

# To study the effect of oral supplementation Vitamin D during pregnancy and status of cord blood



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## ABSTRACT

**Background:** In many nations, low Vitamin D levels in pregnant women have been associated to adverse outcomes for the mother, her baby, and the birth itself. **Aims and Objectives:** To study the effect of oral supplementation of mothers with high dose vitamin D (2000IU/day) in comparison with maintenance dose (400IU/day) during pregnancy on vitamin D status of cord blood at the time of delivery. **Materials and Methods:** Randomized single blind controlled trial conducted in 112 mothers recruited in first trimester, randomized into two groups. One group of mothers received 2000 IU/day, one group 400 IU/day till delivery. Mothers are followed up till delivery age, weight, height, and dressing. **Results:** Vitamin D levels in mothers in study group were showing 88% insufficiency (<20 ng/ml) and 12% sufficiency (>20 ng/ml). Mean values in both groups that is Group A  $6.6 \pm 2.8$ , in Group B  $6.2 \pm 2.2$ , both means are comparable with  $P=0.47$ , but after supplementation mean maternal Vitamin D level that is  $13.4 \pm 3.6$ , with  $P \leq 0.0001$ , this shows that there is a statistically significant. There is a statistically significant correlation is observed between maternal and cord blood Vitamin D levels after supplementation. Statistically significant correlation was observed between maternal and cord blood Vitamin D levels. **Conclusions:** Vitamin D supplementation throughout pregnancy enhances maternal serum and Vitamin D levels at term, according to this study. There is currently sufficient high-quality evidence pertaining to the therapeutic effects of Vitamin D supplementation during pregnancy.

**Key words:** Vitamin D; Cord blood; Oral supplementation

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## INTRODUCTION

Vitamin D deficiency is currently a global pandemic. Yet it is an under diagnosed and under treated in many nutritional deficiency countries affecting all ages and ethnic groups. In spite of the availability of cheap and effective means to prevent this disease the present study was undertaken with an aim to find the effect of Vitamin D.

Supplementation orally to mother on cord blood Vitamin D levels. Vitamin D deficiency in pregnant mothers is

evident by several studies in India with the prevalence of 70–100%.<sup>1</sup>

In India socio religious and cultural practices do not facilitate adequate sun exposure. In India, widely consumed food items such as dairy products are rarely fortified with Vitamin D.

According to Institute of Medicine (IOM) and American Academy of Nutrition doses as high as 10,000 IU/day are safe and does not have hypervitaminosis. But IOM recommends to supplement 4000 IU/day.<sup>2</sup> In spite

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of many studies are showing high prevalence of Vitamin D deficiency in mothers there is no consensus recommendation for screening and supplementation of Vitamin D to all pregnant women.

### Aims and objectives

To study the effect of oral supplementation of mothers with high dose vitamin D (2000IU/day) in comparison with maintenance dose (400IU/day) during pregnancy on vitamin D status of cord blood at the time of delivery.

## MATERIALS AND METHODS

This is a randomized single blind controlled trial (RCT certificate needs to be submitted prior publication) was carried out in the Department of Pediatrics, Hyderabad from January 2013-December 2014.

The study protocol was approved by the Institutional Ethics Committee–Human Research (ECR/180/inst/AP/2013 dated 20/4/2013).

### Sample size

The number of subjects to be studied was based on studies done previously showing high prevalence of Vitamin D deficiency (70-90%) and studies showing correlation of Vitamin D levels with neonatal levels.<sup>3</sup>

$$P_1=0.44, P_2=0.22$$

$$Z\alpha=1.645 \text{ (one-tailed)}$$

$$Z\beta=0.864$$

$$N=56$$

It was revealed that recruitment of 56 mothers in the intervention and control groups would achieve the desired objective.

Pregnant women (primi) who are attending antenatal clinic in Gandhi Hospital with gestation age <16 weeks were recruited after obtaining informed written consent from the mothers and verbal consent from their family members explaining them the purpose and method of the study.

### Inclusion criteria

The following criteria were included in the study:

1. This study includes Vitamin D deficient mothers with single ton pregnancy attending antenatal clinic in Gandhi Hospital with gestational age <16 weeks were residing within 10 km from Gandhi Hospital.
2. Who have planned to receive ongoing Antenatal care in Gandhi Hospital.
3. Women who have given consent for the study.

All mothers were counseled regarding importance of Vitamin D to increase compliance.

### Exclusion criteria

The following criteria were excluded from the study:

1. Pregnant women with gestational age more than 16 weeks.
2. Mothers who are having sufficient vitamin D levels.
3. Mothers who are known to be suffering from chronic illness such as chronic kidney disease, chronic liver disease, tuberculosis, DM, and Malabsorption syndrome.
4. Mothers known to be suffering from endocrinological disorder.
5. Mothers who have not given consent for this study.

### Groups

Mothers were randomly allocated into two groups and named as Group A and Group B.

### Randomization and blinding

All the mothers entering into the study after fulfilling inclusion and exclusion criteria were given a serial number block randomization was done by computer generated randomization table into two groups to receive 2000 IU (Group A) and 400 IU (Group B) accordingly.

### Data collection

Personal and epidemiological data of all mothers were elicited by history and hospital record.

### Maternal data

Mothers identification details (name, address, age, and phone number) were taken. Information specially pertaining to diet, sunlight exposure, dressing habits, and other relevant data were recorded in a pre-designed record form.

### Diet

History was taken regarding food preferences of the family. Veg diet included food obtained from plants as well as from the dairy. Mixed diet was considered when mother consumed food obtained from the plant as well as dairy products and poultry, fish, and meat.

### Sunlight exposure

Mothers were asked about sunlight exposure per day and divided into two groups according to duration. One group had <6 h of sun exposure per day and group two >6 h/day. Mothers were asked to maintain a record of daily sunlight exposure and during follow-up the duration of sunlight exposure per day was noted.

**Dressing preference**

History was taken about dressing preference by mothers and distributed them into two groups. In group one, mothers were classified as partially covered implying that scalp, face, fore arms part of abdomen (if wearing saree), and feet were not covered; about 25–30% of total body surface area was bare. In the second group, mothers kept whole body fully covered except part of the face, wrist, and feet; about 10–15% of body surface area was exposed.

**Socio economic status**

Mothers were asked about their family per capita income. They were divided into two groups with per capita income Rs. <5000/month and group two Rs. 5000–10,000/month respectively.

**Education**

Primary (up to class 9), and secondary (MORE than class 9 to 10 and +2) and graduates.

**Anthropometry**

Mother’s weight, height, and body mass index were measured by standard method and recorded.

Each mother was followed up at every month along with her Antenatal visits.

At each visit mother was counseled regarding importance of intake of Vitamin D and compliance of Vitamin D tab was verified by counting the left over tablets.

At each visit mothers are provided with 30 tablets of Vitamin D along with other Antenatal supplements.

3 ml maternal blood was collected at recruitment and at the time of delivery. 2 ml cord blood was collected at the time of delivery.

The mean age of the mothers in both the groups was 21.7±1.8 years and 21.6±2.4 years, respectively. p=0.82, the weight and height of mothers belonging to two groups were also comparable (Table 1).

The dietary habits of the mothers in both the groups were comparable. So dietary habits were similar in both the groups. The dressing preference of the mothers in both the groups was similar. The mode of delivery in both the groups was comparable (Figure 2).

Total 130 subjects were included in the study, 114 samples came as deficient (that is <20 ng/ml); 16 samples came as

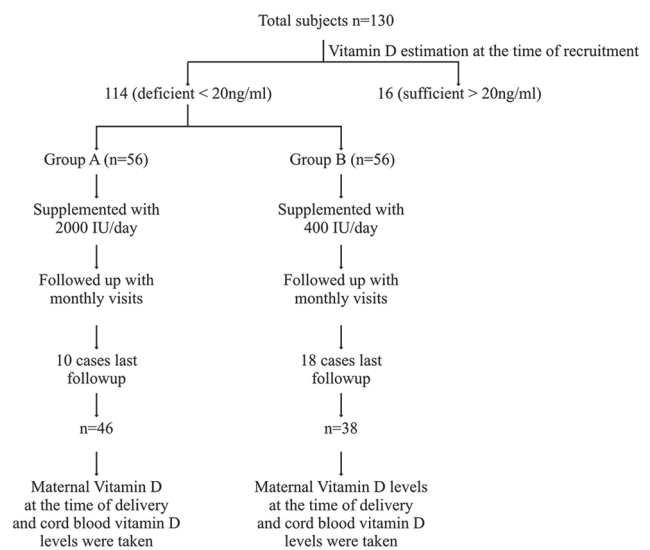


Figure 1: Flow chart for selection of samples

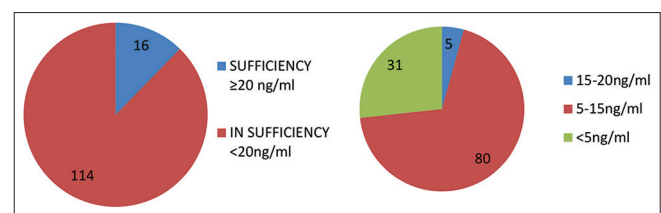


Figure 2: Vitamin D levels in mothers in study group

**RESULTS**

This study was conducted in the department of pediatrics from January 2014 to May 2015. 114 mothers were recruited after taking written informed consent. One group received Vitamin D 400 IU/day till delivery, one group received 2000 IU/day till delivery after randomization. They were followed up till delivery. Finally 46 in Group A supplemented with 2000 IU/day continued till delivery. In Group B supplemented with 400 IU/day 38 continued till delivery. Lost to follow-up was 10 and 18 mothers in Group A and Group B, respectively. The study flow chart detailing the inclusion of subjects is depicted in Figure 1.

**Table 1: Characteristics of the mothers**

Parameters	Group A (N=46)	Group B (N=38)	P value
Age	21.7±1.8	21.6±2.4	0.82
Weight	54.5±5.2	55.2±5.8	0.64
Height	148.7±4.6	151.3±5.2	0.13
Dietary habits			
Vegetarian	15	13	0.87
Mixed diet	31	25	
Dressing habits			
Partially covered	36	26	0.16
Fully covered	10	12	
Mode of delivery			
NVD	36	27	0.23
LSCS	10	11	

sufficient (>20 ng/ml). In this 114 subjects are randomized into two study groups and followed up till delivery.

In total 130 subjects were included in the study, 16 samples came as sufficient (>20 ng/ml), in total 114 samples 80 subjects in deficiency group that is (5–15 ng/ml), and 29 subjects are in severe deficiency group that is (<5 ng/ml) (Figure 3).

Mean values in both groups, that is, Group A  $6.6 \pm 2.8$ , and in Group B  $6.2 \pm 2.2$ , both means are comparable with  $p=0.47$ , but after supplementation mean maternal Vitamin D level that is  $13.4 \pm 3.6$ , with  $p<0.0001$ , this shows that there is a statistically significant difference are observed in both the groups in relation to Vitamin D levels.

Table 2 shows that after supplementation in Group A who are supplemented with 2000 IU 35 (76%) reached sufficient levels, in comparison with Group B, who are supplemented with 400 IU only 2 (5%) reached sufficient levels.  $P<0.0001$ , shows that there is a statistically significant difference is observed in both the groups.

There is a statistically significant difference between the two groups  $P<0.0001$ . But even supplementing 2000 IU/day till delivery is not enough to reach sufficient levels that is >20 ng/ml in cord blood. In this both, Chi-square test and  $\chi^2$  test results show that there is a statistically significant correlation and is observed between maternal and cord blood Vitamin D levels.

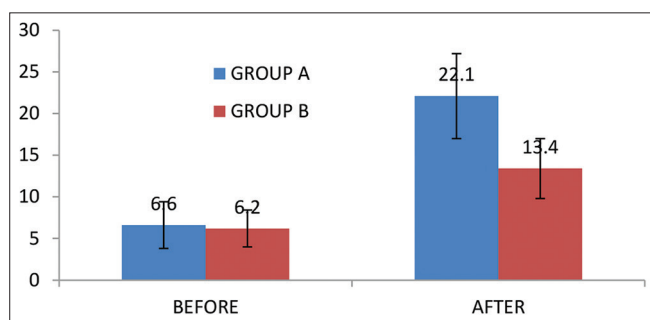


Figure 3: Comparison of mean maternal Vitamin D values before and after supplementation

Table 2: Comparison of maternal and cord blood Vitamin D levels after supplementation		
Vitamin D levels	Group A	Group B
Comparison of maternal Vitamin D levels after supplementation		
<20 ng/ml	11 (24%)	36 (95%)
≥20 ng/ml	35 (76%)	2 (5%)
Comparison of cord blood Vitamin D levels between		
<20 ng/ml	39 (85%)	38 (100%)
≥20 ng/ml	7 (15%)	0

Mean maternal and cord blood Vitamin D levels in Group B. In this both, Chi-square test and ‘T’ test results show that there is a statistically significant correlation and is observed between maternal and cord blood Vitamin D levels (Table 3).

Table 4 shows that there is no statistically significant difference between two groups in relation to the incidence of preterm deliveries. This table shows that there is no statistically significant difference and is observed in between two groups in relation to the incidence of preterm deliveries.

In terms of anthropometric parameters, this table reveals that there is no statistically significant difference between the two groups (Table 5).

## DISCUSSION

Our study was conducted in 114 mothers recruited in first trimester, randomized into two groups. One group of mothers received 2000 IU/day, one group 400 IU/day

Table 3: Association between maternal and cord blood Vitamin D levels in both groups

Vitamin D levels	Maternal levels	Cord blood levels
In Group A		
<20 ng/ml	11 (24%)	39 (85%)
≥20 ng/ml	35 (76%)	7 (15%)
Mean	22	16
In Group B		
<20 ng/ml	36 (95%)	38 (100%)
≥ 20 ng/ml	2 (5%)	0
Mean	17	10

Table 4: Comparison of neonatal variables in both the groups

Neonatal variables	Group A	Group B	Total
Incidence of deliveries			
Preterm	7	7	14
Term	39	31	70
Low birth weight			
≥2.5 Kg	38	28	66
<2.5 Kg	8	10	18
Gender			
Male	22	18	40
Female	24	20	44

Table 5: Comparison of anthropometric parameters of neonates in both the groups

Anthropometric parameters	Group A (N=46)	Group B (N=38)	p value
Weight	2.63±0.62	2.6±0.6	0.94
Length	46.2±8.4	46.1±11.3	0.96
Head Circumference	32.6±5.2	32.8±5.8	0.86

till delivery. Mothers are followed up till delivery. Age, weight, height, dressing preference, dietary habit, and mode of delivery were comparable in both groups of mothers. Vitamin D levels in mothers in study group was showing 88% insufficiency (<20 ng/ml), 12% sufficiency (>20 ng/ml). This study confirmed once again that large number of pregnant women was suffering from hypovitaminosis D. At the time of recruitment almost 88% mothers have Vitamin D levels <20 ng/ml.

In those mothers having Vitamin D insufficiency 70% of mothers having Vitamin D deficiency <15 ng/ml, 26% of mother having severe Vitamin D deficiency that is <5 ng/ml, our observations were in conformity with an earlier studies. Our observations were in conformity with an earlier study done in our institute. Showing Vitamin D deficiency in 70% pregnant mothers at the time of delivery. A large number of reports are available in the literature highlighting the high prevalence of Vitamin D deficiency during pregnancy.

A systematic review of articles published in PubMed (98 studies) shows Vitamin D deficiency in pregnant mothers, further research should focus on deficiency of 25(OH)D levels in pregnancy. Study published in reproductive health literature shows high prevalence of Vitamin D deficiency.<sup>4,6</sup>

RCT's study done by Vitamin D council shows 77% prevalence of Vitamin D deficiency. Study done in Royal College of Obstetrics shows Vitamin D deficiency 47% in Indian Asian Women. About 64% in middle eastern women 68% of black women taking normal limit of vitamin D levels <11 ng/ml.<sup>7</sup>

In our study, mean maternal Vitamin D levels before supplementation in both the groups are almost equal. But after supplementation mean maternal Vitamin D levels in Group A who are supplemented with 2000 IU/day till delivery and in Group B who are supplemented with 400 IU/day difference between these two values are statistically significant ( $P < 0.0001$ ). This shows that supplementing 400 IU/day is not sufficient to reach adequate levels of Vitamin D during pregnancy.

Our observations are consistent with study done by Hollis<sup>8</sup> Study conducted in women with singleton pregnancy at 12–16 weeks gestation received 400/2000/4000 IU of Vitamin D until delivery. It is concluded that Vitamin D supplementation if 4000 IU/day for pregnant women is safe and most effective in achieving sufficiency in all women and their neonates.

Wagner et al.,<sup>9</sup> postulated in a 6-month follow-up pilot research that supplementing mothers with 6400 IU/day

of Vitamin D3 would greatly increase Vitamin D status in both lactating women and their breastfeeding babies. This kind of supplementation is comparable to newborn oral Vitamin D3 supplementation of 300 IU/day and meets the current requirement of 400 IU/day.

Rothberg et al.,<sup>10</sup> concluded a study on maternal infant Vitamin D relationship during breast feeding by supplementing mothers with 1000 IU of Vitamin D for 6 weeks (total 4 lakh IU) and compared their serum 25-OH Vitamin D with that of control group (un supplemented) and demonstrated that maternal 25-OH Vitamin D concentrations correlate directly with infants 25-OH Vitamin D values, implying that maternal Vitamin D intake directly affects the Vitamin D concentration in human milk and the Vitamin D status of the infant.

In comparison of cord blood Vitamin D levels in both groups, 35% of neonates in Group A and 100% of neonates in Group B having Vitamin D levels <20 ng/ml. This shows that even supplementing 2000 IU/day till delivery is not sufficient to reach adequate Vitamin D levels that are  $\geq 20$  ng/ml in neonates. This finding in our study is consistent with J Berk Michal research<sup>11</sup> concluded that Vitamin D supplementation of 4000 IU/day was found to be safe and effective in reaching adequacy in all pregnant women and their newborns.

Studies published in Vitamin D council recommends daily intake for pregnant women as high as 4000–6000 IU/day. In this study found that women who took 4000 IU/day during pregnancy achieved sufficient levels in their neonates.

Studies done by the World Health Organization—shows that women who are supplemented with high dose Vitamin D had higher concentration of Vitamin D in serum at term and their neonates.<sup>12</sup> In our study, it shows that there is a significant correlation and is observed between maternal and cord blood Vitamin D levels. In this study, both Chi-square test and  $\chi^2$  test results are showing  $P < 0.0001$ , this implies that statistically significant correlation is observed between maternal and cord blood Vitamin D levels. All infants in Group B that is supplemented with 400 IU and 85% infants in Group A (2000 IU) are Vitamin D deficient. The cord blood Vitamin D levels were almost 2/3<sup>rd</sup> of the maternal serum Vitamin D levels. The maternal and cord blood Vitamin D levels also exhibited significant correlation.

Cancela et al.,<sup>13</sup> have demonstrated that Vitamin D levels in the infant are directly proportional to Vitamin D levels in the mother. This signifies that infant's Vitamin D level during antenatal period depends in maternal Vitamin

D stores. Mallet et al.,<sup>14</sup> conducted a randomized study in which mothers were divided into three groups one group received daily dose of Vitamin D 1000 IU in the last trimester; other group received single dose of 200,000 IU Vitamin D and the third group kept as control. It was found that a single 200,000 IU Vitamin D orally at 7<sup>th</sup> month of pregnancy produced a sustained rise in 25 OH Vitamin D concentrations lasting months and was preferable to daily supplementation which may give way to long-term neglect.

In a study from Northern India, Sachan et al.,<sup>15</sup> discovered that mean maternal serum 25(OH)D was  $14 \pm 9.3$  ng/ml and cord blood 25(OH)D was  $8.4 \pm 5.7$  ng/ml. Eighty-four percent of women (84.3% in the city and 83.6% in the country) had 25(OH)D levels below the cutoff.  $P=0.001$  showed a positive correlation between maternal serum 25(OH)D and cord blood 25(OH)D.

The 25-hydroxyvitamin D concentration (25(OH)D) in maternal and cord blood of 192 mothers was determined at delivery from June to the end of November in another study by Lamberg-Allardt et al.,<sup>16</sup> in which 99 mothers had received a daily supplementation of 12.5 micrograms of Vitamin D during pregnancy, and this group had a significantly higher 25-OHD concentration both in maternal and cord blood than the corresponding non-supplemented group.

About 96.3% of the individuals had hypovitaminosis D (25(OH)D 50 nmol/l), according to Marwaha et al.,<sup>17</sup> In the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters, serum 25(OH)D levels were considerably lower in the winter. The levels of 25(OH)D in mother-infant pairings had a high positive connection ( $r=0.779$ ,  $P=0.0001$ ). Hypovitaminosis D was shown to be very common during pregnancy, lactation, and childhood.

The effect of high dose prenatal 3<sup>rd</sup> trimester Vitamin D3 supplementation on maternal and new born (cord blood) serum 25-hydroxyvitamin D concentration and maternal serum calcium concentration was investigated by Roth et al.,<sup>18</sup> in a double blinded randomized placebo controlled trial. Pregnant women in Dhaka, Bangladesh, aged 18–35 years old and at 26–29 weeks gestation were recruited. 16 women were randomly assigned to one of two parallel intervention groups in a 1:1 ratio. Placebo or 35,000 IU Vitamin D3/week till delivery ( $n=80$ ). During baseline, the Vitamin D and placebo groups had equal levels of 25(OH) D (45 vs. 44 nmol;  $P=0.001$ ), but the Vitamin D group had significantly greater levels than the placebo group among moms at delivery (134 vs. 38 nmol/l;  $P=0.001$ ) and new mothers (134 vs. 38 nmol/l;  $P=0.001$ ). In the Vitamin D group, 95% of neonates and 100% of mothers attained 25-(OH)D <50 nmol/l versus 21% mothers and 19% neonates in the placebo group.

Mallet et al.,<sup>14</sup> conducted a randomized study in which mothers were divided into three groups one group received daily dose of Vitamin D 1000 IU for 3 last months other group received single dose of 200,000 IU Vitamin D and the third group as control. It was found that a single 200,000 IU Vitamin D orally at 7<sup>th</sup> month of pregnancy produced a sustained rise in 25 OH Vitamin D concentrations lasting months and was preferable to daily supplementation which may give way to long term neglect.

Madelenat et al.,<sup>19</sup> conducted a study on winter supplementation in the third trimester of pregnancy by a dose of 80,000 IU of Vitamin D and found it to be a good compromise between efficacy and tolerance in 59 pregnant mothers raised 25 OH Vitamin D values, implying that maternal Vitamin D intake directly affects the Vitamin D concentration in human milk and the Vitamin D status of infant.

Wailer et al.,<sup>20</sup> investigated the Vitamin D status of mothers during pregnancy and also reported the difference between those receiving Vitamin D supplementation and those who did not. Women who received supplementation had a significantly higher mean 25(OH)D concentration than those relying solely on dietary intake to obtain Vitamin D ( $54.3 \pm 20.2$  nmol/l vs.  $46 \pm 24.8$  nmol/l,  $P<0.05$ ). Median 25(OH)D levels were also significantly lower among those not receiving supplementation compared with those who did ( $5.25$  ng/ml vs.  $7.42$  ng/ml,  $P<0.01$ ). The same conclusions were drawn between those receiving supplementation only during the 3<sup>rd</sup> trimester and those who did not receive the supplementation ( $7.44$  ng/ml vs.  $5.80$  ng/ml,  $P<0.01$ ) that supplementation resulted in an increase in 25(OH)D.

In our study in comparison of Incidence of low birth weight and preterm deliveries there is no statistically significant difference and is observed in both groups.  $p=0.43$ . But in some studies are showing correlation between low Vitamin D levels and incidence of preterm and low birth weight deliveries.

Study done in University of Pittsburgh shows that women who have low levels of Vitamin D during pregnancy are more likely to have preterm babies.<sup>21</sup> Study published by Vitamin D council show that—RCT's have shown that supplementation with recommended dietary allowance of 400 IU dose not improve Vitamin D status of pregnant women. High dose vitamin D supplementation during pregnancy can help in reducing gestational hypertension, pre eclampsia, and preterm births.

Clinical studies establishing an association between Vitamin D levels and adverse pregnancy outcomes such

as low birth weight, preterm labor, and cesarean delivery have conflicting results, according to studies published in PubMed. This is likely due to a small sample size and poor adjustment for confounding variables. The WHO Women who took Vitamin D supplements during pregnancy were less likely to have a baby weighing <2500 g, according to studies. The statistical significance of this outcome was dubious when compared to individuals who received no treatment or a placebo.<sup>4,5</sup>

In our study in comparison of anthropometric parameters of neonates in both the groups there is no statistically significant difference and is observed. Large scale studies are showing statistically significant correlation in anthropometric measurements, but our study was done with small sample size was not showing significant difference. In our study, we found that by giving 2000 IU Vitamin D to mothers during pregnancy in comparison with 400IU/day significantly raised the mean serum Vitamin D levels also in cord blood Vitamin D levels. This would have been possible due to significant rise in the Vitamin D levels in the maternal blood and subsequent transfer of higher amount of Vitamin D to fetus. The raised serum Vitamin D levels in the mothers and cord blood in the Group A could have happened only due to administration of Vitamin D 2000 IU, because of dietary habits, age, weight, and height are comparable in both groups. There was no significant difference in the Vitamin D levels of mothers in both groups at recruitment. There was no clinical evidence of intoxication of hypervitaminosis D.

#### Strength of our study

1. Single blinded randomized controlled study
2. The method used to measure Vitamin D level was based on high-pressure liquid chromatography method which is considered to be the most reliable method for measuring 25-OH-D.
3. The study cohort was similar. Vitamin D levels were estimated in National Institute of Nutrition.

#### Limitations of the study

One of them was lack which was ethically and racial correlation was not done. The concentrations of calcitriol (1, 25(OH)<sub>2</sub>D) were not assayed, either.

## CONCLUSIONS

The purpose of Vitamin D supplementation for pregnant women is to see if taking Vitamin D alone or in combination with calcium or other vitamins and minerals during pregnancy can improve maternal and newborn outcomes safely. Vitamin D supplementation, either in a single dosage

or over time, increases serum Vitamin D concentrations at term, as assessed by 25-hydroxyvitamin D.

Because the number of high-quality trials and outcomes reported is too low to make inferences on its effectiveness and safety, the clinical importance of this result and the possible utility of this intervention as part of normal antenatal care have yet to be determined. To assess the role of Vitamin D supplementation in pregnancy, more thorough randomized trials are needed.

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
**Author's Contributions:**

**SR-** Concept and design of the study, prepared first draft of manuscript; **KV-** Interpreted the results; reviewed the literature, and manuscript preparation; **ACH-** Concept, preparation of manuscript, and revision of the manuscript. **PD-** Coordination, statistical analysis, and interpretation. **VM-** Reviewed the literature and manuscript preparation.

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