Maternal Vitamin D Deficiency: A Risk Factor for Gestational Diabetes Mellitus in North India

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Abstract

Objective: The aim was to assess maternal vitamin D deficiency in early pregnancy and subsequent risk of developing gestational diabetes mellitus (GDM) in north India.

Methods: Nested case control study was done taking 550 antenatal women. Two maternal blood samples, one at <20 wks and the other at term along with cord blood were taken. Vitamin D was estimated by 25-Hydroxyvitamin D 125 I RIA. Kit and categorised according to ACOG (2011) criteria. Patients were categorised into GDM and control groups as per ADA recommendations. Pearson χ2, ANOVA, linear correlation and logistic regression were used for statistical analysis.

Results: High prevalence (72.8%) of vitamin D deficiency was found in early pregnancy. Serum 25(OH)D concentrations were significantly lower (46% less) in women who subsequently developed GDM compared with controls [mean: 11.93 ± 3.42 ng/ml, 95% CI: 10.7-13.17 ng/ml; vs. mean: 22.26 ± 15.28 ng/ml, 95% CI: 20.0-24.52 ng/ml; p<0.001]. Fasting blood sugar in early gestation negatively correlated with 25 (OH) D level (r=-0.489, p=0.004) and at term gestation (r=-0.435, p=0.013). Women with hypovitaminosis D in early pregnancy were eleven times more likely to have GDM compared to controls (p=0.001; r=11.55). Cord serum 25(OH)D concentrations were also significantly lower among neonates of GDM mothers than of controls (mean, 10.39 ± 2.26 ng/ml, vs. 21.33 ± 14.40; p<0.001). In GDM women, maternal 25 (OH) D concentration at <20 weeks positively correlated with vitamin D concentration at term gestation (r=0.781, p<0.001) and also with cord blood levels (r=0.478, p<0.0001).

Conclusion: Maternal vitamin D deficiency is highly prevalent in early pregnancy and is an independent risk factor for GDM in North India. Further clinical trials are needed to find out whether vitamin D supplementation would prevent or improve glycemic control in women with GDM.

Keywords: GDM; Serum 25(OH) D concentration; Vitamin D deficiency; Neonates; Cord serum 25 (OH) D level; Hyperglycemia and adverse pregnancy outcome; Impaired glucose tolerance in pregnancy

Introduction

The prevalence of Gestational diabetes mellitus (GDM) is increasing globally and India is no exception. According to random National Survey in India (2004), prevalence of GDM is 16.55% [1] and in a hospital survey in 2008, it was found to be 21.6% with GDM and impaired glucose tolerance combined [2]. The known risk factors for GDM include maternal overweight and obesity, race/ethnicity, prior history of GDM, family history of T2DM, history of previous fetal death, macrosomic infant, and increasing maternal age [3]. Recently, it has been found that vitamin D receptors are expressed in large number of other tissues including those involved in the regulation of glucose metabolism, such as muscle and pancreatic beta cells [4,5]. Therefore it was hypothesised that GDM might result from pregnancy induced insulin resistance and impaired secretion to compensate for it. It is pertinent to establish a fool proof association between maternal Vitamin D deficiency and GDM, its exact mechanism, and to know the impact of vitamin D supplementation and its dosage during pregnancy among different sets of population through large case control studies. There is also a gap in knowledge on optimal dosing for pre-existing vitamin D deficiency and the optimal gestational age at which to start the supplementation. Further studies are required during pregnancy not only for maternal skeletal preservation and fetal skeletal formation but also for fetal imprinting that may affect neurological development, immune function, and chronic disease susceptibility soon after birth as well as later in life. The present study was undertaken to assess the vitamin D deficiency in early pregnancy and subsequent risk of GDM.

Materials and Method

A nested case control study was conducted in 550 patients younger than 45 years of age enrolled over a period of two years and attending antenatal clinic before 20 weeks gestation.

Inclusion criteria

All maternal patients attending outpatient clinic who had no pre-existing medical conditions like pre-gestational diabetes mellitus or...
chronic hypertension, women with single intrauterine pregnancy and below 45 years of age were included in this study.

**Exclusion criteria**

The patients with history of diabetes mellitus (Type I, Type II), chronic hypertension, chronic renal disease, previous history of vitamin D intake, fat malabsorption, gastric bypass surgery, diagnosis of cancer, lupus, hepatitis, multiple intrauterine pregnancy, and those taking anticonvulsant drugs were excluded.

Participants completed a questionnaire given by an interviewer at enrolment after written informed consent. The schedule was used to gather information on socio-demographic, anthropomorphic, behavioral characteristics, reproductive and medical histories, socioeconomic status (modified Kuppuswami index). Women were enquired about physical activity from 10 am to 2 pm in sun in the year before the index pregnancy or during pregnancy and to rate the usual intensity of this activity as low (<3 hrs) or high (≥ 3 hrs) according to duration of sunlight exposure. In our study population, only face and arms were exposed to sunlight. Since most of the patients belonged to low socioeconomic status, they didn’t have record of weight in prepregnancy period. So in many cases, weight was taken at first visit and was adjusted for prepregnancy weight. Season of sample collection was adjusted for pre pregnancy weight. Sample of season collection at early and term gestation was same in cases and controls(p<0.001 for overweight and obese patients). 84.3% of the patients were primigravida and 81.2% belonged to urban background (p<0.002) and had intake of multivitamins periconceptionally (p<0.01). Patients likely to develop GDM were vegetarians (p<0.001) and had very low level of physical activity in sun (p<0.001, Table 1).

Urban women had higher incidence of vitamin D deficiency compared to rural women. On taking age group, pre pregnancy BMI, season, diet, calcium intake, socioeconomic status, religion, physical activity in sun, educational level, gravidity, periconceptional multivitamin intake, and place of stay as risk factors, likelihood ratio was 33.775 and R² was 0.921. It meant 92.1% of our 25(OH)D levels were correctly identified. Inclusion of these risk factors only slightly changed overall 25(OH)D concentration in cohort study.

During early pregnancy (<20 weeks) among GDM cases (n=32), all except one (31, 96.9%) had 25(OH)D level less than 20 ng/ml. While in control group, 122 out of 178 women (68.5%) were in vitamin D deficiency range, 19(10.7%) were in insufficiency range, and only 37(20.8%) were in normal range. Maternal serum 25(OH)D deficiency in early pregnancy was significantly and inversely associated with GDM risk with eleven times increased risk after adjustment for education, pre pregnancy BMI, religion and socioeconomic status (p=0.004; relative risk=11.55 (deficient vs. non deficient), 95% CI (1.77-7.47), Table 2). Vitamin D deficiency continued to persist in 31 (96.9%) GDM patients at term gestation also (Table 2). However, among controls at term, 125(70.2%) women had vitamin D level <20 ng/ml, 17(9.6%) had value between 20-30 ng/ml, and only 36(20.2%) had value in normal range. There was again 11 times increased risk of having GDM in a Vitamin D deficient patient than in one with normal pregnancy and it persisted at term also (relative risk =11.55, 95% CI (1.77-7.47), p=0.006).
Table 1: Maternal characteristics

| Maternal characteristics | GDM cases (N=32) | Controls (N=178) | χ² | P value |
|--------------------------|------------------|------------------|----|--------|
| Age(years)               |                  |                  |    |        |
| <25                      | 7(21.9%)         | 86(48.3%)        |    |        |
| 26-29                    | 11(34.4%)        | 48(27%)          |    |        |
| ≥ 30                     | 14(44.7%)        | 44(24.7%)        | 8.368 | 0.015  |
| Pre pregnancy BMI(kg/m²) |                  |                  |    |        |
| <18.5                    | 0                | 4(2.2%)          |    |        |
| 18.5-24.9                | 9(28.1%)         | 116(65.2%)       |    |        |
| 25-29.9                  | 16(50%)          | 58(32.6%)        |    |        |
| ≥ 30                     | 7(21.9%)         | 0                | 38.24 | 0.001  |
| Gravida                  |                  |                  |    |        |
| primi                    | 27(84.3%)        | 68(38.2%)        |    |        |
| multi                    | 5(15.7%)         | 110(61.8%)       | 21.52 | 0.001  |
| Education standard       |                  |                  |    |        |
| <12                      | 5(15.6%)         | 114(64.2%)       | 23.96 | 0.001  |
| ≥ 12                     | 27(84.4%)        | 64(35.8%)        |    |        |
| Periconceptional         |                  |                  |    |        |
| Multivitamin use         |                  |                  |    |        |
| No                       | 2(6.4%)          | 49(27.5%)        | 6.679 | 0.01   |
| yes                      | 30(93.6%)        | 129(72.5%)       |    |        |
| Calcium intake           |                  |                  |    |        |
| No                       | 20(62.5%)        | 16(9%)           | 54.68 | 0.001  |
| yes                      | 12(37.5%)        | 162(91%)         |    |        |
| Physical activity in sun |                  |                  |    |        |
| High (≥ 3 hrs)           | 2(6.2%)          | 52(29.2%)        |    |        |
| Low (<3 hrs)             | 30(93.8%)        | 126(70.8%)       | 12.425 | 0.001  |
| Diet                     |                  |                  |    |        |
| Non veg                  | 2(6.2%)          | 56(31.5%)        | 8.82 | 0.003  |
| Veg                      | 30(93.8%)        | 122(68.5%)       |    |        |
| Smoking                  |                  |                  |    |        |
| No                       | 32(100%)         | 107(93.8%)       | 2.087 | 0.149  |
| Yes                      | 0                | 11(6.2%)         |    |        |
| Residence                |                  |                  |    |        |
| Urban                    | 26(81.2%)        | 107(60.1%)       | 5.22  | 0.002  |
| Rural                    | 6(18.8%)         | 71(39.9%)        |    |        |
| Socioeconomic status     |                  |                  |    |        |
| High                     | 25(78.1%)        | 107(60.1%)       | 3.77  | 0.053  |
| Low                      | 7(21.9%)         | 71(39.9%)        |    |        |
| Season                   |                  |                  |    |        |
| Summer                   | 26(81.2%)        | 25(14%)          |    |        |
| Autumn                   | 0                | 22(12.4%)        |    |        |
| Spring                   | 0                | 71(39.9%)        |    |        |
| Winter                   | 6(18.8%)         | 60(33.7%)        | 20.43 | 0.001  |

Table 2: Association between GDM diagnosis and maternal 25 (OH) vitamin D status at <20 weeks gestation and term gestation

| 25 (OH)D values (ng/mL) | gestational age<20 wks | Term gestational age |
|-------------------------|------------------------|----------------------|
|                         | GDM Cases (n=32)       | Controls (n=178)     | GDM Cases (n=32) | Controls (n=178) |
| <20 (deficient)         | 31(96.9%)              | 122(68.5%)           | 31(96.9%)        | 125(70.2%)        |
| 20-29 (insufficient)    | 1(3.1%)                | 19(10.7%)            | 1(3.1%)          | 17(9.6%)          |
| >30 (normal)            | 0                      | 37(20.8%)            | 0                | 36(20.2%)         |

a) gestational age<20 wks : χ²=11.264; p=0.004; Relative risk ratio =11.55 (deficient vs non deficient) 95%CI (1.77-7.47)
b) Term gestational age: χ²=10.372; p=0.006; Relative risk ratio=11.55(deficient vs non deficient) 95%CI (1.77-7.47)
Figure 2: Maternal serum 25(OH)D concentrations among GDM (n=32) and controls (n=178) at term gestation age (mean ± SD)

| Gestational weeks | N  | Mean ± SD(ng/mL) | 95% Confidence Interval | Interval for Mean |
|-------------------|----|-----------------|-------------------------|------------------|
|                   |    | Lower Bound     | Upper Bound              | P               |
| At <20 wks        | GDM| 11.93 ± 3.42    | 10.702                  | 13.175           | P<0.001          |
|                   | Control | 22.26 ± 15.28 | 20.003                  | 24.524           |                  |
| At Term           | GDM| 11.07 ± 3.021   | 9.989                   | 12.168           | P<0.001          |
|                   | Control | 21.33 ± 14.40  | 19.201                  | 23.462           |                  |
| CORDBLOD          | GDM| 10.39 ± 2.26    | 9.578                   | 11.208           | P<0.001          |
|                   | Control | 20.10 ± 13.44  | 18.114                  | 22.09            |                  |

Table 3: Mean 25(OH) D level (ng/mL) in GDM and control group at <20 wks gestation, at term and cord blood serum.

Thus newborns of GDM mothers were eleven times more prone in comparison to newborns of non-GDM mothers to have hypovitaminosis D (relative risk=11.55).

Table 4: Association between neonatal cord blood 25 (OH) vitamin D level and GDM diagnosis

| Cord serum 25(OH)D (ng/mL) | GDM cases (n=32) | Non GDM controls (n=178) |
|-----------------------------|------------------|--------------------------|
| <15 (deficient)             | 31               | 92                       | 51.7              |
| 15-20 (insufficient)        | 1                | 33                       | 18.5              |
| >20 (normal)                | 0                | 53                       | 29.8              |

Figure 4: Correlation between 25(OH)D (ng/ml) at <20 weeks gestation and fasting blood sugar in GDM and controls.

Fasting blood sugar in early gestation was significantly negatively correlated with 25(OH) D level at <20 weeks, r=-0.489, p=0.004; Figure 4), at term gestation (r=0.435, p=0.013; Figure 5) and neonatal cord blood (r=-0.402, p=0.022).

In GDM patients, 25(OH) D values at less than 20 weeks pregnancy positively correlated with its level at term (r=0.781, p<0.001) and also with neonatal cord blood levels (r=0.478, p<0.001; Figure 6). Similarly...
at term, vitamin D values positively correlated with neonatal cord blood levels \( r=0.694, p<0.001 \); Figure 7

Figure 6: Correlation between serum 25(OH)D concentration at <20 wks and cord blood

Figure 7: Correlation between serum 25(OH)D concentration at term and cord blood

Discussion

This study found a high incidence of vitamin D deficiency (72.8%) in early pregnancy in a tropical country like India in spite of abundant sunlight for most of the year. This paradox can be explained due to many prevalent social and cultural practices e.g. increased urbanisation, poor outdoor activity, greater pollution that preclude exposure of women to sunlight besides absorption of UVB photons by melanin present in skin, reducing Vitamin D synthesis by greater than 90%.

This study also indicates that there is a definite association and 11.55 times increased risk of GDM with hypovitaminosis D during pregnancy. This is because Vitamin D helps in modulating pancreatic beta-cell function and secretion by binding its active form, 1, 25(OH)D to beta-cell vitamin D receptor and thus regulates the balance between the extracellular and intracellular calcium pools [11,12]. Secondly, it leads to increased expression of insulin receptors and enhances insulin responsiveness for glucose transport, thus promoting insulin sensitivity. It is also responsible for regulating extracellular calcium and thus ensuring normal calcium influx through cell membranes and an adequate intracellular calcium pool, which is essential for insulin-mediated intracellular processes in insulin-responsive tissues [13].

Cho et al. found deficient Vitamin D levels (serum (OH) D level<20 ng/ml) in 27.5 and 85% of their normal and pregnant women with GDM respectively, a significant difference. They attributed it to significantly higher production of CYP24A1 protein and messenger RNA expression in placental tissue from patients with GDM. Since CYP24A1 catalyzes both 25(OH)D and bioactive 1,25(OH)2D forms to inactive metabolites, elevated levels of CYP24A1 in the placenta of GDM mothers may play a key role in producing Vitamin D deficiency in them [14].

Zhang et al. showed that a risk of developing GDM was only 2.66 times higher in Vitamin D deficient women in a nested case control trial among 57 GDM and 114 controls. Serum 25(OH)D concentration in GDM cases was 60.5 nmol/L compared to control (75.3 nmol/L) after adjustment of established confounding factors including, BMI [15].

However our study showed low level of 25(OH) D concentration and higher risk for development of GDM \( (rr=11.55, p=0.004) \) which might be explained by genetic factors and higher predisposition for insulin resistance in Asian women. It was further supported in a study by Lau et al. in 2011 who found that Indian subcontinent and Middle Eastern groups had similar levels of serum 25-hydroxyvitamin D (median levels: 49 and 38 nmol/L, respectively) and were significantly lower than those for the East or Southeast Asian and Caucasian groups (median levels: 63 and 62 nmol/L, respectively). He also found negative correlation with fasting blood sugar, 2 hours OGTT and HBA1c [16].

Maghbooli et al. performed a study in 741 women in Iran at gestational age of 24-28 weeks after adjusting age, parity and BMI. There was a significant difference in serum 25-(OH)D concentration between the GDM and normal groups \( (16 \pm 10 \text{ versus } 23 \pm 18 \text{ nmol/L}) \) and between the IGT and normal groups \( (19 \pm 12 \text{ nmol/L versus } 23 \pm 18 \text{ nmol/L}) \). They also found that severe vitamin D deficiency was more common in the GDM group than in the IGT and normal groups (44%, 33%, and 23%, respectively) [17]. At the same time, a study conducted in Australia on 307 women at gestation age of 29 weeks showed that fasting blood sugar negatively correlated with 25(OH) D. GDM patients had 25(OH)D concentration of 48 nmol/L versus 55 nmol/l for normal patients. (odds ratio 1.920) [4] Sohelikhyaan et al. also found that GDM women had 2.66 times increased risk of being Vitamin D deficient compared to controls. However, no correlation was found with fasting blood sugar [5].

Contrary to our study, Farrant et al. found no association between maternal Vitamin D status and risk of GDM in a cross sectional study of 559 women from south India at gestational age of thirty weeks. However, he found negative correlation between 25(OH) D and 30 minutes blood sugar level, after adjustment of age and BMI [18].

Poe et al. in a meta-analysis of four out of seven observational studies have reported a high incidence of vitamin D deficiency (>50%, 25 (OH)<50 nmol/L) in pregnant women with the risk of GDM with an Odds ratio of 1.61 [19].

Our study also highlighted a positive correlation between maternal and neonatal Vitamin D levels \( r=0.661, p<0.001 \). Thus if mother is deficient so is the fetus. Since fetal Vitamin D levels are mainly dependent on maternal concentrations, its deficiency in mother may cause adverse effects in the offspring. Inadequate maternal-fetal transfer of 25-hydroxyvitamin D has been found to cause infantile rickets in a study [20]. Furthermore, milk, the primary source of calcium, is an expensive item in India. In a population which has high
prevalence of Vitamin D deficiency and poor dietary calcium intake, the problem is likely to worsen during pregnancy especially due to repeated cycles of pregnancy and lactation. This is consistent with Indian study by Sachan et al. also showed positive correlation of maternal serum 25(OH)D level with cord blood level (r=0.79, p<0.001) [21]. However, Harinarayan et al. did not find any association between maternal Vitamin D status and the birth size of the newborns in spite of having 60% of their south Indian women with low (<50 nmol/L) 25 (OH) D at 30-weeks gestation [22].

Vitamin D deficiency in mothers may not only cause adverse effects in the growing fetus such as low birth weight and poor post-natal growth, lower bone mineral content, impaired glucose homeostasis [23] but also increase risk of health problems later in childhood in the form of Type 1 diabetes mellitus [24] asthma, and improper bone development [25]. This could be attributed to early programming of childhood bone mass during in utero life [26].

However, there are limitations. Firstly, a possibility that some women might have undiagnosed pre pregnancy glucose intolerance when blood specimens were collected cannot be excluded. Secondly India is a country with high predisposition for insulin resistance leading to vitamin D deficiency. Genetic factors in Asian women further add to it. The role of confounding variables such as race, ethnicity, adiposity etc. might play an important role in establishing an association between Vitamin D deficiency and GDM. Therefore large randomised trials are needed to confirm our results and to find if Vitamin D supplementation could improve glycemic control in women with GDM and reduce the adverse outcome in mother and fetus [27].

**Conclusion**

We conclude that there is high prevalence of Vitamin D deficiency in pregnant women of north India as well as in their newborns and is an independent risk factor for development of GDM. Circulating vitamin D can be modified by food consumption (e.g. fatty fish), supplement, and outdoor sun exposure. Thus Vitamin D supplementation in early pregnancy should be explored as a safe and effective way of preventing GDM and promoting neonatal well-being.

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