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Original Research Article

The effect of vitamin D supplementation on glycemic control in diabetic vitamin D deficient pregnant women

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ABSTRACT

Background: This study aimed to evaluate the effect of vitamin D supplementation on glycemic control in diabetic vitamin D-deficient pregnant women and assess the fetomaternal outcomes and compare the fetomaternal outcomes between vitamin D-supplemented and non-supplemented diabetic pregnant women.
Methods: A hospital-based case-control study was conducted at Kasturba Hospital, Delhi, involving 60 pregnant women diagnosed with gestational diabetes mellitus (GDM) or overt diabetes. Participants were randomized into two groups: one receiving weekly vitamin D3 supplementation (60,000 IU) until delivery and a control group receiving routine antenatal care without vitamin D supplementation. Glycemic parameters, oral hypoglycaemic agent and insulin requirements, and maternal-fetal outcomes were assessed. Maternal outcomes included pre-eclampsia, fetal growth restriction, liquor amount, mode of delivery and fetal outcomes included birth weight, neonatal intensive care unit (NICU) admissions, and neonatal hypoglycaemia. Statistical analysis was carried out using statistical packages for IBM statistical package for the social sciences (SPSS) versus 22 for Windows. Two sided p values was considered as statistically significant at $p<0.05$.
Results: With vitamin D supplementation, improved glycemic control was observed in pregnant women with diabetes with a mean change of fasting blood sugar 21.45 (SD=15.99) in the supplemented group compared to 8.37 (SD=9.88) in the controls with p value <0.001 and the mean change of post prandial blood sugar was 39.13 (SD=41.33) in the supplemented group while the control group had a mean change of 8.93 (SD=40.99) with a p value of 0.006. However, vitamin D supplementation does not change the maternal and fetal outcomes of pregnancy in diabetic mothers.
Conclusions: Vitamin D supplementation in diabetic vitamin D-deficient pregnant women improved glycemic control. Universal supplementation is recommended for all diabetic pregnant women along with adequate sun exposure and consumption of vitamin D rich foods.

Keywords: Vitamin D, Gestational diabetes mellitus, Glycemic control, Pregnancy, Insulin resistance

INTRODUCTION

Diabetes during pregnancy, including pre-existing diabetes and gestational diabetes mellitus (GDM), significantly impacts maternal and fetal outcomes. GDM is defined as varying degrees of severity of carbohydrate intolerance with onset or first recognized during pregnancy.[1] It is shown that vitamin D acts directly on pancreatic beta cells through expression of vitamin D receptors and also through the enzyme 25[OH]D-1-alfa hydroxylase, both of which help regulate intracellular calcium levels, enhancing insulin secretion and reducing inflammation associated with insulin resistance.[2] Vitamin D has both anti-inflammatory and immunomodulatory properties that help in controlling systemic inflammation. Since inflammation is a key component in insulin resistance, vitamin D's ability to attenuate inflammation may contribute to improved glucose metabolism in GDM.[3]

Several studies, including cohort, observational, and randomized controlled trials, have been done with conflicting results and conclusions, with limited research

on the fetomaternal outcomes. This study aimed to assess the impact of vitamin D supplementation on glycaemic control and fetomaternal outcome in diabetic pregnant women who were vitamin D deficient.

METHODS

This hospital-based case control study was conducted at the Department of Obstetrics and Gynecology, Kasturba Hospital, Delhi, from August 2023 to October 2024.

Study population

Pregnant women with overt diabetes mellitus, gestational diabetes mellitus in 24-28 weeks of gestation, including both primigravida and multigravida, were recruited at antenatal clinic according to inclusion and exclusion criterion.

Inclusion and exclusion criteria

Inclusion criteria

Pregnant women with pre-gestational diabetes, overt diabetes, and gestational diabetes, both primigravida and multigravida, and gestational period of 24-28 weeks were included.

Exclusion criteria

Multifetal pregnancy, and pregnant women with hypertension, chronic kidney or liver disease, or any other medical disorder were excluded.

The participants fulfilling the inclusion and exclusion criteria were randomized into two groups, group A and group B. Pregnant women belonging to group A were screened for vitamin D deficiency in the first contact. Those who were found to be vitamin D deficient were supplemented with 60,000 IU of vitamin D3 sachet weekly till delivery with maximum of 8 doses. The participants were followed up for antenatal check-up and weekly by telephonic call to remind them to take vitamin D3 sachet as per schedule. A venous blood samples were taken and estimation of the plasma blood glucose levels were done 2-4 weekly after vitamin D supplementation and any change in the oral hypoglycaemic drugs and insulin were noted. They were informed to report any side effects including constipation, abdominal pain, nausea, vomiting, and skin rash if any. They were followed up till delivery.

Pregnant women belonging to group B were given routine antenatal care, and vitamin D level estimation was done at term or at the time of delivery (as it is not ethical not to supplement vitamin D if vitamin D deficiency was detected in the antenatal period).

Pregnant women belonging to both group A and group B, including those found to be vitamin D sufficient, were given routine antenatal care and advised to follow a diabetic diet and regular physical exercise and intake of the medication as advised. The summary of the study design is illustrated in Figure 1.

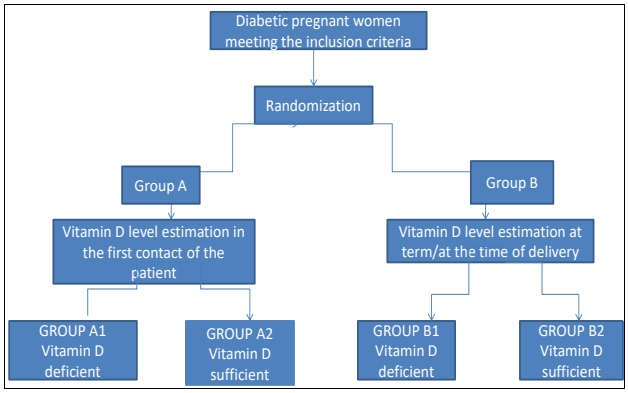

Figure 1: Summary of the study design.

Data collection

Blood samples were collected at baseline and at regular intervals (twice weekly) post-supplementation. Glycemic control, mode of delivery, maternal and fetal outcomes were compared between vitamin D supplemented group and non-supplemented group.

Statistical analysis

Data were analysed using statistical package for the social sciences (SPSS) versus 22 for Windows. Continuous and categorical variables were expressed as mean±SD and percentages, respectively. Two-sided p values were considered as statistically significant at $p<0.05$.

RESULTS

Group A were screened for vitamin D deficiency and 30 were found to be deficient and labelled as group A1 (cases) and were supplemented with vitamin D3 sachet 60,000 IU weekly till delivery. Group B were given routine antenatal care and were screened for vitamin D deficiency at term or when they were admitted for delivery and were studied as control (Ggroup B1). The comparison between these two groups was conducted in terms of glycemic control, mode of delivery, maternal and fetal outcomes.

The baseline characteristics of cases and controls are shown in Table 1. The baseline characteristics of cases and controls were comparable, except that the cases group had a higher number of pregnant women diagnosed with overt diabetes mellitus compared to the control group.

In the present study, the mean baseline levels of vitamin D were comparable in both the cases (supplemented group) and the control group. It can be concluded that vitamin D supplementation effectively increases serum 25(OH)D levels, as evidenced by the significant rise in the supplementation group compared to the control group.

A significant difference in the changes in fasting blood sugar between the case and control groups was seen in the present study. With a mean change of 21.45 (SD=15.99) in the cases, compared to 8.37 (SD=9.88) in the controls, and a p value <0.001, this suggests that fasting blood sugar levels were significantly better controlled in the case group. Also, a significant difference in the changes in postprandial blood sugar between the case and control groups was seen. In the case group, the mean change was 39.13 (SD=41.33), while the control group had a mean change of 8.93 (SD=40.99). With a p value of 0.006, this difference is statistically significant, indicating that the case group had better control of postprandial blood sugar levels compared to the control group. However, vitamin D supplementation did not significantly impact the need for insulin or oral hypoglycemic medications which is reflected by higher number of patients requiring metformin and insulin in the supplemented cases group. Out of 30 cases, 18 patients (60%) required oral hypoglycemic agents (OHA), while 12 patients (40%) did not. In the control group of 30, 11 patients (36.7%) required OHA, and 19 patients (63.3%) did not. But the p-value of 0.07 indicates that the difference between the two groups is not statistically significant. The observed results may also be influenced by the higher number of overt diabetes mellitus (DM) cases in the case group compared to the control group.

Maternal outcomes

In our study, although 6.7% of the study group (2 out of 30 patients) developed pre-eclampsia compared to 0% in the control group, the p-value of 0.15 indicates that this difference is not statistically significant. In both groups, 93.3% of patients had adequate amniotic fluid levels. In the case group, 3.3% had decreased liquor and 3.3% had increased liquor. In the control group, 6.7% had increased liquor, with no cases of decreased liquor. Among the 30 cases, 20 patients (66.7%) required a lower segment cesarean section (LSCS), while 10 patients (33.3%) had a vaginal delivery. In the control group, 19 patients (63.3%) underwent LSCS, and 11 patients (36.7%) delivered vaginally. The p-value was 0.78, indicating no statistically significant difference between the two groups regarding the mode of delivery. There were more LSCS due to foetal indications in control group and more LSCS due to maternal indication in cases group as shown by Figure 1. However, the p value was 0.408, which is not statistically significant.

Table 1: Baseline characteristics of cases and controls.

Variables	Cases (supplemented group)	Control (non-supplemented group)	P value
Age (years)			
20-25	7	9	0.841
26-30	14	13	
>30	9	8	
Mean	28.60±3.59	28.1±34.10	
Religion			
Muslim	21	27	0.104
Hindu	9	3	
Education			
Upto 8th class	13	**7**	0.107
9-10th	9	11	
11-12th	3	9	
Graduation	5	3	
Socioeconomic status			
Low class	1	6	0.079
Lower middle class	3	0	
Middle class	23	22	
Upper middle	3	2	
Nature of work			
Moderate	27	29	0.301
Sedentary	3	1	
BMĪ (mean value)	25.04±4.35	25.61±3.06	0.585
Family history of DM			
Yes	6	4	0.152
No	24	26	
Dietary history			
Veg	28	27	0.64
Non veg	2	3	

Continued.

Variables	Cases (supplemented group)	Control (non-supplemented group)	P value
Previous history of GDM			
Yes	2	2	1.0
No	28	28	
Overt DM			
Yes	9	1	0.006
No	21	29	
Baseline vitamin D levels	24.19 with SD 5.59	23.08 with SD 8.77	0.562
Vitamin D level pre- and post-supplementation	Pre-supplementation-14.19, SD 4.63, post-supplementation-24.19, SD 5.59	Not applicable	<0.001

Table 2: Blood sugar changes, OHA, and insulin requirement.

Parameters	Cases	Controls	P value
Changes in fasting blood sugar (mean)	21.45 with SD 15.99	8.37 with SD 9.88	<0.001
Changes in post prandial blood sugar (mean)	39.13 with SD 41.33	8.93 with SD 40.99	0.006
OHA requirement			
Yes	18	11	0.07
No	12	19	
Insulin requirement			
Yes	8	3	0.095
No	22	27	
OHA+insulin			
Yes	8	2	0.08
No	22	28	

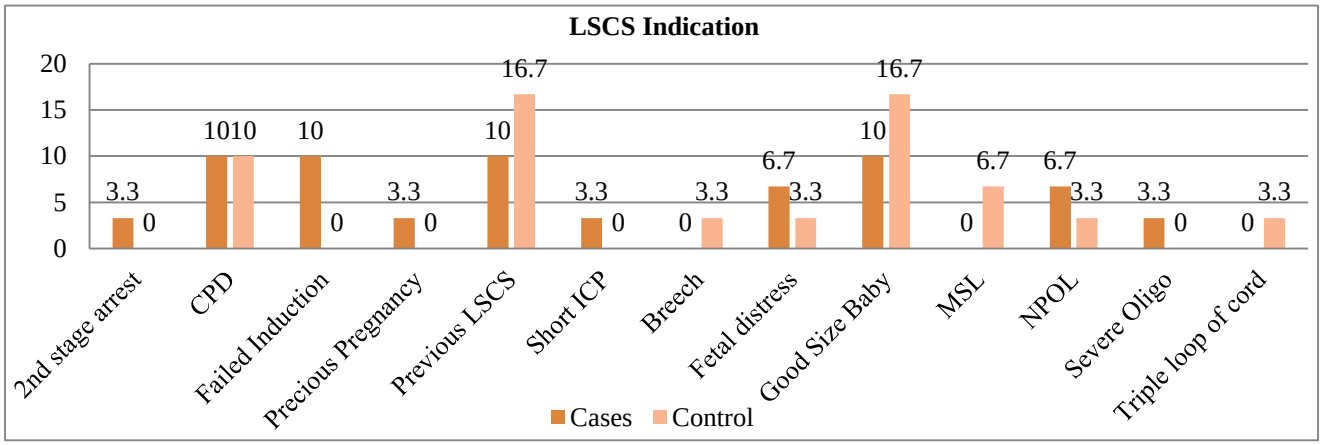

Figure 1: Indications of LSCS.

Table 3: Maternal outcomes.

Maternal outcomes	Cases	Controls	P value
Pre-eclampsia			
Yes	2	0	0.15
No	28	30	
FGR			
Yes	1	0	0.313
No	29	30	
Liqour amount			
Adequate	28	28	0.513

Continued.

Maternal outcomes	Cases	Controls	P value
Oligohydramnios	1	0	
Polyhydramnios	1	2	
Mode of delivery			
LSCS	20	19	0.787
NVD	10	11	

Fetal outcomes

The mean birth weight for cases was 3.03 kg and 3.05 kg for controls with p value of 0.9. The occurrence of macrosomia was low in both groups. In the case group, 1 patient (3.3%) had 86 macrosomia. In the control group, 2 patients (6.7%) had macrosomia. The mean Apgar score at 1 min in cases was 7.93 and 7.9 with p value of 0.7 and mean Apgar score at 5 min in cases group was 8.86 and 8.86 in control group with p value of 1.0. All the p values for these parameters are statistically not significant. Out of 30 cases, 1 baby (3.3%) needed NICU admission and out of 30 controls, 2 babies (6.7%) needed NICU admission. Out of 30 cases, 1 baby was admitted in NICU for 1 day (3.3%) and out of 30 controls, 2 babies were admitted for 1 day in NICU (6.7%). Out of 30 cases, none of the babies had neonatal hypoglycaemia and out of 30 controls, 1 baby (3.3%) had neonatal hypoglycaemia. The p value was 0.3 which is statistically insignificant (Table 4).

Table 4: Fetal outcomes.

Fetal outcomes	Cases	Controls	P value
Macrosomia			
Present	1	2	0.554
Absent	29	28	
Birth weight			
Mean value	3.03	3.05	0.905
Apgar score 1 min			
Mean value	7.93	7.90	0.703
Apgar score 5 min			
Mean value	8.86	8.86	1.0
NICU admission			
Yes	1	2	0.554
No	29	28	
Duration of stay			
1 day stay	1	2	0.801
No stay	29	28	
Neonatal hypoglycaemia			
Yes	0	1	0.313
No	30	29	

DISCUSSION

Adequate vitamin D levels play a crucial role in maternal and fetal health, as vitamin D supports immune function, cell growth, and bone health. Vitamin D deficiency has been linked to an increased risk of preeclampsia, insulin resistance and gestational diabetes mellitus, increased frequency of caesarean section and adverse fetal outcomes including low birth weight and impaired bone development. Pregnancy increases the body's demand for vitamin D, making sufficient levels crucial during this time. In cases of deficiency, especially when coupled with risk factors for GDM, vitamin D insufficiency could further exacerbate insulin resistance. However, while some studies support a positive association between adequate vitamin D levels and improved glycemic control in GDM, the global research findings on this association remain inconsistent.

This study was a case-control study which aimed to evaluate the impact of vitamin D supplementation on glycemic control in pregnant women with GDM and overt DM who were vitamin D deficient.

The mean vitamin D level increased significantly after supplementation, rising from 14.19 ng/ml (SD=4.63) before supplementation to 24.19 ng/ml (SD=5.59) after supplementation of 60,000 IU vitamin D3 weekly. However, the observed increase was not sufficient to restore serum 25(OH)D levels to the normal range. This suggests that higher doses, increased frequency, or longer supplementation periods may be necessary to achieve and maintain optimal vitamin D levels in deficient individuals. Improvement in levels of vitamin D after supplementation has also been observed in the previous studies by Asemi et al and Karamali et al.[4,5]

With vitamin D supplementation, better glycemic control was achieved in pregnant women with diabetes, as evident by improved fasting blood glucose (mean change of 21.45) and post prandial blood glucose levels (mean change of 39.13) in the supplemented group compared to those in a control group. This is in alignment with the findings by Asemi et al, where a significant decrease in fasting blood glucose levels was seen in the supplemented group.[4] However, in a study by Yap et al, after despite supplementation of low dose 400 IU vitamin D and high dose 5000 IU vitamin D, mean fasting blood sugar levels and post-prandial blood sugar levels were not different with p value of 0.72 and 0.42 respectively.[6]

Even though the glycaemic control was found to be better in the vitamin D supplemented group, vitamin D supplementation did not significantly impact the need for insulin or oral hypoglycemic medications which is reflected by higher number of patients requiring metformin (60%) and insulin (26.7%) in the supplemented group. A study conducted by Bhavya et al also showed that

vitamin D supplementation did not reduce the requirement for insulin or oral hypoglycemic agents.[7]

In terms of maternal outcomes, vitamin D supplementation in diabetic pregnant women did not have a significant impact on the maternal outcomes in terms of pre-eclampsia, FGR, polyhydramnios, oligohydramnios and mode of delivery. This finding is consistent with the previous study by Karamali et al, where maternal outcomes were assessed after supplementation and no significant difference in pre-eclampsia and maternal polyhydramnios was found.[5] They also demonstrated that calcium and vitamin D supplementation among pregnant women with GDM was associated with a reduced rate of caesarean sections. Women treated with Ca + vitamin D had a significant decrease in caesarean section rate (23.3% versus 63.3%, p=0.002). However, this is not in agreement with our study, we did not find a decrease in the rate of caesarean sections (66.7%).

No significant differences were found in neonatal outcomes in terms of birth weight, Apgar score, need for NICU admission, and neonatal hypoglycaemia after vitamin D supplementation in diabetic pregnant women. A study by Bhavya et al also concluded that vitamin D supplementation did not improve neonatal outcomes in diabetic pregnant women.[7] However, Benaim et al conducted a cohort study to study the association of vitamin D during pregnancy and birth outcomes.[8] Vitamin D levels (25(OH)D) were found to be directly associated with the risk of preterm birth across all trimesters, with incidence-rate ratios (IRRs) of 1.02, 1.05, and 1.04 for the 1st, 2nd, and 3rd trimesters, respectively. Additionally, the mean rate of change in 25(OH)D during pregnancy was positively associated with birth weight z-score, LGA risk, and preterm birth risk.

CONCLUSION

Given that a high proportion of women with gestational diabetes are vitamin D deficient and insufficient, universal supplementation is recommended for all diabetic pregnant women along with adequate sun exposure and consumption of vitamin D rich foods. Universal supplementation is a cost-effective approach compared to the expense of screening and selectively supplementing only those found deficient. This strategy could help ensure adequate vitamin D levels across this population, potentially help in achieving better glycemic control during pregnancy without the added costs of individualized screening. To better understand the impact of vitamin D supplementation in women with GDM, robust randomized controlled trials (RCTs) with adequate statistical power are essential, focusing on maternal and fetal outcomes. Larger RCTs are needed to evaluate the impact of higher doses of vitamin D or elevated 25(OH)D levels on health outcomes for mothers with GDM and their infants.

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