Annals of Nutritional Disorders & Therapy

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Special Article - Vitamin D Deficiency

Vitamin D Supplementation in Pregnancy and Its Correlation with Fetomaternal Outcome

Vasundhara K, Swapna R*, Prasannalatha A and Shruti K

Department of Obstetrics and Gynaecology, Kamineni Academy of Medical Sciences and Research Centre, India

***Corresponding author:** Rathlawath Swapna, Department of Obstetrics and Gynaecology, Kamineni Academy of Medical Sciences and Research Centre, Assistant professor, India

Received: October 26, 2016; **Accepted:** January 05, 2017; **Published:** January 06, 2017

Abstract

Vitamin D is known as Sunshine vitamin which mainly helps in bone metabolism. It is estimated that one billion people have vitamin D deficiency and it is considered as a public health problem.

Aim: To measure vitamin D levels in 1st trimester and reassess level of vitamin D in 3rd trimester after treatment. To evaluate its correlation with fetomaternal outcome.

Study Design: It is a prospective observational study of 100 pregnant women booked in the 1st trimester and serum vitamin D level tested. Women who were found insufficient (vitamin D level<30ng/ml) were counseled and supplemented in second trimester. Serum vitamin D is tested again in 3rd trimester. Maternal complications and fetal outcome measured complications like preeclampsia and preterm birth recorded.

Observation and Results: In our study the mean vitamin D level was 17.8±7.05 ng/ml, vitamin D deficiency (<20ng/ml) was seen in 69% females, insufficiency (20-30 ng/ml) in 24%. Supplementation was done in 40 vitamin D deficient women. The mean vitamin D level in the 1st trimester increased from 16.88±4.490 to 30.02±5.767 in third trimester (p value = 0.0001). Among the females who were supplemented with vitamin D, only 1 (2.5%) developed preeclampsia and 2 (5%) females developed preterm birth.

Conclusion: The present study concludes that there is high prevalence of vitamin D deficiency in pregnancy. Vitamin D deficiency correlates with preeclampsia and preterm birth. Supplementation of vitamin D is safe and it increases vitamin D levels significantly in 3rd trimester as well as the birth weight of the fetus.

Keywords: Vitamin D supplementation; Preeclampsia; Preterm birth

Introduction

Vitamin D deficiency or insufficiency is currently a global pandemic affecting some one billion of all ages and ethnic groups [1]. Reports from developing and developed countries show high prevalence of vitamin D deficiency. Vitamin D is a fat soluble vitamin produced endogenously in the skin with exposure to sunlight. It is also obtained from consuming fortified milk or juice, fish oils, and dietary supplements of vitamin D that is ingested or produced in the skin must undergo hydroxylation in the liver to 25 hydroxyvitamin D (25(OH)D), then further hydroxylation primarily in the kidney to the physiologically active 1,25 dihydroxyvitamin D. This active form is essential to promote absorption of calcium from the gut and enables normal bone mineralization and growth. The proportion of vitamin D obtained from diet is small as compared to that synthesized from skin in response to sunlight.

Recent evidence suggests that vitamin D deficiency is common during pregnancy especially among high risk groups, including vegetarians and women with limited sun exposure (eg. those who live in cold climate, resides in northern latitudes and wear sun and winter protective clothing) [2-4]. New born vitamin D levels are largely dependent on maternal vitamin D status. Consequently, infants of mothers with vitamin D deficiency are also at risk of vitamin D deficiency [4,5].

Vitamin D intake is essential for maternal health and prevention of adverse outcomes [6]. Vitamin D deficiency is defined as a 25(OH) D below 20ng/ml and vitamin D insufficiency as a 25(OH)D of 21-29 ng/ml [7].

Preeclampsia and hypertensive disorders complicate 3-10% of pregnancies and contribute to maternal and neonatal morbidity and mortality [8]. Several studies have shown that women with preeclampsia have lower urinary calcium excretion, lower ionized calcium levels, higher Parathormone (PTH) levels and lower 1,25 dihydroxyvitamin levels compared with normotensive pregnant control subjects [9]. Patients with 25(OH)D levels <15ng/ml have a 5fold increase in the risk of preeclampsia, despite receiving prenatal vitamins [10]. Maternal vitamin D levels have been shown to positively correlate with birth weight centile [11]. Women with vitamin D deficiency have a 2.4 fold increased risk of having a small for gestational age baby [12]. Low vitamin D levels in late pregnancies were associated with reduced intrauterine long bone growth and lower gestational age at delivery [13].

Vitamin D is important to maternal health, fetal development

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Citation: Vasundhara K, Swapna R, Prasannalatha A and Shruti K. Vitamin D Supplementation in Pregnancy and Its Correlation with Fetomaternal Outcome. Ann Nutr Disord & Ther. 2017; 4(1): 1037.

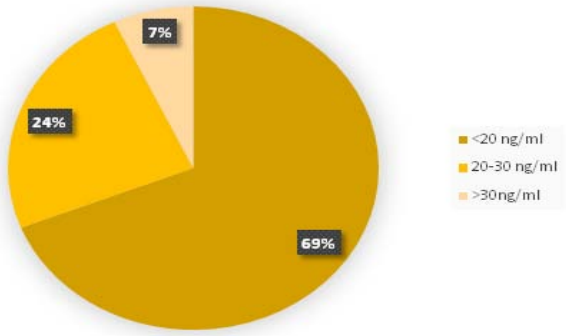

Figure 1: 1st trimester Vitamin D levels.

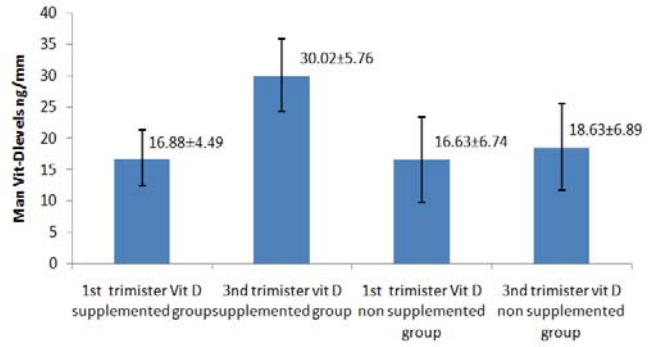

Figure 2: Mean vit-D levels in 1st and 3rd trimester.

and postnatal life. Current prenatal care does not include the monitoring of vitamin D levels. Though the current recommendation for vitamin D intake during pregnancy is 200-400 IU/d, prenatal supplements that contain 400 IU of vitamin D are not adequate to achieve normal vitamin D levels in pregnant women or their infants [14]. Supplementation of 800-1600 IU per day during last trimester in women with 25(OH)D <15ng/ml showed increase in vitamin D levels [15,16]. Therefore, supplementation of vitamin D in doses that exceed 1000 IU per day (2000-10000 IU/d) may be required to achieve a normal concentration of circulating vitamin D in severely deficient patients [17].

According to recent committee opinion of American College of Obstetrics and Gynaecology (ACOG), till now there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency. Also there is insufficient evidence to recommend vitamin D supplementation for the prevention of preterm birth and preeclampsia [18]. Thus in view of above cited evidences and persisting lacunae the current study was planned. In this study we assessed the vitamin D status of 100 consecutive females in 1st and 3rdtrimester and observed for complications like preeclampsia and preterm birth.

The present study aims to measure vitamin D levels in 1st trimester and reassess vitamin D levels in 3rd trimester after treatment with 60000IU Cholecalciferol per week for 6 weeks was done in second trimester and to evaluate its correlation with fetomaternal outcome.

Materials and Methods

100 pregnant women attending antenatal clinic at Kamineni hospital L.B nagar, Hyderabad, India in the first trimester of pregnancy. Ethical committee approval taken from KAMS&RC institution ethics committee.

Inclusion criteria

Pregnant women booked in first trimester of pregnancy.

Exclusion criteria

Pregnant women diagnosed with chronic kidney disease, chronic liver disease, known hyper parathyroid, malabsorption syndrome, women on antitubercular drugs, anti epileptics, steroids, known cases of diabetes mellitus.

Study design

It is a prospective observational study of 100 pregnant women, booked at antenatal clinic of Kamineni Hospital, in the first trimester. Detailed history, physical and obstetric examination was done in all subjects. Serum vitamin D levels were tested in first trimester of pregnancy. Women who were found deficient (vit D <20ng/ml) or insufficient (vit D 20-30 ng/ml) were counseled about the potential harms of vitamin D deficiency and supplementation, its benefits. Final choice for supplementation was left on the patient. Supplementation with 60000IU Cholecalciferol per week for 6 weeks was done in second trimester for vitamin D deficient women. Serum vitamin D was tested again in all subjects during third trimester. Observation for antenatal complications like preeclampsia and preterm birth was done and correlated to serum vitamin D levels. Serum vitamin D was assessed by using ELISA kit (IDS 250 vitamin D EIAKIT). Statistical analysis of data was conducted by using SPSS software (version 15.0; SPSS). Data presented as mean ± SD. For categorical variables t test was used and for comparison of percentages and proportions chi-square test was used, p-value of <0.05 was considered significant.

Results

Mean age in the study was 25.62±4.04 years. Mean vitamin D level was 17.8±7.05 ng/ml. vitamin D deficiency (<20 ng/ml) was seen in 69% females, insufficiency (20-30 ng/ml) in 24% and sufficiency (>30 ng/ml) in 7% of pregnant women (Figure 1). Supplementation was done in 40 vitamin D deficient women. It increased mean vitamin D levels from 16.88±4.490 to 30.02±5.767 from first to third trimester (p value = 0.0001). Vitamin D levels in third trimester were significantly higher than first trimester even in 53 women who were deficient in vitamin D, but not supplemented (p = 0.0001) (Figure 2, Table1,2). Preeclampsia developed in 14% women with mean first trimester vitamin D level of 12.43±3.435 ng/ml and third trimester vitamin D level of 14.00±5.009 ng/ml which were significantly lower than women not developing preeclampsia (mean vitamin D 18.68±7.107 ng/ml in first trimester and 26.11±8.048 ng/ml in third

Table 1: Distribution of cases according to supplementation status.

		1stTrimesterVitD level			
		<20ng/ml	20-30 ng/ml	>30ng/ml	Total
Supplementation	YES	31	9	0	40
		77.50%	22.50%	0%	100.00%
	NO	38	15	7	60
		63.33%	25.00%	11.66%	100.00%
Total		69	24	7	100

Table 2: 1st and 3rd trimester vitamin D levels in 40 females having vitamin D <30ng/ml who were supplemented and not supplemented.

		Mean Vit D level (ng/ml)	N	Std. Deviation	P Value
Vit D supplemented group	1stTrimester Vit D level	16.88	40	4.49	0.0001
	3rdTrimester Vit D level	30.02	40	5.767	
Vit D **not** supplemented group	1stTrimester Vit D level	16.63	60	6.74	0.0001
	3rdTrimester Vit D level	18.63	60	6.69	

Table 3: Correlation of 1st & 3rd trimester Vitamin D levels with Preeclampsia & Preterm birth.

Vitamin D Levels		<20ng/ml	20-30 ng/ml	>30ng/ml	Total	P Value
1stTrimesterVitD level						
Preeclampsia	YES	13	1	0	14	0.002
	NO	56	23	7	86	
Preterm Birth	YES	22	1	0	23	0.0001
	NO	47	23	7	77	
3rd Trimester Vit D level						
Preeclampsia	YES	13	1	0	14	0.0001
	NO	22	32	31	85	
Preterm Birth	YES	22	1	0	23	0.0001
	NO	13	32	31	76	

trimester) (p value = 0.0001). Preterm birth developed in 23% of women with mean first trimester vitamin D levels of 12.43±3.31 ng/ml and third trimester vitamin D of 14.43±3.740 ng/ml compared to first trimester mean vitamin D of 19.40±7.109 ng/ml and third trimester level of 27.41±7.537 ng/ml in those who did not develop preterm birth (p value = 0.0001) (Table 3). Among the females who were supplemented with vitamin D, only 1 (2.5%) developed preeclampsia compared to 13 (21.6%) among the non-supplemented group. Similarly, in the vitamin D supplemented group only 2 (5%) female's developed preterm birth compared to 21 (35%) females in the non-supplemented group. The mean birth weight of women who were supplemented with vitamin D is 2.82kg when compared to non supplemented group which is 2.52kg, and it is statistically significant (p value=0.006) (Table 4).

Discussion

Despite the fact that daily prenatal vitamin D supplementation is advised and observed in most countries, an alarmingly high prevalence of vitamin D insufficiency has been demonstrated in nearly all populations studied [19-21]. There is a growing concern about the various adverse health impacts of vitamin D deficiency during pregnancy may have on mother as well as on fetus and later in life [6].

Prevalence of vitamin D deficiency depends on the definition of deficiency. Optimal serum levels during pregnancy are still undetermined and remain an area of active research. The discrepancy of different cut-offs in different studies leads to varied worldwide prevalence of vitamin D deficiency in pregnancy. However, results of current study are consistent with various other studies. Sachan et a1. [19], in their study reported 66.7% females had vitamin D level<15 ng/ml and 84% females had vitamin D level below cut-off of 22.5ng/ml. In another study done by Jain et al. [5], vitamin D deficiency <15ng/ml) was found in 81.1 % mothers; and insufficiency (15-20 ng/ml) in an additional 11.6% mothers. Sahu et al. [23] measured 25(OH) D in 121 adolescent girls in a rural low socioeconomic community and 139 pregnant women in the second trimester. The age-adjusted community prevalence of vitamin D deficiency (250HD <50nmol/l) in adolescent girls was 88.6%. Seventy-four percent of pregnant women had vitamin D deficiency. Marwaha et al. [24] studied 541 apparently healthy women with uncomplicated, single, intra-uterine gestation reporting in any trimester. Mean serum 25(OH)D of pregnant women was 23.2 (SD 12.2) nmol/l, hypovitaminosis D (25(OH)D < 50nmol/l) was observed in 96.3% of the subjects.

In current study, mean 1st trimester vitamin D levels in 53 pregnant women who had vitamin D levels <30ng/ml and who refused for supplementation even after counseling were 16.636±6.745 ng/ml. When reassessed in 3rd trimester the mean vitamin D levels in this subset were 18.6346±6.891 ng/ml. Thus, even in females who were not supplemented, vitamin D levels in 3rd trimester were significantly higher than the 1st trimester vitamin D levels, with a P value = 0.0001. However, the vitamin D level remained below the deficiency cut off level (<20ng/ml).

The mean 1st trimester vitamin D levels in 40 pregnant women who had vitamin D levels <30 ng/ml and who accepted supplementation is 16.88±4.49 ng/ml; they were supplemented with 60000 IU cholecalciferol per week for 6 weeks. On reassessment in 3rd trimester, mean vitamin D levels were 30.02±5.76 ng/ml. Thus, post supplementation vitamin D levels significantly increased (p = 0.0001). Out of these 40 females, 20 had 3rd trimester vitamin D levels higher than 30 ng/ml. Hollis BW et al. did a randomized, controlled trial in which women with a singleton pregnancy at 12 to 16 weeks gestation received 400, 2000, or 4000 IU of vitamin D per day until delivery. The mean 25(OH)D concentrations by group at delivery and 1 month before delivery were significantly different (p<0.0001), and the percent who achieved sufficiency was significantly different by group, greatest in 4000-IU group (p<0.0001) [2]. According to Cochrane database systematic review [25], four trials with a total of 414 women reported the maternal vitamin D status at term. The results consistently showed that women who received vitamin D supplements had higher 25(OH)D concentrations than those women who received no intervention or a placebo. The response to supplementation was highly heterogeneous and ranged from 11.00 to 151.80 nmol 25(OH)D.

In current study, 14 women had preeclampsia during pregnancy, out of these 13 had 1st trimester vitamin D levels <20ng/ml and 1 had levels between 20-30 ng/ml. The mean 1st trimester vitamin D level in these 14 females was 12.43±3.435 ng/ml compared to 18.68±7.01 ng/ml in females who had no preeclampsia. Mean 3rd trimester vitamin D levels in 14 females developing preeclampsia was 14.0±5.09 ng/ml compared to 26.11±8.04 ng/ml in rest of the females. Thus, females who had preeclampsia had much lower 1st and 3rd trimester vitamin D levels as compared to rest of the females.

Bodnar LM et al. [10], conducted a nested case-control study and found that adjusted serum 25(OH)D concentrations in early

Table 4: Comparison of Birth weight among the supplemented and not supplemented group.

	Vit D supplementation	Number	Mean	Std. Deviation	P value
Birth weight	YES	40	2.82	0.395	0.006
	NO	60	2.5	0.73	

pregnancy were lower in women who subsequently developed pre-eclampsia compared with controls [p<0.01]. There was a monotonic dose-response relation between serum 25(OH)D concentrations at less than 22wk and risk of preeclampsia. Baker AM et al. [26] and Robinson CJ et al. [11], also found that decreased maternal 25-hydroxyvitamin D was significantly associated with diagnosis of early onset severe preeclampsia.

In present study, preterm birth was seen in 23 pregnancies, out of these 22 had 1st trimester vitamin D levels <20ng/ml and 1 female had levels between 20-30 ng/ml. The mean 1st trimester vitamin D level in these 23 females was significantly lower compared to females who had term babies (12.43±3.13 ng/ml vs. 19.40±7.10 ng/ml, P=0.0001). Similarly, mean 3rd trimester vitamin D level was also significantly lower (14.43±3.74 ng/ml vs. 27.41±7.53 ng/ml). Thus, females who had preterm birth had much lower 1st and 3rd trimester vitamin D levels as compared to rest of the females.

A Japanese retrospective study found mothers with threatened premature delivery had significantly lower 25-0HD levels (11.2±3.2 ng/ml) than those in mothers with normal delivery (15.6±5.1 ng/ml) [27]. Recently a multi centre study involving US cohort of twin pregnancies showed an independent association between maternal 25-hydroxyvitamin D concentrations at 24-28 weeks of gestation and preterm birth [28].

In our study, the mean birth weight in women who are supplemented with vitamin D is 2.82kg, which is statistically significant than women who were not supplemented. A systematic review and meta-analysis by Pérez-López et al. found that gestational vitamin D supplementation was associated with increased birth weight and birth length (Table 4) [29]. In a recently published study Gernand AD et al. also showed that mothers with 25(OH)D of 37.5nmol/liter or greater gave birth to newborns with 46 g higher compared with mothers with less than 37.5nmol/liter [30].

Conclusion

The present study concludes that there is high prevalence of vitamin D deficiency in pregnancy. Though India is a tropical country more than 90% of pregnant women are either deficient or insufficient. Vitamin D deficiency correlates with preeclampsia and preterm birth. There is significant increase in birth weight in women who were supplemented with vitamin D. Supplementation of vitamin D is safe and it increases vitamin D levels significantly in 3rd trimester. Thus, this study emphasizes the need of screening of pregnant females for vitamin D deficiency and supplementation if required for better feto-maternal outcomes.

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Ann Nutr Disord & Ther - Volume 4 Issue 1 - 2017
ISSN : 2381-8891 | www.austinpublishinggroup.com
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Citation: Vasundhara K, Swapna R, Prasannalatha A and Shruti K. Vitamin D Supplementation in Pregnancy and Its Correlation with Fetomaternal Outcome. Ann Nutr Disord & Ther. 2017; 4(1): 1037.