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A study of maternal vitamin D3 levels in pregnancy with relation to obstetrics and medical complications

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Abstract
Aim of the study was to assess the Vitamin D levels in the antenatal women in pregnancy, to find out the prevalence of vitamin D deficiency and to correlate that with obstetrics complications like Pre-eclampsia, GDM, Anemia and IUGR. Vitamin D levels were done by measuring 25- hydroxy vitamin D in the serum by Chemiluminescent Immunoassay and accordingly patients were grouped as sufficient, insufficient and deficient.
Despite ample available sunshine throughout the year, Vitamin D hypovitaminosis is quite prevalent in our country. Majority of antenatal women have Vitamin D insufficiency or deficiency. There is an extreme lack of awareness regarding the importance of Vitamin D in pregnancy and its sources. Vitamin D hypovitaminosis increases the incidence of pregnancy related complications like Preeclampsia, GDM, anaemia, Preterm delivery and IUGR. This warrants the need to increase the awareness regarding sources, serum levels of vitamin D preconceptionally and revise guidelines for supplementation.

Keywords: 25-hydroxyvitamin D, PIH (Pregnancy induced hypertension), Pre-eclampsia, GDM (Gestational Diabetes mellitus), IUGR (Intrauterine growth restriction).

1. Introduction
Vitamin D, a "sunshine Vitamin E" [1, 2] refers to a group of fat-soluble secosteroids, important for bone mineralisation through intestinal absorption of *calcium*, *magnesium*, *phosphate* and *zinc* influencing the maternal and fetal wellbeing as well. In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol) and vitamin D_2 (ergocalciferol). Cholecalciferol and ergocalciferol can be ingested from the diet, mainly through fatty fish, eggs and from fortified foods [1, 2]. Dermal endogenous production, where transformation of 7-dehydrocholesterol into vitamin D in the skin occurs after exposure to ultraviolet B radiation from the sun. In the liver, vitamin D is hydroxylated to 25-hydroxyvitamin D. Subsequent hydroxylation in the kidney forms the active metabolite 1,25-OH vitamin D. This depends on the colour and amount of surface area of skin exposed to sun rays. In pregnancy, there is 2-fold higher concentration of 1,25-OH vitamin D in maternal serum due to activity of placental 1-α-hydroxylase.
Deficiency of Vitamin D is defined as a serum concentration of 25-hydroxyvitamin D ($25D_3$; the main circulating form of vitamin D) less than 50 nM. Insufficiency is 25-D_3 <75nM. Deficiencies and insufficiencies of vitamin D complicates nearly 67% of pregnanacies [3], a worldwide epidemic. Studies have reported a prevalence that ranges from 18-84%, depending on the country of residence and local clothing customs [4, 5]. In the United States, vitamin D deficiency is estimated to occur in 50-60% of pregnant women [6, 7].
Recent studies have shown a strong association between vitamin D deficiency and pre-eclampsia with an odds ratio of 2.09 (95% CI 1.50-2.90) [8]
Dr. Lisa Bodnar and her colleagues found women with 25(OH) D levels less than 15 ng/mL had a five-fold (5 fold) increase in the risk of preeclampsia [9].
Dr. Lisa Bodnar *et al.* further studied in 2009 and concluded that lowest 25(OH) D levels during pregnancy are associated with the 2 fold increase in chance of developing bacterial vaginal infections during pregnancy which is a major cause of Preterm Delivered [10].
A syndrome, pre-eclampsia, composing maternal hypertension, proteinuria and endothelial dysfunction affects 8% of pregnancies and is a leading cause of maternal and perinatal

morbidity and mortality [11]. During early pregnancy cytotrophoblast of chorionic villi differentiates into extravillous trophoblast (EVT) having an invasive property, invading decidua and maternal spiral arterioles from first trimester to 24 weeks of gestation, which is essential for spiral arteriolar remodelling for establishing maternal placental blood flow for effective maternal- fetal exchanges. Impairment of this process predisposes uteroplacental insufficiency and significantly increased risk of pre-eclampsia and fetal growth restriction (FGR).

Chan S *et al.* in their study have investigated the direct effect of 1,25-D_3 upon isolated human first trimester primary EVT *in vitro,* demonstrating a role of vitamin D in decasualization and utero-placental remodelling and a significant pro-invasive effect of 25-D_3 at its optimal circulatory concentration [3].

Gestational diabetes mellitus (GDM) and Diabetes during pregnancy affects about 5% of all pregnant women, is further increasing in incidence, and has deleterious effects on the fetus. Dr. Cuilin Zhang and colleagues at the NIH found women with low 25(OH) D levels were almost 3 times more likely to develop diabetes during pregnancy [12].

Yuan-Hua chen *et al.* in their studies in relation to vit D levels in the cohort of 3658 patients and birth weight of their newborns showing threshold of about 40 ng/ml for normal birth weight. With addition of 1 ng/ml of 25(OH) D in maternal serum will increase the birth weight by 23.66 gms, showing the close association between maternal serum vit. D and birth weight [13].

The vitamin D council, 1241, Johnson Ave, 134, San Luis, California, United States, 93401, recommend that your normal vitamin D levels should be 50-60 ng/ml. and if you are not light-skinned and not getting 20 min noontime sun (in bikini) every day and live below 38 degrees latitude, it is must to have the supplements with 4000 IU of an oil based D3 for adults. Healthy children need about 1,000 IU per 25 pounds of body weight and their 25(OH) D levels should be >50 ng/mL.

2. Method and Material

A cross sectional Study was performed in the Department of Obstetrics and Gynaecology, Dr. D.Y Patil Medical College & Hospital and Research Centre, Pimpri, Pune during July 2013 to September 2015. Total 150 antenatal patients with their written consent were enrolled in the study after the ethical committee's permission. All these patients in their third trimester, were subjected to an estimation of serum 25-hydroxy vitamin D levels and accordingly were classified as sufficient, insufficient and deficient. Vitamin D levels were done by measuring 25- hydroxy vitamin D in the serum by Chemiluminescent Immunoassay.

3. Results

Table 1: Vitamin D level wise distribution of cases in study group

Vitamin D Level (ng/ml)	No of cases	Percentage
<12 (Deficient)	14	9.33
12 – 30 (Insufficient)	122	81.33
>30 (Sufficient)	14	9.33
Total	150	100

136 out of 150 (90%) women were deficient / insufficient of vitamin D. This is the statistically significant number of patients to draw the attention to the seriousness of the problem. Out of these 14 patients having deficient vitamin D levels, 13 showed different grades of pre-eclampsia.

Table 2: Association between Obstetric complication and vitamin D level in study group.

Complication	Vit. D (ng/ml)		Z Value	P Value
	Deficient/ Insufficient (n=136)	Sufficient (n=14)		
Anaemia	17 (12.5)	0	4.41	<0.0001
Oligohydroamnios	3 (2.20)	0	1.75	>0.05
Teenage pregnancy	3 (2.20)	0	1.75	>0.05
Threatened preterm	3 (2.20)	0	1.75	>0.05
PIH	13 (1.47)	1 (7.14)	0.81	>0.05
GDM	4 (1.47)	0	1.75	>0.05
Multiple gestation	2 (1.47)	0	1.42	>0.05
PROM	1 (0.75)	0	1.003	>0.05
Bacterial Vaginosis	1 (0.75)	0	1.003	>0.05
Bad obstetrics His	1 (0.75)	0	1.003	>0.05
Bicornuate uterus	1 (0.75)	0	1.003	>0.05
IUD	1 (0.75)	0	1.003	>0.05
IUGR	1 (0.75)	0	1.003	>0.05

In our study group, high risk patients included were pre-eclampsia, gestational diabetes, intrauterine growth restriction, threatened preterm, preterm labour and anemia. Clearly the table 2 shows that vitamin D deficiency is directly associated with these obstetrics complications.

Out of 14 patients having pre-eclampsia, 13 were vitamin D deficient.

All 4 cases of GDM were showing insufficient vitamin D levels. In the group 17 patients who had severe to moderate degree of anemia, all were showing insufficient vitamin D. All the patients with Oligohydramnios, IUGR, IUD, Threatened preterm, PROM, Pregnancy with BV had insufficient vitamin D. P values of the clinical disorders were found to be statistically significant. This is really a serious problem as vitamin D is directly related to bone mineralisation of mother and fetus, resulting in early age rickets in children and osteoporosis in women as a long term effect as well.

4. Discussion

High prevalence of vitamin D deficiency in the general population and in women of child-bearing age, worldwide, is known to be associated with an increased prevalence of preeclampsia. SGA and LBW babies are the associations with low maternal vitamin D levels [13]. These infants also have to suffer from common childhood diseases like ashma [14], type I Diabetes Mellitus [15], schizophrenia [16] and autism [17].

Sachan A *et al.*, India, in their study found high prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. Maternal serum 25(OH) D <10 ng/mL was found in 88 women (42.5%), whereas 138 women (66.7%) had values <15 ng/mL. Whereas in our study 12 women (9.33%) had levels below 12ng/ml and 122 women 81.33% ranged between 12-30 ng/ml. In the same study conducted by Sachan *et al.*, it was found that urban and rural women had equally low mean serum concentrations and equally high prevalence of the deficiency [18] which is correlates with our study.

The explanation could lie in the prolonged deficiency of natural dietary calcium intake among poorer parts of India, because the milk and milk products are expensive and they were might not affordable to purchase the supplements.

Awareness among the women regarding the importance and natural sources of vitamin D during pregnancy in our study was found to be only 2%. Which is statistically significant figure warrants the need to arrange vitamin D awareness campaigns, especially for reproductive age group women regarding dietary sources of vitamin D and sun-rays.

Not much data is available for the prevalence of awareness. There is only one study donre in Bangladesh in undergraduate students of pharmacy where the results were disappointing [19].

The data in the study done by Abdulbari Bener *et al.* showing the mean serum levels of vitamin D in pregnant women with GDM (17.78±7.7), anemia (17.65±7.8), iron deficiency (16.01±7.4), and preeclampsia (18.01±8.6) which revealed vitamin D insufficiency in pregnant women. It was reported that vitamin D status in women with risk factors of maternal complications like GDM, anemia, and preeclampsia was significantly lower as compared to women without risk factors. Even multivariate logistic regression analysis supported this finding that vitamin D deficiency was a significant contributor for GDM (OR 1.387, P=0.019) and anemia (OR 1.87, P<0.001) [20]. Similar results were observed in our study where linear correlation was seen in low levels of Vitamins D and Obstetrics complications.

In a case control study carried out by Taru Gupta ESIC-PGIMSR, New Delhi, India from August 2012–April 2014. A total of 100 patients were divided into two equal groups (control and study groups of 50 each). They found more incidence of severe vitamin D deficiency (90%) in preeclamptic patients as compared to normotensive patients (62%).

Also preeclamptic group had lower median vitamin D levels (3.9 ng/ml) when compared to normotensive group (9 ng/ml). Concluding preeclampsia is indeed associated with lower vitamin D levels, and its pathophysiology involves vitamin D and calcium metabolism [21].

Similarly, in our study, 14 out of 150 patients were preeclamptic and 13 out of those, were vitamin d deficient (92%). Preeclampctic patients had low mean vitamin D levels mean (8.2ng/ml) clearly suggesting a strong association between the PIH and hypovitaminosis.

Madhu Jain *et al.* in 2015 in Banaras, India did a study and found a high incidence of vitamin D deficiency (72.8%) in pregnancy in a tropical country like India in spite of abundant sunlight for most of the year. They studied a total of 550 antenatal cases and to find Serum 25(OH) D concentrations significantly lower (46% less) in women who subsequently developed GDM compared with controls [mean: 11.93±3.42 ng/ml, 95% CI: 10.7-13.17 ng /ml]. Concluding maternal vitamin D deficiency is highly prevalent in early pregnancy and is an independent risk factor for GDM in North India [22].

Similar results were obtained in our study where 4 out of 150 patients were diagnosed as GDM out of which all 4 (mean 12.43±3.37 ng/ml) showed significantly lower levels of serum Vitamin D.

In our study group total 14 patients were suffering from Pre-eclampsia and 13 had deficient Vitamin D levels, Odds being 13, which is a significant and serious problem. Which suggests that these women must have been deficient of vitamin D in their pre-pregnant state as well causing mal-placentation resulting into the syndrome of pre-eclampsia leading to serious maternal and fetal consequences.

5. Conclusion

Despite ample available sunshine throughout the year, Vitamin D hypovitaminosis is quite prevalent in our country. Majority of antenatal women have Vitamin D insufficiency or deficiency. There is an extreme lack of awareness regarding the importance of Vitamin D and its sources. Vitamin D hypovitaminosis increases the incidence of pregnancy related complications like GDM, PIH, anaemia, Preterm delivery and IUGR. Patients who were deficient were advised 60,000 IU of Vitamin D supplements to be consumed orally, once a week for eight weeks. Our study shows an alarmingly high prevalence of insufficiency and deficiency of Vitamin D compelling a need to study the causal relation between low 25-OHD levels and adverse maternal obstetrics outcomes.

Bruce W Hollis concluded that Vitamin D supplementation of 4,000 IU/day for pregnant women was safe and most effective in achieving sufficiency. The current available amount of Vitamin D in supplements is comparatively ineffective to achieve adequate circulating 25(OH) D levels [23].

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