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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 χ^2, 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 pre-pregnancy period. So in many cases, weight was taken at first visit and was adjusted for pre pregnancy weight. Season of sample collection was defined as winter (December to February), Spring (March to May), summer (June to August), and autumn (September to November). A history of maternal education (<12 or ≥ 12 std), and Multivitamin intake at least once per week in the periconceptional period (defined as the 3 months before and 3 months after conception) was also taken.

The blood sample was collected aseptically in a 5 ml glass tube. Serum samples were stored at -20°C or lower for estimation of 25 hydroxy vitamin D [25(OH)D] at later stage. Subjects were followed in second and third trimester and at delivery maternal blood and cord blood samples were again collected. After delivery, Medical records were abstracted to ascertain antepartum and delivery events, family history of DM, oral glucose tolerance test result and neonatal outcomes. At this point patients were categorised into GDM group [6] and control group. Among total of 550 women enrolled in the study, 360 returned for follow up at first visit, 110 were subsequently lost in second and third trimester follow up, and 20 had delivery at other hospital or at home. Eleven samples were found to be contaminated and 9 hemolysed. Finally, only those subjects were taken in study, who had at least one sample at less than 20 wks of gestation and one at term along with cord blood sample. Thus only 210 patients had proper follow up till term delivery. 32 women out of them were identified as GDM and 178 were taken as control in the cohort. Mean gestation of sample collection at early and term gestation was same in cases and controls(16 ± 2.2 wks and 37 ± 2.4 wks respectively). According to the recommendations of the American Diabetes Association (ADA) 2004 [6], pregnant women were screened at 24-28 weeks gestation using a 50 gram 1-hour oral glucose challenge test. Those patients who had blood glucose level above the cut-off value (7.8 mmol/L), were followed-up within 1-2 weeks with a 100 g, 3-hr oral glucose tolerance test (OGTT). Women were diagnosed with GDM if two or more of the 100 gram OGTT glucose levels exceeded the ADA criteria: fasting: 5.3 mmol/L; 1-hour: 10.0 mmol/L; 2-hour: 8.6 mmol/L; 3-hour: 7.8 mmol/L. The study was approved by Ethical Committee of the Institute.

Banked serum samples were taken out and subjected to 25-(OH) D 125 I RIA Kit estimation. Serum 25-(OH) D concentrations were measured using DiaSorin enzyme immunoassay reagents and procedures (Metametrix, Norcross, GA). We categorized serum 25-[OH] D concentrations according to criteria of ACOG (2011) for vitamin D sufficiency (≥ 30 ng/ml), insufficiency (20-29 ng/ml) and deficiency (<20 ng/ml) [7]. However in neonates, Vitamin D status was classified according to Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society; Vitamin D [25(OH) D) 20-100 ng/ml: sufficiency, 15-20 ng/ml: insufficiency, 5-15 ng/ml: deficiency, <5 ng/ml: severe deficiency [8-10].

Statistical analysis was done using SPSS 16. Pearson χ^2 statistics was used to compare proportions of women or neonates with vitamin D deficiency by case status. One way analysis of variance was used to compare the significant difference in mean among the group and if this test resulted significant then multiple range test (SNK) was used to find out pair wise difference in means. Linear correlation and regression coefficient was used between maternal 25(OH) D at <20 weeks and term and cord serum 25(OH) D levels. We used binary logistic regression to assess the independent effect of maternal early-pregnancy 25(OH) D concentrations on the risk of GDM. The sample size was calculated assuming the prevalence of hypovitaminosis D as 75%; absolute error 6% at 5% level of significance at two tailed tests. The sample size came out to be 200. Taking dropout of 60%, 550 cases were registered for the study.

Results

GDM patients were in the age group of greater than 30 years (44.7%). Patients who developed GDM later on had higher body mass index (71.9%)from the beginning of pregnancy as compared to 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 R^2 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 age, 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), $p=0.006$).

Maternal characteristics		GDM cases (N=32)	Controls (N=178)	χ^2	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%)	8.62	0.003
	Veg	30(93.8%)	122(68.5%)		
Smoking	No	32(100%)	167(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 1: Maternal characteristics

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 : χ^2=11.264; p=0.004; Relative risk ratio =11.55 (deficient vs non deficient) 95%CI (1.77-7.47)				
b) Term gestational age: χ^2=10.372; p=0.006; Relative risk ratio=11.55(deficient vs non deficient) 95%CI (1.77-7.47)				

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

Serum 25(OH)D concentrations in early pregnancy were 46% lower in women who subsequently developed GDM compared with controls [mean, 11.93 ± 3.42 ng/ml, and 95% CI; 10.7-13.17 ng/ml, vs. 22.26 ± 15.28 ng/ml; 95% CI 20.0-24.52 ng/ml; p<0.001 respectively] independent of age, pre pregnancy BMI, gravidity, socioeconomic status, religion, calcium intake (Tables 2, 3 and Figure 1).

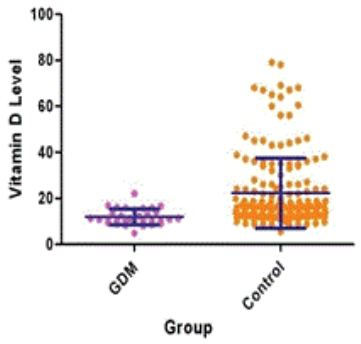

Figure 1: Maternal serum 25(OH)D concentration among GDM(n=32) and 178 controls(n=178) at gestation age<20 wks. (mean ± SD)

Similar vitamin D concentrations were found in women at the time of delivery, which remained almost half (48% lower) in women with GDM compared with controls (mean, 11.07 ± 3.021 ng/ml, and 95% CI, 9.9-12.16 ng/ml, vs., 21.33 ± 14.40; 95%CI 19.20-23.46 ng/ml; p<0.001 respectively; Tables 2, 3 and Figure 2).

On further analysis of GDM mothers with Vitamin D deficiency (n=31), we found that their neonates were also deficient as measured by 25(OH)D concentration in cord blood. 96.9% of neonates of GDM mothers had Vitamin D deficieny, and 3.1% had insufficiency. On contrary, among neonates in control group, 92(51.7%) were deficient, 33(18.5%) insufficient and 53(29.8%) within normal limits. Cord serum 25(OH) D concentrations were also found 51.3% lower among neonates of GDM mothers than among neonates in control group (mean, 10.39 ± 2.26 ng/ml, and 95% CI, 9.5-11.2 ng/ml, vs., 21.33 ± 14.40 and 18.1-22.0 ng/ml; p<0.001, Tables 2, 4 and Figure 3).

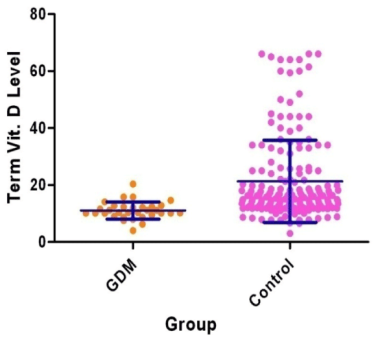

Figure 2: Maternal serum 25(OH)D concentrations among GDM (n=32) and controls(n=178) at term gestation age (mean ± SD)

Gestational weeks		N	Mean ± SD(ng/mL)	95% Confidence Interval for Mean		
				Lower Bound	Upper Bound	
At <20 wks	GDM	32	11.93 ± 3.42	10.702	13.175	P<0.001
	Control	178	22.26 ± 15.28	20.003	24.524	
At Term	GDM	32	11.07 ± 3.021	9.989	12.168	P<0.001
	Control	178	21.33 ± 14.40	19.201	23.462	
CORDBLOOD	GDM	32	10.39 ± 2.26	9.578	11.208	P<0.001
	Control	178	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.

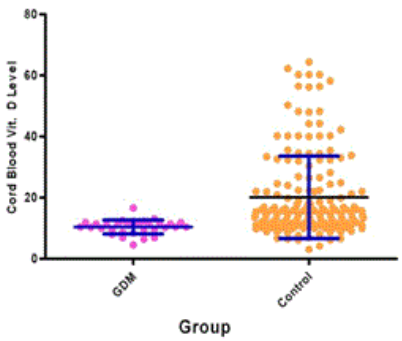

Figure 3: Neonatal serum cord blood 25(OH) D concentrations among neonates of 32

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).

Cord serum 25(OH)D level (ng/mL)	Neonates of GDM cases(n=32)	Neonates of non GDM controls(n=178)		
	No.	%	No.	%
<15(deficient)	31	96.9	92	51.7
15-20(insufficient)	1	3.1	33	18.5
>20(normal)	0	0	53	29.8

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

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).

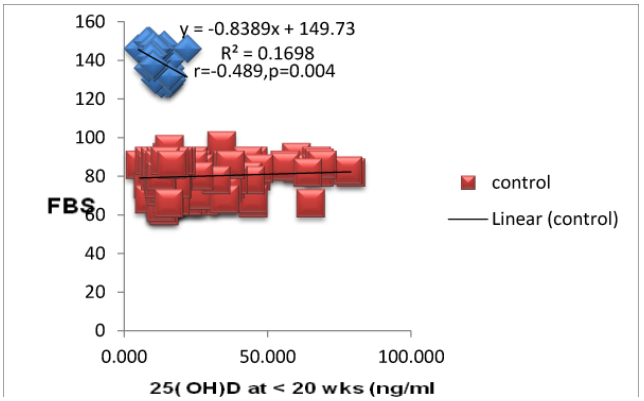

Figure 4: Correlation between 25(OH)D (ng/ml) at <20 wk gestation and fasting blood sugar in GDM and controls.

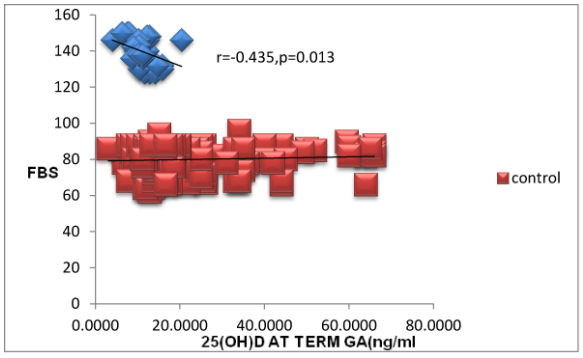

Figure 5: Correlation between 25(OH)D(ng/ml) at term gestation and fasting blood sugar in GDM(n=32) and controls(n=178)

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)

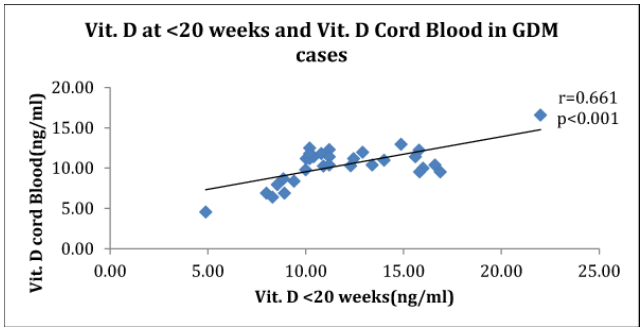

Figure 6: Correlation between serum 25(OH)D concentration at <20 wks and cord blood

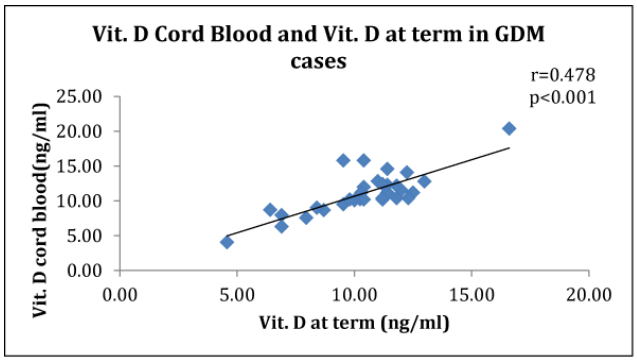

Figure 7: Correlation between serum 25(OH)D concentration at term and cord blood

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 β-cell 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 catabolizes 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 ± 10 versus 23 ± 18 nmol/L) and between the IGT and normal groups (19 ± 12 nmol/L versus 23 ± 18 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].

Poel 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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