ORIGINAL ARTICLE

Perinatal Outcome in Vitamin D Deficiency and Effect of Oral and Intramuscular Vitamin D3 Supplementation in Antenatal Women on Pregnancy Outcomes

Shikha Singh[1], Ruchika Garg[2], Ankita Meena[3], Deesha Kumar[4]

Abstract

Introduction: There is a high prevalence of low levels of Vitamin D in the pregnant women. Vitamin D deficiency is accompanied with adverse maternal and neonatal outcomes.

Aim and objective: To study perinatal outcomes in vitamin D deficiency, and effect of oral and intramuscular vitamin D3 supplementation in antenatal women on pregnancy outcomes.

Materials and methods: It is a randomized prospective comparative cohort study. Antenatal women attending antenatal outpatient department were screened for vitamin D deficiency (<20 ng/dL), and deficient women were divided into two groups and treated with 60,000 IU oral tablet/capsule weekly and injection vitamin D intramuscular 60,000 IU every fortnight for 8 weeks, respectively. Both the groups were compared both before and after supplementation for variables like clinical profile and maternal and fetal outcomes.

Results: In our study, vitamin D deficiency <20 ng/dL was found in 90.9%. About half of the women had vitamin D3 less than 10 ng/mL and 40.6% women had their vitamin D3 level between 10 ng/mL and 20 ng/mL.

After the oral treatment, mean 25-hydroxy vitamin D level increased to 25.6 ± 1.37 ng/mL and 22.8 ± 2.1 ng/mL at 6 weeks and 12 weeks, respectively, in intramuscular treatment. Mean vitamin D level increased to 26.4 ± 1.85 ng/mL and 29.3 ± 2.08 ng/mL at 6 weeks and 12 weeks, respectively. At 12 weeks, the mean vitamin D level in the IM vitamin D group was higher as compared to the oral vitamin D group.

In the present study, no statistically significant differences could be found in the incidence of preeclampsia, GDM, and preterm birth but low birth weight babies were more in the vitamin D deficiency group (13.33%) as compared to the normal vitamin D group (6.67%).

Conclusion: There is a high prevalence of vitamin D deficiency in pregnant women in India. Supplementation of Vitamin D as a part of routine antenatal care needs to be established. Both oral and intramuscular vitamin D are effective.

Keywords: Deficiency, Pregnancy, Pregnant, Vitamin D, Vitamin D3 supplementation.

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Introduction

Vitamin D deficiency has been recognized as an international public health problem due to its important role in health and disease mainly for skeletal system. There is a high prevalence of low levels of vitamin D in pregnant women; it could be a modifiable risk factor with important public health implications.[1] Supplementation of vitamin D as a part of routine antenatal care needs to be studied.

Vitamin D deficiency develops commonly in pregnancy. It is accompanied by adverse maternal and neonatal outcomes, increased risk of gestational diabetes, cesarean section, and postpartum depression.[2]

The Institute Of Medicine, USA, defined adequate vitamin D as serum 25-hydroxyvitamin D concentrations greater than 50 nmol/L (or 20 ng/mL) in both the general population and pregnant women.[3] It has been suggested that a supplemental dose of vitamin D of 1,000–1,600 IU (25–40 µg/day) might be necessary to achieve the optimal level of vitamin D3 in the body.[4]

This study aims to compare the effect of intramuscular vitamin D and oral vitamin D supplementation in vitamin D-deficient women on the level of vitamin D and the fetomaternal outcome of vitamin D deficiency in vitamin D-deficient antenatal women.

[1–4]Department of Obstetrics and Gynaecology, SN Medical College, Agra, Uttar Pradesh, India

Corresponding Author: Ruchika Garg, Department of Obstetrics and Gynaecology, SN Medical College, Agra, Uttar Pradesh, India, Phone: +91 9720004485, e-mail: ruchikagargagra@gmail.com

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Materials and Methods

The study was conducted on antenatal women attending OPD in the Department of Obstetrics and Gynecology, S.N. Medical College and Hospital, Agra, from January 2017 to December 2019.

It is a randomized prospective comparative cohort study.

A total of 165 antenatal women attending the antenatal outpatient department were screened for vitamin D deficiency (<20 ng/dL) and out of which 150 (90.91%) were diagnosed cases of vitamin D deficiency. Only 127 women were found to be eligible for the study after meeting the exclusion criteria, among which about three cases dropped out during the study period.

Inclusion Criteria

Antenatal women from 16-week gestation onwards willing to participate and found to be vitamin D deficient (i.e. <20 ng/mL).

Exclusion Criteria

The following are the exclusion criteria:

- Those who were not willing to participate;
- Antenatal women of less than 16 weeks of gestational age;
- Extreme of bodyweight (BMI >30 and <17 kg/m^2);
- Bleeding per vaginum, antepartum hemorrhage at the time of enrollment by history and clinical examination;
- History of past chronic medical illnesses like chronic hypertension, diabetes mellitus, hypothyroidism, hyperthyroidism, hypoparathyroidism, hyperparathyroidism, preexisting renal diseases, liver diseases, jaundice, malabsorption syndromes, osteomalacia, multiple myeloma, bone disease, and carcinomas;
- Women who were on medication that could interfere with normal function of vitamin D: phenobarbitone, phenytoin, cholestyramine, verapamil, thiazide, antacids, barbiturates, carbamazepine, Fosphenytoin, heparin, antiretroviral therapy, isoniazid, rifampicin, Orlistat, cholestyramine, steroids.

Women who were diagnosed as vitamin D deficient were randomly allocated in two groups:

- *Group I*: 61 antenatal women were treated with 60,000 IU. oral tablet/capsule weekly for 8 weeks and
- *Group II*: 63 antenatal women were given injection vitamin D intramuscular 60,000 IU every fortnight for 8 weeks.

Both the groups were compared both before and after supplementation for variables like clinical profile, maternal and fetal outcome.

Results

Table 1: Distribution of cases and control according to vitamin D status

Sl. No.	*Vitamin D status*	*No. of cases*	*Percentage*
1.	Normal (control)	15	9.09
2.	Vitamin D deficiency <20 ng/dL (cases)	150	90.91
	Total cases	165	100
	Vitamin D level (ng/mL)		
1.	<10	83	50.30
2.	10–20	67	40.60
3.	20–30	15	9.10
	Total	165	100

Discussion

Vitamin D deficiency is a common health problem worldwide in both children and adults.[5,6] Vitamin D deficiency has been linked to its effect on bone metabolism and mineral homeostasis and has also been associated with a wide range of adverse health outcomes, including cancer, cardiovascular diseases, diabetes, infectious diseases, and autoimmune diseases.[7] Low levels of vitamin D have been associated with an increased risk of preeclampsia.[8] Vitamin D deficiency may also be linked with preterm births given the immunomodulatory and anti-inflammatory properties of vitamin D.[9] The fetus relies entirely on vitamin D stores of mother, so if the mother is deficient so is the fetus. Thus, vitamin D deficiency is also linked with small-for-gestation-age babies[10] and low birth weight newborns.[11] Vitamin D may exert a protective effect on spontaneous preterm birth. Vitamin D reduces the response to microbial pathogens by abrogating the production of interleukin-6, interleukin-1, and tumor necrosis factor-alpha by macrophages.[12] Certainly, there is a strong biologic possibility linking vitamin D status to spontaneous preterm birth.[9]

Largest cohort study found the odds of birthing a baby small-for-gestation age was higher among women with severe vitamin D deficiency in early pregnancy. Boston study of 300 women found that those with a vitamin D3 level less than 37.5 ng/dL had four times the odds of cesarean delivery than those with higher levels.

Our study was a randomized prospective comparative cohort study, in which a total of 165 antenatal women attending antenatal OPD were screened for vitamin D deficiency (<20 ng/dL) and out of which 150 (90.91%) were diagnosed as vitamin D deficient. Only 127 women were found to be eligible, among which about three cases dropped out during the study period Table 1.

In our study, 52.46% of the cases were primigravida and 47.54% of the cases were multigravida in group I, while in group II, 52.38% of the cases were primigravida and 47.62% of the cases were multigravida Table 2.

Ustner et al. estimated 25(OH)D levels in 79 pregnant women in third trimester and found that 45.6% of the women had severe vitamin D deficiency which was defined as <10 ng/mL by the researchers; the mean 25(OH)D level was 11.95 ± 7.20 ng/mL Table 3.[13]

Table 2: Demographic characteristics of the participants

		Group I		*Group II*	
Sl. No.	*Age (in years)*	*No.*	*%*	*No.*	*%*
1.	18–23	19	31.15	20	31.75
2.	24–29	27	44.26	26	41.27
3.	30–35	15	24.59	17	26.98
Total		**61**	**100**	**63**	**100**
Mean ± SD		**20.33 ± 6.11**		**21.00 ± 4.58**	
	Parity	*No.*	*%*	*No.*	*%*
1.	Primigravida	32	52.46	33	52.38
2.	Multigravida	29	47.54	30	47.62
Total gestational age in weeks		**61**	**100**	**63**	**100**
1.	16–28	25	40.98	26	41.27
2.	29–34	29	47.54	29	46.03
3.	>34	7	11.48	8	12.70
Total		**61**	**100**	**63**	**100**

Table 3: Mean vitamin D level after giving oral and intramuscular vitamin D supplementation

Sl. No.		*Oral (N = 61)*	*IM (N = 63)*	*t-value*	*p value*
		Mean ± SD	**Mean ± SD**		
1.	Baseline	8.9 ± 0.99	8.5 ± 1.85	−1.477	0.1424
2.	6 weeks	25.6 ± 1.37	26.4 ± 1.85	2.239	0.0271
3.	12 weeks	22.8 ± 2.1	29.3 ± 2.08	17.034	<0.0001

In another cross sectional study on Indian pregnant women, conducted by Marwah et al. in 2011, 541 apparently healthy women with singleton intrauterine gestation were recruited. The prevalence of vitamin D deficiency (<50 nmol/L) was 96.3%. The mean 25(OH)D level was 23.2 nmol/L.[14]

In the present study, a maximum number of cases were in the range of 29–34 weeks of gestation in both groups. In group I, 47.54% of the cases were in the range of 29–34 weeks of gestational age, 40.98% of the cases were in the range of 16–28 weeks of gestation, and 11.48% of the cases belonged to >34 weeks of gestation. In group II, 46.03% of the cases were in the range of 29–34 weeks of gestational age, 41.27% of the cases were in the range of 16–28 weeks of gestation, and 12.70% of the cases belonged to >34 weeks of gestation.

Marwaha et al. conducted a cross-sectional study on 541 apparently healthy women with uncomplicated single live intrauterine gestation in any trimester and observed that the mean 25(OH)D of pregnant women was 23.2 nmol/L. Hypovitaminosis D [25(OH)D <50 nmol/L] was observed in 96.3% of the subjects. It was concluded that there is a high prevalence of hypovitaminosis in pregnancy, lactation, and infancy with no significant intertrimester differences.

In our study, both oral and IM routes were effective for the treatment of vitamin D deficiency. In the oral group, mean 25 hydroxy vitamin D level increased to 25.6 ± 1.37 ng/mL and 22.8 ± 2.1 ng/mL at 6 weeks and12 week, respectively, in IM vitamin D group, mean vitamin D level increased to 26.4 ± 1.85 ng/mL and 29.3 ± 2.08 ng/mL at 6 weeks and12 weeks, respectively, but at 12 weeks, the mean vitamin D level in IM vitamin D group was higher as compared to the oral vitamin D group.

A study by Gupta et al. shows that both oral and IM routes are effective for the treatment of vitamin D deficiency. 25-hydroxyvitamin D level in the IM cholecalciferol group showed a sustained increase from baseline. This study evaluated the efficacy and tolerability of oral cholecalciferol (60,000 IU) vs IM cholecalciferol (300,000 IU) in correcting vitamin D deficiency in vitamin D-deficient apparently healthy individuals working in a tertiary care hospital; there was no significant difference in the mean serum 25(OH)D at 6 weeks and 12 weeks in the oral cholecalciferol group. In the IM cholecalciferol group serum, 25(OH)D level increased to 20.74 ± 1.81 ng/mL and 25.46 ± 1.37 ng/mL at 6 and 12 weeks, respectively, at 12 weeks, the mean serum 25(OH)D level in IM cholecalciferol group was higher as compared to the oral D3 group (25.46 ± 1.37 vs 16.66 ± 1.36 ng/mL; $p < 0.001$).[15]

A longitudinal study in 2012 by Wei et al. on vitamin D status in pregnancy and risk of preeclampsia measured maternal plasma 25(OH)D concentration at 12–18 and 24–26 weeks of gestation using chemiluminescence immunoassay and concluded that maternal 25(OH)D level of <50 nmol/L at late mid trimester of pregnancy was associated with an increased risk of preeclampsia.[16]

In the present study, no statistically significant difference ($p = 0.750$) could be found in the incidence of preeclampsia between the normal vitamin D group, 6.67%, and the vitamin D deficiency group, 13.33%.

Table 4: Comparison of maternal and fetal complication in vitamin D-deficient group in patients who were more than 34 weeks of gestational age (who could not complete vitamin D treatment schedule because of delivery) and normal vitamin D-level group (control)

		Normal vitamin D (N = 15)		*Vitamin D deficiency (N = 15)*	
Sl. No.	*Complication*	*No.*	*%age*	*No.*	*%age*
1.	Preeclampsia	1	6.67	2	13.33
2.	Gestational diabetes	1	6.67	2	13.33
3.	Preterm birth	0	0	1	6.67
4.	IUGR	1	6.67	1	6.67
5.	Low birth weight	1	6.67	2	13.33

$X^2 = 0.750$, p value 0.945

Table 5: Comparison of maternal outcome in both groups

		Oral (N = 61)		*IM (N = 63)*	
Sl. No.	*Maternal outcome*	*No.*	*%age*	*No.*	*%age*
1.	Gestational diabetes	2	3.28	1	1.59
2.	Preeclampsia	3	4.92	2	3.17
3.	Cesarean section	12	19.6	11	17.46

$X^2 = 0.289$, p value 0.865

Table 6: Comparison of fetal outcome in oral and intramuscular group

		Oral (N = 61)		*IM (N = 63)*	
Sl. No.	*Fetal outcome*	*No.*	*%age*	*No.*	*%age*
1.	Low birth weight	2	3.28	1	1.59
2.	APGAR score <7	6	9.84	2	3.17
3.	Admission to NICU	7	11.47	3	4.76

$X^2 = 0.0933$, p value 0.954

Iranian women are at high risk for vitamin D deficiency, Hossein-Nezhad found that 29% of 741 women had 25(OH)D levels <15 nmol/L and the prevalence of GDM in this group was higher compared to women with 25(OH)D levels ≥35 nmol/L.

In our study, a high risk of GDM found in the vitamin D deficiency group (13.33%), compared to the normal vitamin D group (6.67%), in which no statistically significant difference could be found in the incidence of GDM Tables 4 and 5.[17]

In present study, preterm birth was found only in vitamin D deficiency group (6.67%); none of the cases were present in normal vitamin D group; however, the difference in preterm birth in both groups was not statistically significant (p value 0.922).

Recently, a study conducted by Gernand et al. found that first-trimester 25(OH)D levels are associated with small-for-gestation age. But they found no relationship between second-trimester 25(OH)D levels and small-for-gestation-age fetus.[10]

In our study, there was no significant difference among normal vitamin D and vitamin D-deficient antenatal women giving birth to IUGR babies.

A randomized controlled trial conducted by Brooke et al. has found that third-trimester vitamin D supplementation reduced the risk of small-for-gestation age (15 vs 28%).[18]

In our study, low birth weight babies were more in vitamin D deficiency group (13.33%) as compared to normal vitamin D group (6.67%) Table 6.

Conclusion

There is strong biological plausibility for the role of vitamin D in the pathophysiology of poor pregnancy outcomes. During pregnancy, 25(OH)D diffuses through the placental barrier. The fact that the placenta decidua has vitamin D receptors and expresses 1-a-hydroxylase for the synthesis of 1,25-dihydroxy vitamin D indicates potential links between vitamin D and birth outcomes. In pregnancy, vitamin D deficiency and insufficiency are thought to be common.

Given the high prevalence of low levels of vitamin D in pregnant women, it could be a modifiable risk factor with important public health implications. Supplementation of vitamin D as a part of routine antenatal care needs to be established.

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