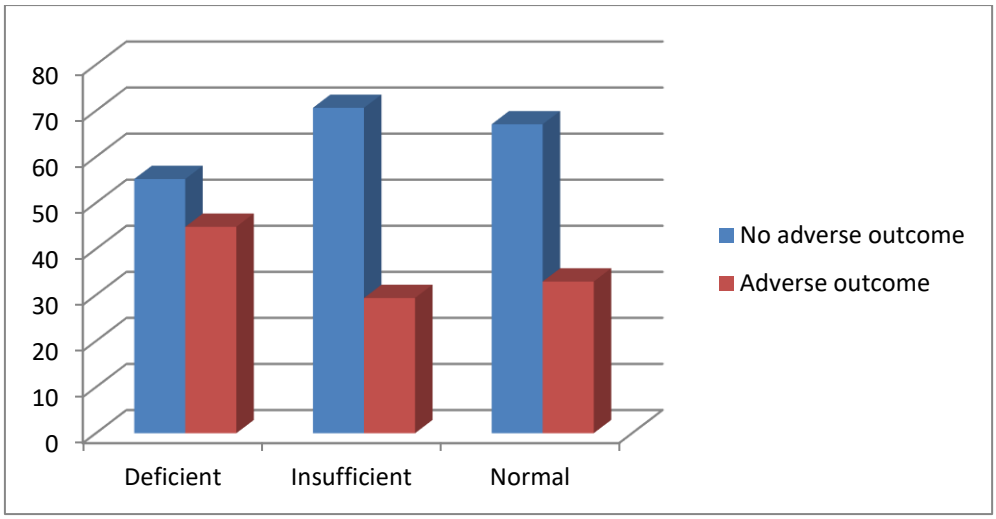
As shown in table 3 antenatal women with 25(OH)D <20ng/ml were associated with significant odds of 3 fold increase in delivering a low birth weight baby as compared to women with normal vitamin D level. Also antenatal women with deficient vitamin D level showed an odds ratio of 2.65 (95%CI 1.44-4.88)and those with insufficient vitamin D level an odds ratio of 1.48(95%CI 0.81-2.73), with respect to development of pre-eclampsia.

Table 1 : Showing the breakup of vitamin D status in the study population.

Vit D	N(%)
Deficient	183(37.89)
Insufficient	218(45.13)
Normal	82(16.98)
Total	483(100)

Table 2 : Mean Serum 25(OH)D in different groups of pregnant women with adverse outcome.

Outcome of Pregnancy	**Number(%)**	**Mean ± SD**	**P-value**
No adverse outcome	310(64.18)	23.16 ± 8.3	
Adverse Outcome	173(35.82)	20.8 ± 7.06	.0017
• Pre-eclampsia	153(31.68)	21.46 ± 7.2	.0239
• Low birth weight	82(16.98)	20.32 ± 8.14	.0059
• Preterm birth	116(24.02)	23.11 ± 5.31	0.94
• IUD	6(1.24)	13.33 ± 6.92	.0042
• Primary Caeserian Section	140(53.03)	22.64 ± 7.27	0.523



Fi g 1: Pregnancy outcome according to 25(OH)D Levels.

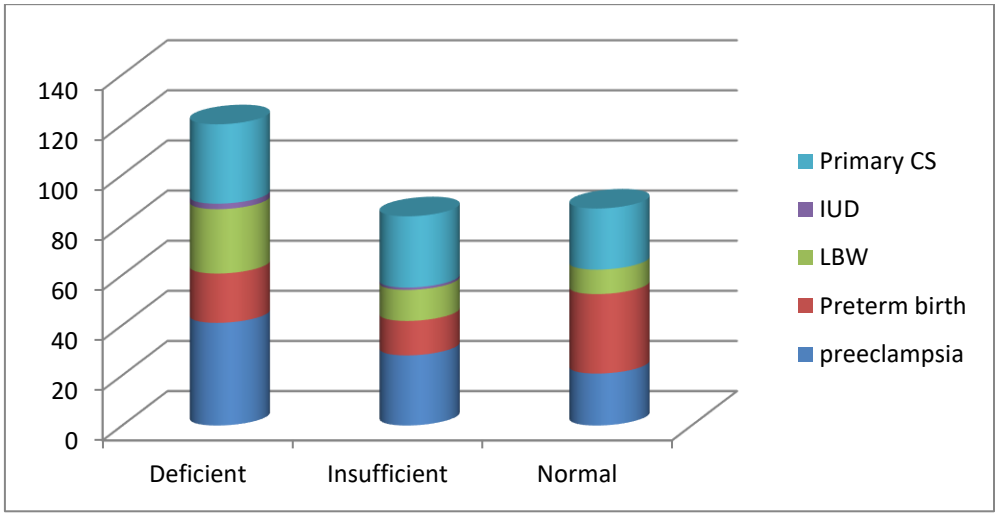


Fig 2: Adverse pregnancy outcome in pregnant women according to vitamin D status.

Table 3 : Association of Serum 25(OH)D with pregnancy outcome.

Outcome of pregnancy	SERUM 25(OH)D Conc.					
	Deficient		Insufficient		Normal	
	n (%)	Odds ratio (95%CI)	n(%)	Odds ratio (95%CI)	n(%)	Odds atio (95%CI)
No adverse pregnancy outcome	101(32.58)	ref	154(49.68)	ref	55(17.74)	ref
Adverse pregnancy outcome	82(47.4)	1.65(0.96-2.85)	64(37)	0.85(0.49-1.46)	27(15.6)	0.60(0.35-1.04)
Pre-eclampsia	75(49.02)	2.65(1.44-4.88)	61(39.87)	1.48(0.81-2.73)	17(11.11)	0.38(0.2-0.69)
Low birth weight	47(57.31)	3.2(1.43-7.12)	27(32.93)	1.30(0.57-3)	8(9.76)	0.31(0.14-0.70)
IUD	4(66.67)	4.14(0.22-77.73)	2(33.33)	1.90(0.09-40.11)	0(0)	NE
Preterm birth	36(39.13)	0.53(0.29-0.95)	30(32.61)	0.34(0.19-0.63)	26(28.26)	1.90(1.05-3.42)
Primary CS	58(31.69)	1.44(0.79-2.60)	62(28.44)	1.23(0.69-2.21)	20(24.39)	0.69(0.38-1.26)

DISCUSSION*:*

Several studies conducted in different parts of the world have reported low vitamin D levels in the study population [9-11]. An estimated 1 billion people worldwide have vitamin D deficiency or insufficiency [12].

Several studies have concentrated on the pregnant population and have found low vitamin D status in pregnant women [13-15]. In India vitamin D deficiency has been shown to be widely prevalent by many studies [16-18]. A study conducted among pregnant women of North India found 42.5% of women with vitamin D <10ng/ml and 66.7% with vitamin D<15ng/ml [19]. In another study 76% of South Indian women of reproductive age group were found to be vitamin D deficient [20]. The findings of this study where only 16.98% of studied antenatal women were found with normal vitamin D levels and 83.02% with deficient or insufficient levels goes on to confirm the findings of previous researchers.

The classical role of vitamin D is now well established. Studies recently have laid more emphasis on the non-classical roles of vitamin D . As for example the role of vitamin D in the outcome of pregnancy like pre-eclampsia, low birth weight, preterm birth and primary caeserian section in nulliparous women. An

increased risk of adverse pregnancy outcome was found in this study in women who were vitamin D deficient (44.81%)than in those with normal vitamin D levels(32.93%). Of the different aspects of pregnancy outcome, preeclampsia has been the most studied outcome.

The findings of these studies have however not been consistent. Several studies have found that women who go on to develop pre-eclampsia tend to have lower vitamin D levels as compared to healthy pregnant women [21-25].In the present study also it has been found that an increased percentage of women (33.91%)with below normal vitamin D levels suffered from preeclampsia as compared to pregnant women with normal levels(20.73%).

The findings of some other studies [26], are however contradictory like the prospective cohort study conducted in a group at high risk for pre-eclampsia, by A W Shand *et al* [9], which found no association between low serum vitamin D levels in 1st half of pregnancy and subsequent risk of preeclampsia. Again there are studies which have shown that the rates of PIH and preeclampsia in a study population undergo seasonal variation with increased rates in the winter months [27], suggesting a role of vitamin D in preeclampsia. Also many researchers have tried with supplementation of vitamin D , and have gone to show that vitamin D supplementation indeed reduces preeclampsia risk [28].

In the present circumstances it may be concluded that vitamin D deficiency or insufficiency may increase the risk of preeclampsia but there may be other confounding factors which may ultimately determine who develops preeclampsia. These potential confounders have to be adjusted before the findings attain significance.

Another outcome which has beenanalysed is the birth weight of the baby.Since vitamin D is central to calcium homeostasis , it is only logical to think that vitamin D level of the mother has a bearing on the birth weight of the baby. The present study and several other studies [29], have gone on to establish this positive correlation . But again there are studies which demonstate no such relationship but did demonstate that low vitamin D was associated with reduced Intra uterine long bone growth and lower gestational age at delivery [30-32].

The highest percentage of preterm delivery was found in the group of women with normal vitamin D level in comparison to women with below normal levels of vitamin D(31.71% VS 16.46%).This can be interpreted as vitamin D of the mother has no role in determining the time of delivery of the baby.Similar to the findings of this study, other studies which examined the relationship between blood levels of 25(OH)D during pregnancy and preterm birth and observational studies of intake of vitamin D and mean duration of gestation, have reported no significant association between levels of vitamin D and preterm delivery [33-35]. However there are studies which have shown that vitamin D supplementation was associated with reduced risk of caeserian section and preterm delivery [36-38].

Serum 25(OH)D levels have been found to be inversely related to primary C/S in nulliparous women [39]. Risk has been found to be four fold higher in women with vitamin D<15 ng/ml [40].This adverse effect may be because vitamin D normally increases skeletal muscle function. Thus low levels of the vitamin probably results in muscle weakness reducing the likelihood of normal delivery.The findings of different studies are however contradictory with studies reporting no significant difference in the mode of delivery based on vitamin D status of the mother [33,41,42]. In the present study no significant increase in primary caeserian section have been found in women with low vitamin D levels (OR in deficient group 1.44, 95%CI 0.79-2.60, OR in insufficient group1.23,95%CI 0.69-2.21).

Apart from all these adverse pregnancy outcomes of vitamin D deficiency in would be mothers and the new borns, neonatal hypocalcemia and rickets are the major consequences of neonates born with vitamin D deficiency. As breast milk is a relatively poor source of the vitamin, so maternal vitamin D status during pregnancy is important for vitamin D status of the child during early infancy.

CONCLUSION:

Just after hypothyroidism has taken over the world, vitamin D deficiency is now emerging in epidemic proportions. Changing lifestyle and work environments may be the major contributing factors. The adverse effects of this deficiency on Calcium metabolism is well established.

Non classical actions of vitamin D is now the topic of most research works. One important subject of research is the role of vitamin D in pregnancy and its outcome. The findings of many such research works undertaken to study the adverse effects of vitamin D deficiency on pregnancy outcome has not been consistent. Many

factors prevailing during pregnancy are responsible for the outcome of pregnancy.

These factors should be taken into account and adjusted for while planning research studies. However from the findings of the present study we can draw the conclusion that vitamin D deficiency definitely has an adverse effect on the outcome of pregnancy. It is also sensible action to maintain the different elements required for the body's normal function in the normal range. So creating awareness among the public on the beneficial effects of sun exposure should be implemented as a first step towards improving vitamin D status of the population.

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