Introduction

Rising incidence of varying degree of glucose intolerance and diabetes mellitus (DM), especially in certain populations points at environmental trigger acting on an underlying genetic susceptibility. Vitamin D (Vit D) is known to influence insulin secretion and insulin resistance. Vitamin D deficiency during early pregnancy significantly increases the risk for gestational DM (GDM) in later pregnancy. It is well-known that Vit D deficiency is prevalent among pregnant Indian women. With increasing obesity, insulin resistance and better screening protocols, GDM is increasingly being diagnosed in Indian women. Any degree of glucose intolerance is a risk factor for adverse maternal and fetal outcomes in pregnancy. It contributes to prematurity, macrosomia,
congenital anomalies, and neonatal hypoglycemia. It may also contribute to obesity and DM in the offspring later in life. Adverse maternal outcomes include pregnancy-induced hypertension and a heightened risk for subsequent development of Type 2 DM (T2DM). Vit D replenishment restores insulin secretion and sensitivity in patients with Type 2 diabetes with established Vit D deficiency, thus suggesting a role for Vit D in the pathogenesis of T2DM. The data on this subject have shown varied results with some showing positive changes in glucose tolerance and some studies negating any beneficial effect of Vit D. Indian data are lacking on the subject.

We designed this prospective study to assess the frequency of glucose intolerance in varying severity of low Vit D. We intervened with Vit D replacement to study its impact on glucose tolerance in women with GDM.

**Aim and objectives**
1. To compare Vit D status in pregnant women with or without GDM
2. Frequency of GDM in women with Vit D insufficiency and deficiency
3. To reassess glucose tolerance after replacement of Vit D in those women with Vit D deficiency and GDM.

**Subjects and Methods**

This was a prospective, pilot study conducted on women attending the antenatal clinic at a tertiary care center in western India during the period July–September 2014. Women with preexisting DM or glucose tolerance test (GTT) values of fasting blood glucose > 126 mg/dl or 2 h postglucose > 200 mg/dl or those taking metformin for polycystic ovary syndrome (PCOS) were excluded from the study. Women with bad obstetric history (>3 spontaneous abortions), hypertension, renal, or hepatic dysfunction were also excluded. Pregnant women with gestational period < 28 weeks, referred from antenatal clinic for deranged blood glucose during the study period were screened. Informed consent was obtained from the subjects, and the nature of the study explained in the language they understood. All subjects underwent routine antenatal tests as per existing institutional protocol. They were screened for GDM using oral GTT with plasma glucose estimated at 2 h after 75 g glucose ingestion. GDM was diagnosed in women with values greater than as specified (2 h plasma glucose > 140 mg/dl). Out of 78 consecutive pregnant women screened, a total of 59 women were diagnosed to have GDM. Eight of them were excluded from the study due to various exclusion criteria as specified (preexisting DM – 02, on metformin for PCOS – 04, bad obstetric history – 01, hypertension – 01). Remaining 51 women with a gestational period of < 28 weeks were included in the study. In these women, serum 25-OH Vit D level was estimated by radioimmunoassay (RIA) using SR-300 automated RIA machine (ABDIACHEM) (STRATEC Biomedical Systems AG, Birkenfeld, Germany). Vit D deficiency and insufficiency were diagnosed in those with serum 25-OH Vit D levels < 20 ng/ml and 20–29 ng/ml, respectively. Standard advice regarding diet and exercise were given to all those diagnosed to have GDM by the same dietician. Women with Vit D levels below 20 ng/ml were prescribed 60,000 IU of cholecalciferol to be administered orally twice weekly for 4 weeks. GTT was repeated after 6 weeks in these patients. Nineteen women attending the same antenatal clinic with normal glucose tolerance (NGT) were included as controls. Institutional ethical clearance was obtained.

Frequency of glucose intolerance was compared between Vit D sufficient and insufficient/deficient groups. Number of glucose intolerant patients with Vit D insufficiency or deficiency who revert to NGT after the restoration of normal Vit D levels was evaluated. Relevant statistical tests of significance for comparing means and proportions were applied.

**Observations and Results**

A total of 70 pregnant women presenting for antenatal care were studied. Fifty one women were diagnosed to have GDM. Remaining 19 women with NGT were taken as controls.

Baseline characteristics of these two groups with respecting to their age, prepregnancy body mass index (BMI), and gestational period were comparable. Serum 25-OH Vit D levels in the GDM group were significantly lower compared with the group with NGT [Table 1]. However, the frequency of GDM in the group of women with Vit D deficiency and insufficiency was not significantly different from those with normal Vit D. Following standard advice on diet and exercise with Vit D supplementation in women with GDM and Vit D insufficiency or deficiency, there was no significant change to NGT when compared to those with GDM and normal Vit D levels who received similar standard advice on diet and exercise [Table 2].

**Discussion**

We noted a greater frequency of Vit D deficiency in women with GDM compared to those with NGT, whereas they were similar in age, gestational period and BMI. Standard advice on diet and exercise was given to all women with GDM, whereas those with Vit D deficiency received supplementation of Vit D in addition. There was no
Table 1: Baseline characteristics

| Characteristics | GDM (n=51) | NGT (n=19) | P |
|-----------------|------------|------------|---|
| Age (years)     | 26.5 (4.5) | 27 (4.7)   | 0.68 |
| Gestational period (weeks) | 25.2 (3.0) | 24.3 (4.5) | 0.33 |
| BMI (kg/m²)     | 26.2 (3.2) | 25.7 (4.7) | 0.61 |
| Vit D levels (ng/mL) | 24.7 (17.6) | 45.8 (28) | 0.0004* |
| Proportion of patients with Vit D deficiency (%) | 34/51 (67) | 8/19 (42) | 0.09 |

GDM: Gestational diabetes mellitus, NGT: Normal glucose tolerance, BMI: Body mass index, Vit D: Vitamin D, SD: Standard deviation, P<0.05 – Only for Vit D levels

Table 2: Effect of diet, exercise counseling and Vit D supplementation (in women with Vit D deficiency only) on glucose intolerance

| Vitamin D Status | Pretreatment (n) | Posttreatment (n) | P |
|------------------|-----------------|-----------------|---|
|                  | GDM             | NGT             | GDM   | NGT   |
| Vit D deficiency | 34/8            | 30/12           | 0.63 |
| Normal Vit D     | 17/11           | 14/14           |     |
| Total            | 51/19           | 44/26           |     |

Vit D: Vitamin D, GDM: Gestational diabetes mellitus, NGT: Normal glucose tolerance

Although evidence exists about the co-existence of Vit D deficiency and glucose intolerance in pregnancy, the cause-effect relationship and effect of replenishment of Vit D is not clear. The reason for replacement of Vit D not having a significant impact on the reversal of glucose intolerance may be due to various reasons. It is possible that Vit D deficiency is just a chance association without any causative implication due to its high prevalence. Vit D deficiency may be an effect of obesity as has been noted in the literature and hence co-existent with GDM as an effect of obesity. However, in our study, we did not note any difference in BMI between GDM and NGT patients. Effect of intestinal mucosa and its flora causing Vit D deficiency due to malabsorption and GDM is a possibility that needs further study with the recent development of data in this regard.

In this small study, we found that supplementing Vit D reversed GDM in 11.7% of patients with Vit D deficiency, which was statistically similar to those in normal Vit D group (17.6%) following a similar advice on diet and lifestyle modification.

The strengths of this study are its prospective design with intervention to assess the effect of Vit D replacement and comparison with a control group. The relevance of the results in day-to-day clinical practice and present day scenario are immense. The small size of the subject population and open-label intervention were weaknesses of the study. Lack of physical activity as a cause of Vit D deficiency due to less sun exposure and of glucose intolerance may have been a confounder which we did not assess. We replaced Vit D with standard protocol without documenting normalization of serum Vit D levels in those in whom it was replaced which may be a weakness which was mainly due to short duration of time assigned for the study. This study can act as a template for future large studies in this field.

Conclusions

In this pilot study, we found that Vit D deficiency is more frequently associated with GDM than women with NGT during pregnancy. However, replacing Vit D in those with deficiency did not significantly alter the glucose intolerance. This study further highlights the complex interaction between Vit D deficiency and glucose intolerance in pregnancy. It needs a larger, appropriately blinded randomized controlled trial to ascertain the truth. Until then, it will not be prudent to recommend routine screening for Vit D deficiency or its treatment in pregnancy. However, adequate Vit D supplements should be prescribed during pregnancy for its classical benefits on bone and mineral metabolism.

The role of Vit D deficiency in GDM is not clear. Although the association is well recognized, the cause-effect relationship has not been established. In this open-labeled prospective study, we assessed the association of Vit D deficiency with GDM in comparison with a group with NGT and found that Vit D levels were more frequently low in pregnant women with GDM. However, the frequency of GDM was not different in Vit D deficient women compared with those with normal Vit D. The replacement of Vit D did not significantly alter the change to NGT in women with GDM over and above that achieved by diet and exercise counseling. The findings of this study require further confirmation by a larger study addressing its weaknesses.

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