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Original Research Article

A study of safety and efficacy of vitamin D3 supplementation in pregnancy

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ABSTRACT

Background: Vitamin D is a lipid-soluble prohormone that is vital for the maintenance of bone and muscle health. Vitamin D deficiency is an unrecognized epidemic, common in all age groups and is associated with preeclampsia, gestational diabetes, preterm birth, early labour and pregnancy loss.
Methods: Our study was conducted in Batra hospital and medical research centre, New Delhi from October 2018 to May2019. 126 women were taken, of those seen before 20 weeks of pregnancy who received vitamin D3 supplementation comprised of study group and control group were those who came directly for delivery and without vitamin D3 level done. The outcomes measured were vitamin D3 level at 20 weeks, at delivery, in cord blood and clinical outcomes like pre-eclampsia, gestational diabetes, preterm delivery.
Results: Gestational hypertension was seen in 4 (6.3%) of subjects while in control group it was seen in 11 (17.5%), Gestational diabetes was seen in 3 (4.8%) women while it was observed in 10 (15.9%) women of control group. Premature rupture of membranes was seen in 2 (3.2%) women in study group and 8 (12.7%) women of control group. Vitamin D level at the time of delivery in study group was significantly higher than control group (56.84±15.78 versus 18.12±8.97ng/ml).
Conclusions: Preterm labor, low birth weight and preeclampsia were uncommon in the subjects and the administered vitamin D3 dose had no adverse effects but more research with larger sample size is strongly urged to assess the safety and effect of vitamin D3 supplementation.

Keywords: Vitamin D3, Singleton pregnancy, PROM

INTRODUCTION

Vitamin D deficiency is prevalent worldwide, and its unrecognized epidemic is common in all age groups ranging from 46-90%.[1-5] Its prevalence ranging between 40-93% and is even higher during pregnancy ranging from 45-100% worldwide.[6] Poor vitamin D status during pregnancy has been associated with preeclampsia, gestational diabetes, preterm birth, early labour and preclinical pregnancy loss. It is associated with endometritis, PID, cervical intraepithelial lesion and tubal infertility.[7-8] The need, safety and effectiveness of vitamin D3 supplementation during pregnancy is contentious as there is limited data available on the subject. Therefore, the present study was undertaken.

Aim and objectives

Aim was to study the safety and effectiveness of a higher dosage of vitamin D3 supplements in vitamin D deficient

pregnant patients. Objectives were; to check vitamin D3 level after supplementation among pregnant women attending antenatal clinic and to study the impact of vitamin D3 supplementation during antenatal period on maternal and neonatal vitamin D3 status.

METHODS

The study was an observational prospective study conducted in department of obstetrics & gynaecology, Batra Hospital & Medical Research Centre, New Delhi on total 126 pregnant women divided in two groups of 63 each with singleton pregnancies over a period of 8 months from October 2018 to May 2019.

Group 1/study group: Pregnant women who were seen before 20 weeks of pregnancy had their Vitamin D3 level done and if deficient started on Vitamin D3. Group 2/control group: This group was consisted of patients who came directly for delivery and without having their vitamin D3 level done in antenatal period.

Inclusion criteria

Inclusion criteria were; All booked pregnant women attending antenatal clinic and delivering at hospital during the study period and all unbooked pregnant women delivering in Batra hospital and medical research centre, New Delhi during the study period.

Exclusion criteria

Exclusion criteria were; Multi fetal gestation, known diabetes, hypertension, thyroid dysfunction or other comorbid conditions e.g. heart disease, renal disease etc, not willing to participate in study and pregnant women who planned to delivered at another hospital.

Sample size

Sample size was calculated using the formula mentioned below;

$$n = Z\alpha 2\, p\, q \,/\, L2,$$

Where n=sample size, Zα=1.96 value of the standard normal variate corresponding to level of significance alpha 5%, p=prevalence of the cause, q=1–p and L=Allowable error. At 95% confidence level and 80% power and with a relative error of 20%.

After obtaining informed consent, a detailed proforma was recorded which included subjects sociodemographic data, medical history, detailed obstetric history, exposure to sunlight, and dietary intake. This was followed by a routine antenatal investigation like blood glucose levels, viral markers, routine urine examination, blood pressure etc. Pre pregnancy height and weight were recorded at first OPD visit. During subsequent visits, only the subject's weight was recorded. Birth weight was recorded for each infant. Serum Vitamin D level of the subject was estimated at first visit and after giving supplementation Vitamin D level was checked at time of delivery. Data was captured for all routine investigation done for all booked and un-booked cases. The following outcomes were measured from pregnant mother and captured by routine investigation: vitamin D3 level at 20 weeks of pregnancy (Group 1), vitamin D3 level at the time of delivery (Group 2) and Clinical outcomes Pre-eclampsia, Gestational diabetes, Preterm delivery. The outcomes measured in Baby and captured from routine investigation were vitamin D3 level in cord blood and Clinical outcome-length. Booked Pregnant women with vitamin D deficiency were started vitamin D supplements at 20 weeks in doses of 60,000 IU weekly for three weeks and 1,000 IU daily till term and un-booked pregnant women coming for delivery with vitamin D deficiency may or may not have received supplements. All vitamin D supplementation were given in the form of tablets. Subjects were followed monthly either personally or through telephonic calls till delivery, coinciding with their routine obstetrical visits with an obstetrician. Subsequent blood samples of the study subjects were collected at term for assessing vitamin D levels. A sample of fetal cord blood was also be collected at the time of delivery for assessing fetal 25(OH)D levels. Adherence to the prescribed vitamin D supplementation regimen was assessed by maternal self-report and pill count that was provided on each visit.

Statistical analysis

The collected data was entered in Microsoft Excel and then analysed and statistically evaluated using SPSS-PC-17 version. Quantitative data was expressed by mean, standard deviation and difference between comparable groups were tested by student's t test (unpaired) or Mann Whitney 'U' test, while qualitative data was expressed in percentage. Difference between the proportions was tested by chi square test or Fisher's exact test, p value less than 0.05 was considered statistically significant.

RESULTS

The observations and results of the study are presented as below. Age distribution was almost similar in both the groups. 22 (34.9%) and 23 (36.5%) patients were between the age group of 26-30 years in Vitamin D supplementation and control group respectively while 23 (36.5%) and 22 (34.9%) subjects were between the age group of 21-25 years in both groups respectively. 8 and 9 subjects in both the groups were >35 years of age (Figure 1). The mean maternal ages for the Vitamin D supplementation and the control groups were 24.70±3.98 and 25.68±4.54 years respectively. There was no significant difference within age distribution of the groups (p=0.19) (Figure 2). Total 25 (39.7%) and 23 (36.5%) subjects in both groups were primi-gravida while rest were multigravida (Figure 3). Total 39 (61.9%) subjects of vitamin D supplementation group and 33 (52.4%) subjects of study group were vegetarians whereas 24 (38.1%)

subjects of vitamin D supplementation group and 30 (47.6%) subjects of control group were non vegetarians (Figure 4).

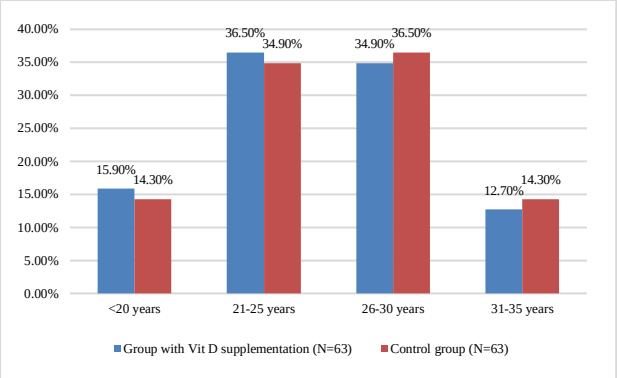

Figure 1: Age distribution of study subjects.

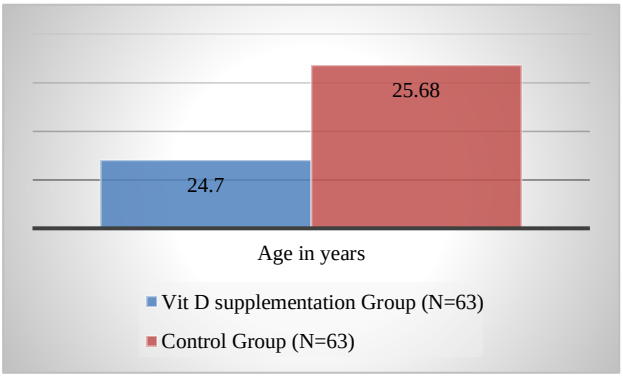

Figure 2: Comparison of age between vitamin D supplementation and control group.

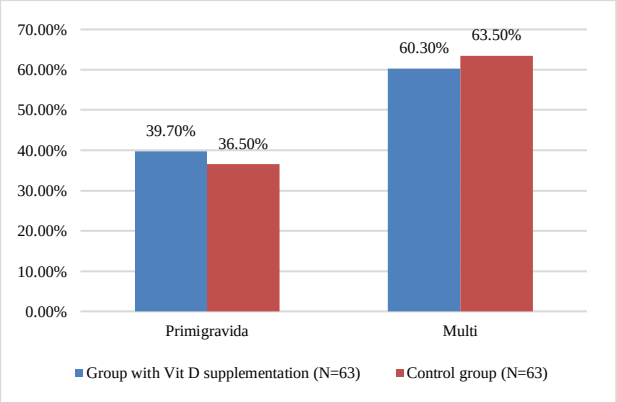

Figure 3: Gravida distribution of study subjects.

In 63 pregnant women where vitamin D supplementation was given, Gestational hypertension was seen in 4 (6.3%) of subjects while in control group it was seen in 11 (17.5%) of pregnant women. Gestational DM was seen in 3 (4.8%) pregnant women in vitamin D supplementation group while it was observed in 10 (15.9%) women of control group. Another complication PROM was seen in 2 (3.2%) pregnant women in vitamin D supplementation group while it was seen in 8 (12.7%) control group pregnant women as shown in (Figure 5). Women with vitamin D supplementation had a lesser chance of preterm labor (less 37 weeks of gestation) compared with the control group (9.5% vs. 15.9%) but the difference was not found to be statistically significant (p=0.28) (Figure 6).

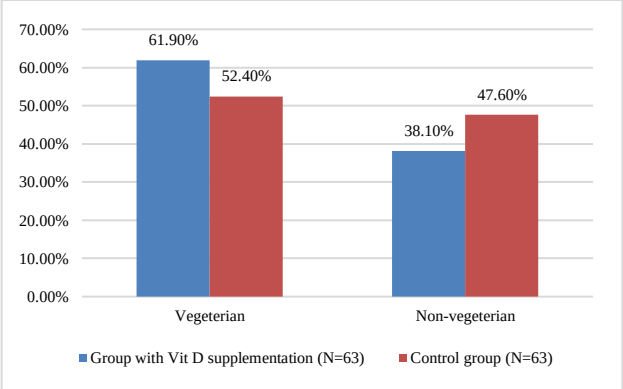

Figure 4: Dietary pattern of study subjects.

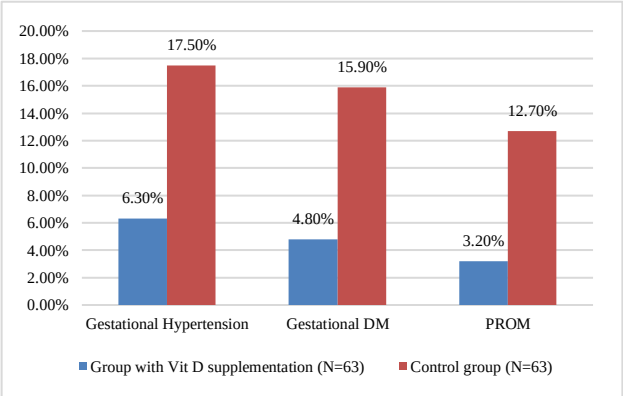

Figure 5: Maternal complications in study subjects.

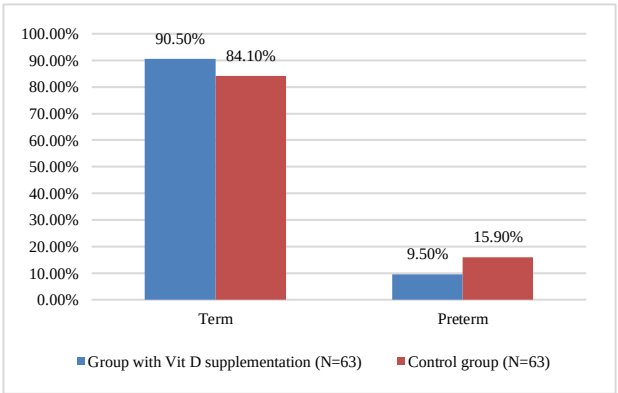

Figure 6: Type of delivery in study subjects.

There were 4 (6.3%) cases of small-for-gestational age infants in the vitamin D supplementation group and 7 (11.1%) in the control group. These differences were not significant (p=0.53). IUGR was observed in 3 (4.8%) cases in vitamin D supplementation group and 8 (12.7%) cases

in control group. Although IUGR was higher in control group but the difference was not significant (Figure 7).

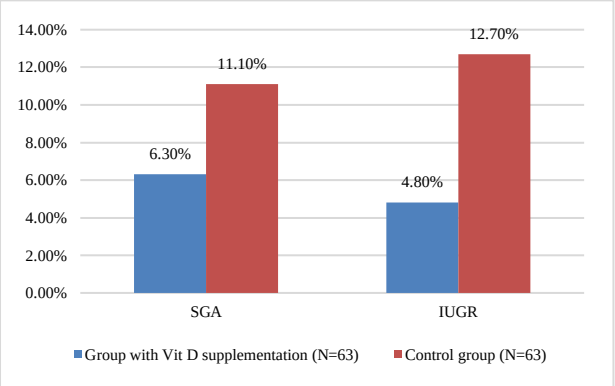

Figure 7: Neonatal outcome in study subjects.

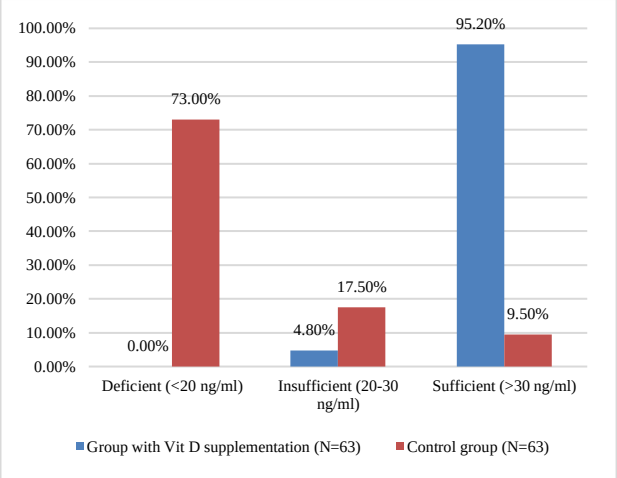

Figure 8: Vitamin D3 level at the time of delivery in both groups.

Table 1: Vitamin D3 level of cord blood in both groups.

Vitamin D3 level of cord blood	Vitamin D supplementation group (n=63)		Control group (n=63)		P value
	N	%	N	%	
Deficient (<20 ng/ml)	0	0.0	46	73.0	<0.001
Insufficient (20-30 ng/ml)	3	4.8	11	17.5	
Sufficient (>30 ng/ml)	60	95.2	6	9.5	

Table 2: Comparison of mean vitamin D3 level between both groups.

Vitamin D level (ng/ml)	Vitamin D supplementation group (n=63)	Control group (n=63)	P value
At the time of delivery (Mean±SD)	56.84±15.78	18.12±8.97	<0.001
In cord blood	41.05±13.25	15.18±7.19	<0.001

The level of vitamin D in cord blood was found to be significantly correlated with the maternal vitamin D3 level at the time of delivery (r value =0.91; p<0.001). Forty-six patients (73.0%) were found to have vitamin D levels of less than 20 ng/ml while in 10 (15.9%) subjects level of vitamin D was insufficient (20-30ng/ml). Only in 7 (11.1%) subjects vitamin D level was found to be sufficient (>30 ng/ml).

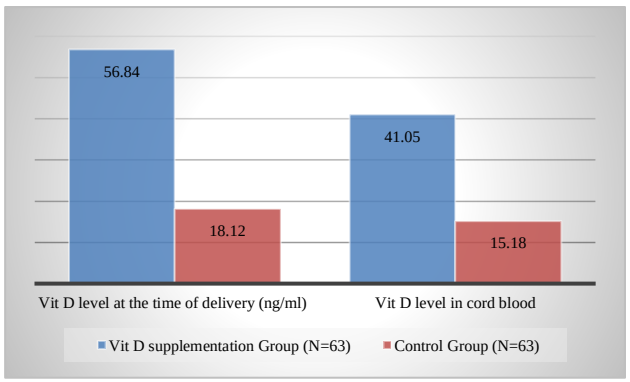

Figure 9: Maternal and cord blood vitamin D3 level in both groups.

Total 95.2% of mothers (at delivery) attained 25(OH)D>30 ng/ml compared to only 9.5% of mother in the control group. In vitamin D supplementation group deficient (<20 ng/ml) level could not find in any mother while it was observed in 46 (73.0%) pregnant women in control group as shown in (Figure 8).

Similarly, in cord blood of neonates in vitamin D supplementation group also 95.2% attained 25(OH)D>30 ng/ml compared to only 9.5% of cord blood of neonates in the control group. In vitamin D supplementation group deficient (<20 ng/ml) level could not find in any neonatal cord blood while it was observed in 46 (73.0%) neonate's cord blood in control group as shown in (Table 1-2).

DISCUSSION

Age distribution was almost similar in both the groups. The mean maternal ages for the vitamin D supplementation and the control groups were 24.70±3.98 and 25.68 ±4.54 years respectively.

Maternal complications

In our study, 63 pregnant women where vitamin D3 supplementation was given, Gestational hypertension was seen in 4 (6.3%) of subjects while in control group it was seen in 11 (17.5%) of pregnant women. Gestational DM was seen in 3 (4.8%) pregnant women in vitamin D3 supplementation group while it was observed in 10 (15.9%) women of control group. Another complication PROM was seen in 2 (3.2%) pregnant women in vitamin D3 supplementation group while it was seen in 8 (12.7%) control group pregnant women. Similar findings were also reported by Mojibian et al, Aghajafari et al in a meta-analysis reported that vitamin D insufficiency was associated with greater risk of gestational diabetes, preeclampsia, and small for gestational age infants.[9,10] Poel et al also showed that maternal vitamin D status it was correlated with gestational diabetes.[7]

Finding of our study was also corroborated by Yap et al who showed that supplementation with 5000 IU vitamin D3 daily at a mean 14 weeks gestation did not cause to improvement in maternal glucose level compared with a control group (400 IU of vitamin D3 daily) and Soheilykhah et al demonstrated that insulin resistance significantly decreased when pregnant women were supplemented with 50,000 IU of vitamin D every two weeks from 12 weeks of pregnancy until delivery.[8,11] In a meta-analysis of three trials, De Regil et al found that women who received vitamin D3 supplements during pregnancy had a lower risk of having a preterm birth than those women receiving no intervention or placebo (3.3% versus 9.9%; average RR 0.36; 95% CI 0.14 to 0.93) whereas meta-analysis by Roth et al on the other hand, showed no effect of vitamin D3 supplementation on risk of preterm birth.[12,13]

Neonatal outcome

In present study, there were 4 (6.3%) cases of small-for-gestational age infants in the vitamin D3 supplementation group and 7 (11.1%) in the control group. These differences were not significant (p=0.53). IUGR was observed in 3 (4.8%) cases in vitamin D3 supplementation group and 8 (12.7%) cases in control group. Although IUGR was higher in control group but the difference was not significant. Our findings were similar to study by Hollis et al, Yap et al and meta-analysis by Aghajafari et al also indicated that pregnant women with low serum vitamin D had a heightened risk of lower birth weight infants.[10,14,15] However, in contrast to our study Nadal et al show significant high birth weight in baby with vit D3 supplementation compare to controls (3.1±0.485 kg vs. 2.8±0.705 kg).[10,14,15]

Maternal and cord blood vitamin D correlation

The level of vitamin D in cord blood was found to be significantly correlated with the maternal vitamin D3 level at the time of delivery (r value =0.91; p<0.001). Similar to our study Hossain et al also reported significant positive correlation between maternal and neonatal Vitamin D levels, Sablok et al also informed that newborns of mothers in un-supplemented group had lower cord blood levels of Vitamin D levels, other studies by Aly et al and Al Emadi et al also found significant correlation between maternal Vitamin D3 level in third trimester and newborn.[16-19]

Vitamin D status

In our study 46 patients (73.0%) were found to have vitamin D levels of less than 20 ng/ml while in 10 (15.9%) subjects level of vitamin D was insufficient (20-30ng/ml) and in 7 (11.1%) subjects vitamin D level was found to be sufficient (>30 ng/ml), 95.2% of mothers (at delivery) attained Vitamin D >30 ng/ml compared to only 9.5% of mother in the control group. In Vitamin D3 supplementation group deficient (<20 ng/ml) level could not find in any mother while it was observed in 46 (73.0%) pregnant women in control group. Similarly, in cord blood of neonates in vitamin D3 supplementation group also 95.2% attained vitamin D >30 ng/ml compared to only 9.5% of cord blood of neonates in the control group. In Vitamin D3 supplementation group deficient (<20 ng/ml) level could not find in any neonatal cord blood while it was observed in 46 (73.0%) neonate's cord blood in control group. Therefore, vitamin D3 supplementation had a substantial, statistically significant effect on maternal and neonatal vitamin D3 status at the time of delivery; Level of vitamin D3 was increased significantly i.e., from 18.25±10.75 ng/ml to 56.84±15.78 ng/ml. Our results were similar to the study conducted by Yap et al, Hollis et al and Nandal et al that indicated mean neonatal cord Vitamin D was higher in neonates of the group that supplemented with vitamin D3.[8,14,15] In contrast to our study, Al-Emadi et al found no significant differences in the level of vitamin D3 in the second and third trimester and in the newborns vitamin D3 levels between vitamin D3 supplementation and control group.[19]

Safety

Our study indicated that supplementation of pregnant women with 60,000 IU vitamin D3 weekly for three weeks and 1,000 IU daily till term caused no adverse consequences for pregnant women and the level of vitamin D3 reached over 30 ng/ml, it remained below the toxic level (more than 100 ng/ml) at the time of delivery. Our results are in concordance with the Hollis et al study that presented 4000 IU daily is safe during pregnancy.[14] Yap et al and Soheilykhah et al had similar results.[8,11]

Limitations

Limitations of current study were: Estimating vitamin D concentrations did not take into consideration the season, small sample size and compliance was measured by pill count in this study which may not be a reliable predictor of compliance.

CONCLUSION

The number of subjects who developed preeclampsia, preterm labor and low birth weight was low and we need to perform a blind randomized clinical trial in a large population to assess the effect of vitamin D3 supplementation on these outcomes. The dose given in this study was seems to be safe without any adverse effect but as the sample size was low large clinical trial can lead to know about the safety and efficacy of this dose and health in future implications.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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