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ORIGINAL ARTICLE

The Effect of Vitamin D Supplementation on Improving Glycaemic Control in Diabetic Vitamin D-Deficient Pregnant Women: A Single-Blinded Randomized Control Trial

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Abstract

Introduction Gestational diabetes mellitus is one of the most common conditions complicating pregnancy. Vitamin D deficiency is closely associated with gestational diabetes mellitus.

Objectives To study the effect of vitamin D supplementation on diabetic pregnant women with vitamin D deficiency.

Methods This randomized controlled study was conducted with 100 diabetic pregnant women. They were randomized into group A and group B. Group A were screened for vitamin D deficiency once diagnosed with GDM of which 40 were found to be deficient and allotted to group D ($n=40$) and were supplemented with 60,000 units of vitamin D3 per month. Group B were given routine antenatal care and were screened for vitamin D deficiency when they were admitted for delivery, and 39 of them were found to have vitamin D deficiency and were studied as control group C ($n=39$). Ten women in both the groups had normal levels of vitamin D, and one of them was excluded from the study as she had molar pregnancy. The vitamin D supplemented group D and the control group C were matched for age and parity at the baseline.

Results There was a significant increase in the mean insulin and metformin requirements in both the supplemented and control groups. Vitamin D supplementation did not improve the glycaemic control in diabetic pregnant women.

Conclusion Vitamin D supplementation did not decrease insulin resistance or improve the glycaemic control in diabetic pregnant women with vitamin D deficiency.

Keywords Vitamin D deficiency · Gestational diabetes mellitus · Glycaemic control · Vitamin D supplementation · Neonatal outcomes

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying degrees of severity with onset or first recognized during pregnancy [1]. In the general population the role of vitamin D is being explored in view of its role in modulation of several inflammatory pathways which could influence the metabolic control in diabetes [2, 3]. Requirement for vitamin D is increased in pregnancy. Therefore, insufficient nutritional status during this important period of life might increase the risk of GDM. Various studies done across the globe showed that the actual association of vitamin D with gestational diabetes mellitus (GDM) is conflicting [2, 4]. In the Indian context, only few studies were done demonstrating the association of vitamin D deficiency with gestational diabetes and the effect of its supplementation on improving glycaemic control [5]. This study was done to see the

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effect of vitamin D supplementation in diabetic pregnant women who were found to be deficient in vitamin D and the effect of its supplementation on improving the glycaemic control. If vitamin D does indeed have an effect in achieving glycaemic control, it will be a cost-effective and safe intervention that can be applied in all gestational and overt diabetic patients with significant public health benefit. It would open up a plethora of options for wide-scale public policy change including nutritional supplementation during pregnancy.

Objectives

In this trial, we studied the effect of vitamin D supplementation on diabetic pregnant women with vitamin D deficiency.

Materials and Methods

This study was conducted between March 2015 and June 2016 at Obstetrics and Gynaecology Department of Bangalore Baptist Hospital, Karnataka.

The study was powered to detect 0.5% difference in glycaemic control between the groups. The estimated sample size of 50 subjects in each group (total of 100) would give a power of 80% with 95% confidence interval.

This study was a randomized open-labelled trial on 99 pregnant women diagnosed with overt diabetes and gestational diabetes.

The criteria for eligibility were pregnant women with a diagnosis of pregestational diabetes (if diagnosed before pregnancy), overt diabetic (if FBS > 126 mg/dl, HbA1c- > 6.5 and RBS > 200 mg/dl, to be confirmed with FBS or HbA1c), gestational diabetes based on 75 g OGTT (DIPSI)—2 h > 140 mg/dl, 75 gms OGTT (HAPO)—FBS > 92 mg/dl, 1 h > 180 mg/dl, 2 h > 153 mg/dl, 100 gm OGTT (ACOG)—FBS > 95 mg/dl, 1 h > 180 mg/dl, 2 h > 155 mg/dl, 3rd h > 140 mg/dl and gestational glucose intolerance based on 75 g OGTT (DIPSI)—2 h > 120–139 mg/dl.

Pregnant women with multiple pregnancies, hypertension, chronic kidney or liver disease and those not giving consent were excluded from the study.

The summary of the study design is illustrated in Fig. 1. The recruited participants were block randomized by a computer-generated random number sequence into group A and group B by the central randomization team of the research department. Rigour in allocation and concealment was addressed through techniques like central randomization, using sequentially numbered, opaque and sealed envelopes (SNOSE).

Pregnant ladies belonging to group A were screened for vitamin D deficiency as soon as they entered the study. Women in group B were screened for vitamin D deficiency when they were admitted for delivery as it is not ethical to leave them as a control group if vitamin D deficiency was detected in the antenatal period.

Forty women in group A were found to be vitamin D deficient and were included in the supplemented group (group D). They were given 60,000 units of vitamin D3 once a month till delivery. Vitamin D supplementation is not teratogenic, and ACOG guidelines recommend vitamin D supplementation in those who are found to be deficient [5, 6]. A number of Indian trials with 60,000 IU/month indicated better patient compliance as compared to 2000 IU/4000 IU per day doses. There is substantial evidence that a higher dose (60,000 IU) per month does not show any clinical side effects in vitamin D-deficient pregnant women [7]. The participants were contacted every month when they came for their antenatal check-ups or by telephone after the initiation of the trial. This was to ensure that the study medication was taken correctly and to register any adverse events. Telephonic reminders were made to the patients to remind them to take vitamin D capsules as per schedule every month. They were also informed to report any interval morbidity including nausea, vomiting, excessive thirst, frequent urination, constipation, abdominal pain, weakness and confusion.

Both arms were given routine antenatal care. Participants were advised to maintain their usual medical care and life style in the study period. Glycaemic control, medication changes, mode of delivery and neonatal outcomes were recorded.

Group B were screened for vitamin D deficiency when they were admitted for delivery, and those who were found to be vitamin D deficient were included in the control group (group C). At the completion of study glycaemic control, mode of delivery and neonatal outcomes were compared between vitamin D-deficient women in the intervention group (group D) and the control group (group C).

This study was approved by the institutional review board of the hospital.

Statistical Analysis

Statistical evaluations were performed using SPSS. Shapiro–Wilks test, skewness, kurtosis, visual inspection of histograms, box plots, *Q*–*Q* plots when analysed showed that the mean insulin and metformin requirements were normally distributed in the supplemented D group and the control C group. Comparison between the groups at baseline was made using Student's *t* test. Before and after intervention comparison was made by paired *t* test. All statistical tests performed were two sided, and p value ≤ 0.05 was considered statistically significant.

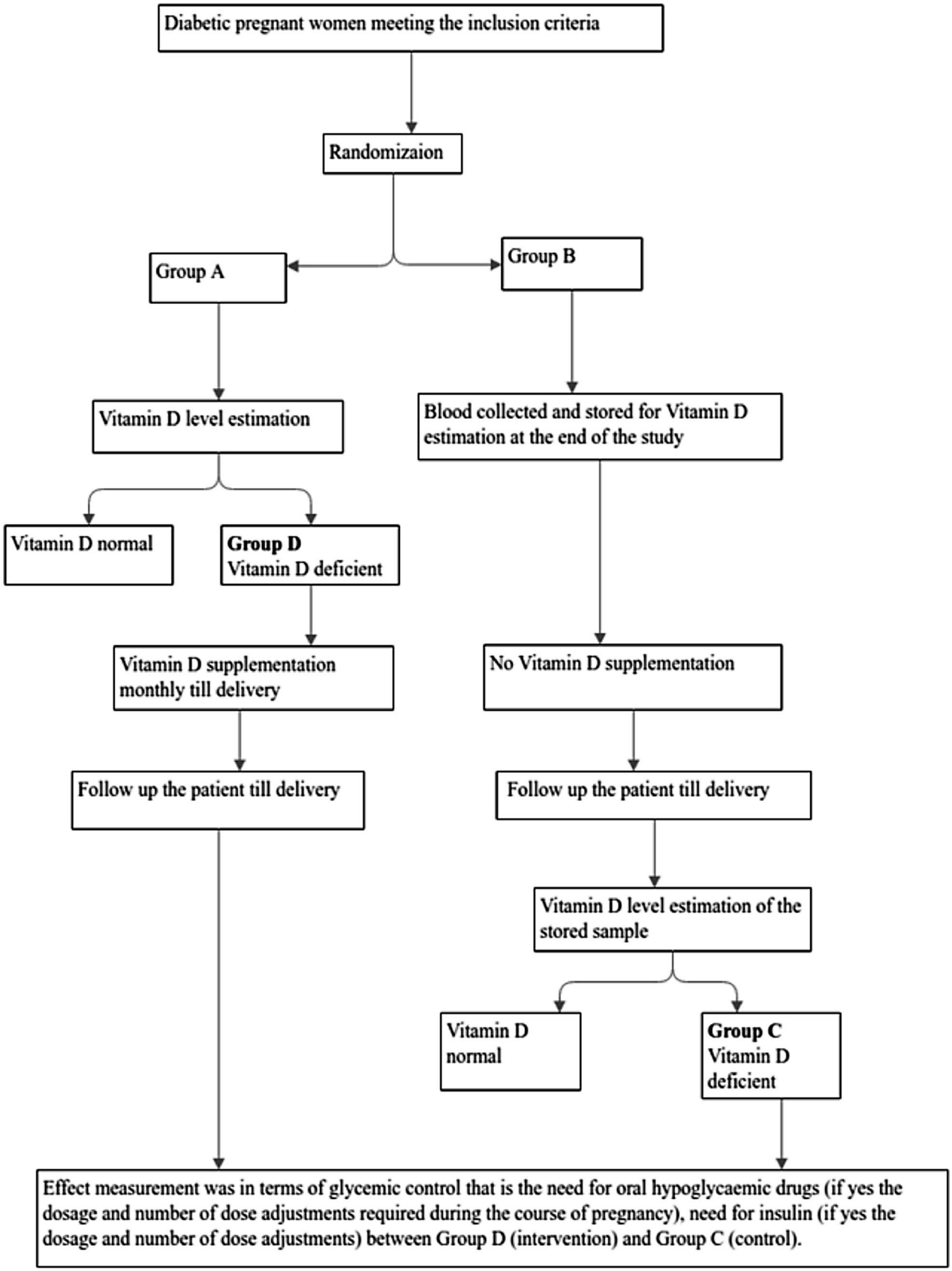

Fig. 1 Summary of the study design

Table 1 Baseline characteristics of group D (supplemented group) versus group C (control group)

	Group D $N=40$	Group C $N=39$	p value
Age (mean ± SD)	28.1 ± 4.4 years	28.3 ± 4.5 years	0.83
Weight (mean ± SD)	73.4 ± 11.8 kg	72.1 ± 9.9 kg	0.58
Height (mean ± SD)	155.5 ± 5.99 cm	156.6 ± 6.29 cm	0.43
BMI (mean ± SD)	30.4 ± 5.3	29.7 ± 4.4	0.54
Gravida			
Primigravida	23 (57.5%)	25 (64.1%)	0.548
Multigravida	17(42.5%)	14(35.8%)	–
Overt DM			
Yes	05(12.5%)	05(12.8%)	0.96
No	35(87.5%)	34(87.1%)	–
H/O GDM in previous pregnancy			
Yes	08(20%)	04(10.2%)	0.37
No	32(80%)	35(89.7%)	–
Family history of DM			
Yes	18(45%)	14(35.8%)	0.48
No	22(55%)	25(64.1%)	–

gravida, family history of diabetes and history of GDM in earlier pregnancies were similar in both the groups.

The baseline characteristics of women, doses of metformin and insulin were comparable between both the groups. At delivery also, the dose of oral hypoglycaemics and number of people on metformin and insulin were comparable between both groups.

Discussion

This study was a single-blinded randomized control trial. This was done to study the effect of vitamin D supplementation in vitamin D-deficient diabetic pregnant women in terms of glycaemic control, maternal and neonatal outcomes.

As shown in Table 2, glycaemic control in the supplemented (group D) and control (group C) group was studied, and it was found that there is no significant difference in the mean metformin and insulin requirements at the time of delivery in the supplemented and unsupplemented groups with p values of 0.06 and 0.55, respectively.

Table 2 Mean requirement of insulin and metformin in (group D) versus control (group C)

	Vit. D no.	Control no.	p value Chi-square	Group D dosage median (range)	Group C dosage median (range)	p value Mann–Whitney U test
Baseline						
Metformin	19	13	0.53	1000 (500–500)	1000	0.14
Insulin	10	10	0.94	14.5, (4–32),	11, (4–45)	0.91
Post-intervention						
Metformin	24	15	0.06	1000, 500–1500	1000, (1000–1500)	0.86
Insulin	17	14	0.554	20, 4–40	13, 6–61	0.37

Results

Hundred diabetic pregnant women meeting the inclusion criteria were recruited for the study and randomized by block randomization into group A and group B. One woman from group B was excluded as her pregnancy was terminated in view of molar pregnancy.

Of the 50 women randomized to group A, 40 were found to be vitamin D deficient. They were included in group D (interventional group) and were given vitamin D supplementation with 60,000 IU per month till delivery. In group B, vitamin D levels were analysed at the time of delivery. Thirty-nine were found to be vitamin D deficient and were included in group C (control group).

The baseline characteristics of the vitamin D-deficient women in group D and group C are shown in Table 1. Age,

To start with, 42.5% of the women in the supplemented group D had their blood sugars controlled with diet alone against 58.9% in the control group C. In total, 32.5% of the women required metformin in group D versus 17.9% in group C. In total, 10% of women in group D and 10.2% in group C required insulin. In total, 15% of women in group D required both insulin and metformin compared to 12.8% in the group C. This is depicted in Fig. 2.

At the end of the study, glycaemic control, need for insulin and oral hypoglycaemics were compared between the supplemented group D and the control group C. It showed that only 30% of the women in group D had adequate glycaemic control with nonpharmacological methods compared to 51.2% in group C. In total, 27.5% in group D required metformin against 15.3% in group C. In total, 12.5% required insulin against 15.3% in group C. In total, 30% of the women

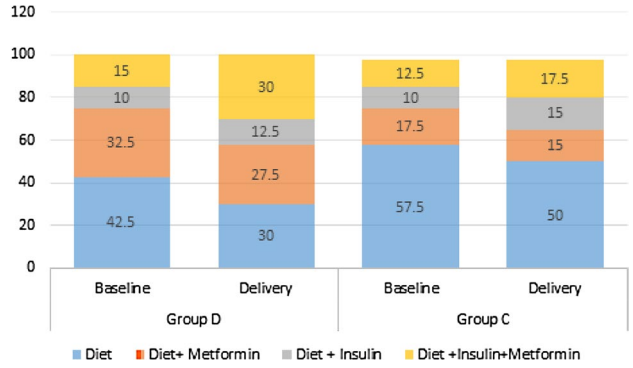

Fig. 2 Glycaemic control in interventional versus control group

When compared with the study done by Asemi et al. [8], in Kashan, Iran, women with gestational diabetes were supplemented with calcium plus vitamin D 50,000 IU twice during the study period and they observed a significant reduction in the plasma glucose levels when compared with the placebo group $p = 0.001$. However, serum vitamin D levels were not measured in this study population. Therefore, we do not know whether the women who were supplemented were actually vitamin D deficient or not.

In our study, only those women with gestational diabetes and vitamin D deficiency were included and given supplementation. We did not find a significant difference between the supplemented and the control groups in terms of glycaemic control or neonatal outcomes, thereby indicating that

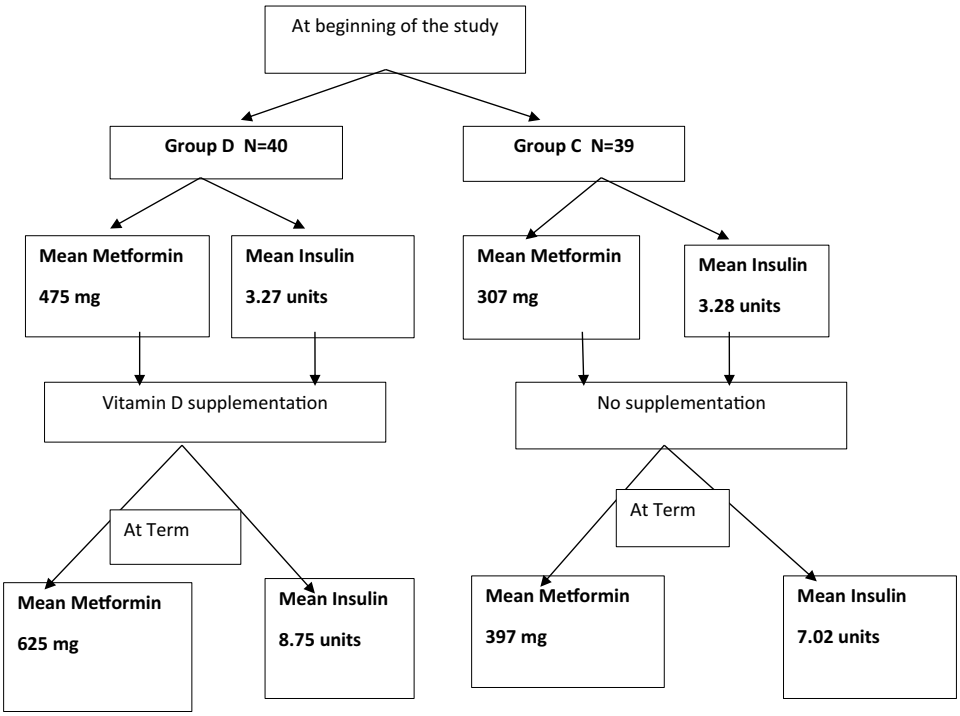

Fig. 3 Mean requirement of insulin and metformin in group D versus group C

in group D required both insulin and metformin compared to 17.9% in the control group C.

As shown in Fig. 3, over the course of pregnancy the insulin resistance and the need for insulin and metformin increased in both the groups. Vitamin D supplementation did not bring about a decrease in the requirement of insulin and oral hypoglycaemic agents. Overall, the women in group C are observed to have a better glycaemic control compared to the vitamin D supplemented group. This may be attributed to the chance effect due to the limited number of diabetic pregnant women studied here.

As shown in Table 3, when neonatal outcomes were compared between group D and group C, NICU admission rates were less in group D at 12.5% against 20.5% in the control group C.

Table 3 Neonatal outcomes

	Group D	SD	Group C	Chi-square value	*p* value
NICU admission	5 (12.5%)	–	20.5%	0.922	0.337
Neonatal seizures	5%	–	2.5%	0.321	0.571
Low birth weight	3 (7.5%)	0.9	6 (15.3%)	1.03	0.33

vitamin D supplementation in women with gestational diabetes and vitamin D deficiency will not have any significant improvements in glycaemic control or pregnancy outcomes.

When compared with the study done by Lau et al. [9], in Australia, they found that 41% of the women with gestational diabetes were vitamin D deficient. In my study, 100 women with gestational diabetes were screened for vitamin D deficiency and 90% were found to be deficient. This high prevalence of vitamin D deficiency is unacceptable; it may be because of low baseline vitamin D levels in the Indian women compared to their western counter parts. The cut-off used to define vitamin D deficiency may not be applicable to the Indian population. This may also partly explain why gestational diabetes is more prevalent in the Indian population. This mandates that all pregnant women should be screened or supplemented with vitamin D, as vitamin D deficiency predisposes not only to gestational diabetes, but it has a role in the development of pre-eclampsia, neonatal seizures and other long-term effects like osteoporosis.

When compared to the study done by Dawodu et al. [10], in UAE, vitamin D-deficient pregnant women were supplemented with vitamin D 2000 IU and 4000 IU/day till delivery and they found that this dose helped to correct the vitamin D deficiency in them. In our study, vitamin D supplementation was started at around 24–28 weeks of gestation in most of the women with 60,000 IU/month. Vitamin D levels were not tested after supplementation, so we do not know whether the amount of vitamin D supplemented was enough to correct the vitamin D deficiency in them.

Conclusion and Recommendation

Vitamin D supplementation did not decrease insulin resistance or improve the glycaemic control in diabetic pregnant women with vitamin D deficiency.

It did not improve the neonatal outcomes in terms of NICU admissions and neonatal seizures. However, vitamin D supplementation did not cause any adverse effects to the mother or the foetus.

As majority of the women with gestational diabetes (90%) were found to be vitamin D deficient and there were no adverse effects with vitamin D supplementation, universal supplementation of vitamin D is recommended in all diabetic pregnant women. Universal supplementation is cost-effective when compared to screening and supplementation.

This study was done on a small number of women in Karnataka. Therefore, the results obtained in our study cannot be extrapolated to larger populations.

Furthermore, Indian women may have a lower threshold for vitamin D deficiency compared to their western counterparts. A metacentric pan Indian study involving larger number of diabetic pregnant women is needed to define baseline vitamin D levels in Indian population and to come to a conclusive evidence regarding the role of vitamin D on the metabolic profile of women with gestational diabetes.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval An ethical clearance was obtained from Bangalore Baptist Hospital Institutional Review Board on 19 February 2015.

Informed Consent A written informed consent was taken from all the participants. Subjects participated voluntarily with full right to withdraw from the study at any point of time.

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