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Original Research Article

Role of vitamin D in prevention of adverse maternal and perinatal outcome: a randomized controlled trial

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ABSTRACT

Background: Vitamin D deficiency is thought to be common among pregnant women and is associated with adverse maternal and perinatal outcome. Maternal and foetal outcome in pregnant women with standard obstetric care was compared with women with additional vitamin D supplementation.

Methods: A randomized comparative study was conducted on 100 patients attending the antenatal clinic at JSS Medical College and Hospital, Mysuru, Karnataka, India who were randomly grouped into group A (50 patients) who received standard obstetric care (500 mg calcium+200 IU vitamin D) and group B (50 patients) who received in addition to standard obstetric care supplementation of Vitamin D 1000 IU/day starting from 14 weeks of gestation till delivery. Vitamin D levels were assessed in both the groups with onset of labour by chemiluminescence immunoassay and obstetric and neonatal outcomes in both groups were compared.

Results: High incidence of vitamin D deficiency (96%) in standard care group compared to vitamin D supplemented group ($p < 0.0001$) was noted. The study showed significant reduction in risk of Preeclampsia ($P = 0.004$), GDM ($P = 0.02$) and primary caesarean delivery (0.008) in Vitamin D supplemented group. Significantly high birth weight in vitamin D supplemented group, an increase in 320 grams in birth weight was noted ($P < 0.0001$).

Conclusions: There is a high incidence of subnormal vitamin D levels in antenatal women and is associated with maternal and neonatal adverse effects. Measuring Vitamin D levels and appropriate supplementation of higher dose of vitamin D is an effective strategy in prevention of adverse maternal and neonatal outcomes.

Keywords: Birth weight, Gestational diabetes mellitus, Primary caesarean delivery, Preeclampsia, Vitamin D

INTRODUCTION

Vitamin D deficiency is an unrecognized pandemic common among children, adults and pregnant women throughout the world even in tropical countries.¹⁻⁵ Maternal Vitamin D deficiency has been associated with numerous adverse maternal outcomes such as preeclampsia, gestational diabetes as hormonally active form of Vitamin D has a role in placental development and function, inflammation, angiogenesis, immunomodulation, insulin sensitivity.⁵

Vitamin D deficient mothers have adverse infant and foetal outcomes such as low birth weight, low APGAR scores, hypocalcaemia, rickets as maternal and infant vitamin D levels are highly correlated as vitamin D stores in infant starts with transplacental transfer of 25 (OH) Vitamin D in early pregnancy.⁶⁻¹⁰ The research about Vitamin D related problems had resurfaced the medical world as it is a preventable health problem. Hence understanding of vitamin D deficiency among pregnant women and its offspring is of global health importance.

Screening for Vitamin D deficiency in pregnancy

Current prenatal care does not include the monitoring of Vitamin D levels and no national organisation recommends routine Vitamin D screening and supplementation during pregnancy unless a woman is at nutritional risk.¹¹⁻¹³ As the test is expensive, offering it to all at risk women may not be cost effective compared to offering universal supplementation, particularly as treatment is regarded as being very safe. Women with more than one risk factor for Vitamin D deficiency which includes women with low calcium concentration, bone pain, gastrointestinal disease, alcohol abuse, a previous child with rickets and those receiving drugs which reduce Vitamin D levels should have plasma 25 (OH) Vitamin D level drawn at the beginning of gestation and at mid pregnancy.^{14,15} Due to differences in 25(OH) D measurement techniques and variability of Vitamin D levels in the human body, there is a lack of consensus on the cut off points. The conservatively used cut off points are deficient if <20ng/ml, insufficient if 21-30ng/ml and optimal if > 30ng/ml.⁷

METHODS

The study was conducted at JSS Medical college and hospital, Mysore in Department of Obstetrics and Gynaecology over a period of 23 months from November 2014 to September 2016 after getting approval from Institutional Ethical Committee (IEC). 100 antenatal women attending JSSH who registered in 1st trimester of pregnancy were included in the study and enrolled in pretested proforma and were randomized into group A and group B by computer generated randomized sampling technique after excluding chronic hypertension, overt diabetes, chronic renal disease, chronic liver disease, patients treated with anti tubercular and anti epileptic drugs within past 3 months.

Group A included pregnant women receiving standard obstetric care (SOC) (500 mg calcium +200IU Vitamin

D), group B included pregnant women who received in addition to standard obstetric care, vitamin D supplementation of 1000 IU of cholecalciferol, every day starting from 14 weeks of gestation till delivery. Vitamin D assay were done at the onset of labour. 3ml of plain blood samples were collected and sent for 25 (OH) vitamin D estimation by Chemiluminescent method using instrument Roche cobas e411 and Vitamin D Total kit. Maternal and foetal outcomes were compared in both groups.

Statistical analysis

Statistical analysis was carried out using commercial software SPSS (Statistical Package for Social Science) version 20. Descriptive statistics, t-test for independent samples, chi-square test were performed. Level of significance was expressed as P value < 0.05.

RESULTS

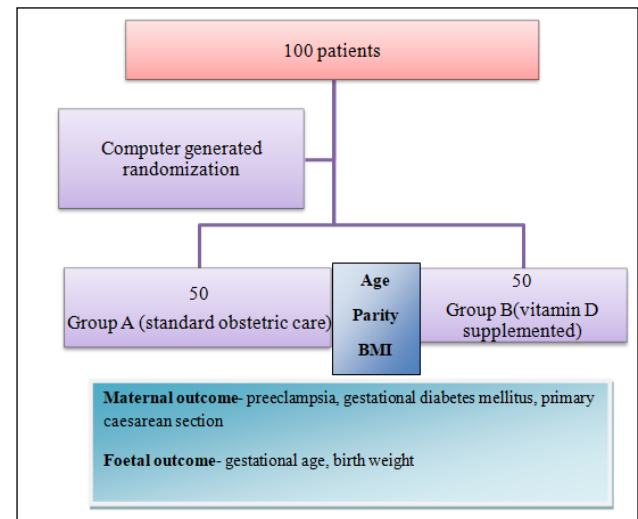


Figure 1: Diagram showing the randomization and follow-up of patients.

Table 1: Comparison of demographic parameters.

Parameter	Standard Obstetric care group		Vitamin D supplemented group	
	N	%	N	%
Age <20 years	6	12	5	10
21-29 years	38	76	39	78
>30 years	6	12	6	12
Mean age (years)	25.8±3.3		25.9±3.2	
BMI- <25 kg/m ²	8	16	7	14
23.1-30 kg/m ²	16	32	17	34
> 30.1kg/m ²	26	52	26	52
Mean BMI(kg/m ²)	29.62±3.41		29.28±2.98	
Parity primigravida	32	64	34	68
multigravida	18	36	16	32

Among the total of 100 patients, 50 patients belonging to group A who received standard obstetric care and the other 50 patients belonging to group B who received additional vitamin D of 1000IU along with standard obstetric care were followed up till delivery. There was no loss of follow up of patients in our study as shown in Figure 1. The results was analysed and compared in both the groups with respect to age, parity, BMI and were

comparable in both groups as shown in Table 1. Maternal outcome analysed in terms of preeclampsia, Gestational diabetes mellitus and primary caesarean section. Neonatal outcome was compared in terms of preterm delivery and birth weight. The significant finding noted in our study was relatively high incidence of vitamin D deficiency (96%) in standard care group compared to vitamin D supplemented group ($p < 0.0001$) as shown in Table 2.

Table 2: Comparison of Vitamin D levels.

Vitamin D levels	Standard obstetric care group		Vitamin D supplemented group	
	N	%	N	%
Vitamin D Deficient	48	96	0	0
Vitamin D Insufficient	2	4	4	8
Vitamin D Sufficient	0	0	46	92
Mean Vitamin D level (IU/dl)	11.24± 5.83		31±2.17 p value:<0.0001	

Table 3: Comparison of maternal outcome.

Outcome	Standard Obstetric care group		Vitamin D supplemented group		P value
	N	%	N	%	
Preeclampsia	17	34	5	10	0.004
Gestational diabetes mellitus	11	22	3	6	0.02
Primary caesarean section	9	18	1	2	0.008

Table 4: Comparison of neonatal outcome.

Outcome	Standard obstetric care group		Vitamin D supplemented group		P value
	N	%	N	%	
Gestational age at delivery <37 weeks	11	22	7	14	
>37 weeks	39	78	43	86	
Mean gestational age (weeks)	37.88		38.88		0.053
Birth weight <2500 grams	15	30	2	4	
>2500 grams	35	70	48	96	
Mean birth weight (grams)	2730±400		3050±320		0.0001

When maternal outcomes were compared in both the groups, the study showed significant reduction in risk of Preeclampsia ($P=0.004$), GDM ($P=0.02$) and primary caesarean delivery (0.008) in Vitamin D supplemented group compared to standard care group as depicted in Table 3. Mean gestational age in both groups were comparable ($p=0.053$) indicating negative correlation between gestational age of delivery and vitamin D status. One more important finding noted was significantly high birth weight in vitamin D supplemented group, compared to standard care group, an increase in 320 grams in birth weight was noted ($P<0.0001$) and the same is shown in Table 4.

DISCUSSION

During pregnancy the requirement of vitamin D is increased, and the synthesis, metabolism and functions of

vitamin D compounds throughout gestation are different. The aim of the present study was to contrast the maternal and neonatal outcomes in the standard obstetric care subjects (group A) with the subjects who received additional 1000 IU of vitamin D daily (group B) starting from 14 weeks of gestation. The most important finding observed in the present study was significantly high incidence of vitamin D deficiency in standard obstetric care group compared to vitamin D supplemented group ($P < 0.0001$). Of the 50 patients who received standard obstetric care, 48(96%) patients showed vitamin D deficiency with mean vitamin D level 11.82 ± 5.83 . In contrast to this, patients who received additional Vitamin D supplementation of 1000IU/day throughout pregnancy starting from 14 weeks, 46(92%) patients showed sufficient Vitamin D levels at the end of delivery with mean vitamin D levels 31 ± 2.17 , ($P<0.0001$). In line with the present study kalra et al and Sahu M et al also showed

significant increase in Vitamin D levels following supplementation.^{16,17} The main difference between study done by Kalra et al and our study was supplementation of single high dose, whereas in the present study same dose was supplemented in divided doses. The results in all the three studies were comparable and 25 (OH) D levels were higher in Vitamin D supplemented groups in all the studies. In this study patients supplemented with 1000 IU/day Vitamin D showed reduced risk of preeclampsia by 24% (10% vs. 34%, $p=0.004$) consistent with Haugen M et al who also observed 27% reduction in risk of preeclampsia after vitamin D supplementation.¹⁸ Ullah et al and Bodnar LM et al also showed that vitamin D deficiency was an independent predictor of preeclampsia and patients with 25 (OH) vitamin D levels $<15\text{ng/mL}$ had a 5 fold increase in the risk of preeclampsia.^{19,20} The incidence of gestational diabetes in pregnant women who were supplemented with 1000 IU vitamin D daily was lower than the group that received 200 IU vitamin D daily (6% vs. 22%, $P = 0.02$). Mojibian M et al, also showed the incidence of GDM in supplemented group was significantly lower compared to controls (6.7% vs. 13.4%, $P=0.01$) which is in comparison with the present study.²

A positive correlation is noted between vitamin D levels and risk of nulliparous caesarean delivery. Vitamin D deficient group showed 18% risk of primary caesarean delivery compared to vitamin D sufficient group 2% , $p = 0.008$. In line with the present study Merewood et al also found an inverse relationship between 25(OH) D levels and risk of having primary caesarean section. Women with 25 (OH) vitamin D levels $<37.5\text{nmol/mL}$ almost carried fourfold higher risk of primary caesarean section.²² Similar findings was observed in a study by Loy SL et al who found risk of emergency caesarean section was greater in Chinese (OR = 1.90, 95% CI = 1.06, 3.43) and Indian women (OR = 2.41, 95% CI = 1.01, 5.73) who are vitamin D deficient.²³ The role of Vitamin D in prevention of preterm labour is controversial. Current study showed no significant effect of vitamin D supplementation on prevention of preterm birth. The mean gestational age of delivery in both the groups were comparable (37.88 ± 1.44 versus 38.38 ± 1.09 weeks, $P = 0.053$). Similar findings were observed in a study conducted by Baker AM et al and Thorp et al.^{24,25} Whereas Bodnar LM et al and Thota C et al showed Vitamin D deficiency is associated with significant risk of preterm delivery.^{26,27} Several studies have reported an association between infant size and vitamin D status. Birth weight is slightly but significantly greater in the neonates of mothers who received vitamin D supplements, compared with those who did not.²⁸⁻³¹ Our study noted 320 gms increase in birth weight in vitamin D supplemented group compared to controls (Mean birthweight: 3050 ± 400 vs. 2730 ± 320 gms, $P < 0.0001$). Scholl et al found pregnant women with vitamin D intakes 200 IU/d had infants with birth weights that were 60g below women with vitamin D intakes at or above 200 IU/d.³²

CONCLUSION

- Decreased risk of preeclampsia, GDM, primary caesarean delivery in vitamin D supplemented group compared to standard care group
- Increase in birth weight by 30g in Vitamin D supplemented group compared to standard obstetric care group
- High incidence of vitamin D deficiency in standard care group.

In view of the high incidence of subnormal vitamin D levels in antenatal women, and increased incidence of maternal and neonatal adverse effects associated with Vitamin D deficiency, vitamin D supplements should be given to all pregnant women during their antenatal visits. The possible limitations of the present study that should be addressed and noted in future studies are unmeasured sun exposure, maternal baseline 25 (OH) D. Also only one blood sample during delivery was obtained, which restricts our ability to evaluate 25 (OH) vitamin D concentrations in other windows. Level of calcium in studied women was an important unmeasured covariate in our study. Therefore, calcium intake may confound an association between maternal vitamin D deficiency and maternal and neonatal outcomes. The sample size of the present study was small and does not represent wide range of population. Due to limited number of interventional studies conducted in this area of interest, future RCTs should consider initiating Vitamin D supplementation early in pregnancy or even before pregnancy with good sample size that control other confounding factors will be necessary to determine a potential role for vitamin D in prevention of adverse maternal and neonatal outcome..

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