ORIGINAL RESEARCH PAPER | Medical Science | Volume : 6 | Issue : 11 | November 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

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

KEYWORDS: 25 OH Vitamin D; Gestational Diabetes Mellitus; HbA1c; Fasting Plasma Glucose; Lipid Profile.

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ABSTRACT *Backgroud: Vitamin D is being increasingly recognized to have multiple non classical actions, such as promoting insulin action , secretion and immune modulation . Nuclear receptors for 1,25(OH)2D are discovered in a range of tissues including bone, intestine, kidney, lung, muscle and skin and pancreatic beta cells. The interaction of 1,25(OH)2D with nuclear vitamin D receptors influences gene transcription. This study aimed to estimate the levels of 25 OH Vitamin D in pregnant women with Gestational Diabetes Mellitus (GDM) and their glycemia control by HbA1c and its comparison with age and gestational age matched controls.*

Methodology: Hospital based case control study with 35 pregnant women diagnosed with GDM were taken as cases and 35 pregnant women age and gestational age matched without GDM were taken as controls. F. Plasma Glucose , HbA1c and Lipid profile were estimated using standard reagents and kits.25 OH Vit D levels were estimated by immunoassay system from Tosoh Biosciences.

Results: Mean serum 25 OH Vit D levels in both the groups were coming <30 ng/ml which indicates vitamin D insufficiency. There was significant difference between 25OH Vit D levels in cases compared to controls with p<0.001. A significant inverse correlation was found between HbA1C and Vit D levels with (r = -0.499, p<0.001) in study group suggesting lower vit D levels in women with GDM have poor glycemic control.

Conclusion: We found that vitamin D level in GDM patients were lower and correlated negatively with HbA1c as a glycemia control marker. Ours being a small study ,we would recommend population wide study of 25 OH Vit D in pregnancy to come to establish its role in GDM and its further inclusion in routine antenatal investigation.

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]. Vitamin D (vit D) deficiency during early pregnancy significantly increases the risk for gestational DM (GDM) in later pregnancy [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]. It is well known that Vit D deficiency is prevalent among pregnant Indian women. [6,7]. 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.

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 [8]. There's a great association between vitamin D deficiency and type 2 diabetes mellitus [9]. In addition, some papers reported a prevalence of inadequate 25(OH) D levels in 41% of the women with GDM, and they consequently proposed routine 25(OH) D testing of all pregnant women when screening for GDM or earlier, and treatment of women who are found to be deficient [10]. It was hypothesised that GDM might result from pregnancy induced insulin resistance and impaired secretion to compensate for it. It is pertinent to establish an association between maternal Vitamin D deficiency and GDM.

The present study was undertaken to estimate levels of 25 OH vitamin D levels in pregnant females diagnosed with GDM and comparing it with age and gestational age matched controls without GDM.

METHODOLOGY: A hospital based case control study was conducted in RMCH & RC ,Ghaziabad. Total of 70 subjects were enrolled from patients visiting antenatal clinic,out of this 35 were diagnosed cases of Gestational diabetes mellitus by OGTT as per ADA guidelines for GDM. All the cases were in 24th-28th weeks of gestation. 35 age matched pregnant females without GDM with 24th-28th weeks of gestation were taken as controls. F. Plasma Glucose ,HbA1c and Lipid profile were estimated using standard reagents and kits on fully automated clinical chemistry analyzer c311 (Roche Diagnostics).25 OH Vit D levels were estimated by immunoassay system from TOSOH AIA series from Tosoh Biosciences.

STASTICAL ANALYSIS:

Statistical analysis was performed using SPSS version 20.0

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software program. Continuous variables were expressed as mean ± SD. Student's t-test was used to assess statistical significance between normally distributed continuous variables. A value of p ≤0.05 was considered statistically significant. Pearson correlation coefficient was used to evaluate associations between serum HbA1C and serum Vit D and Fasting Plasma Glucose.

RESULTS:

Seventy (35 cases & 35 control population) pregnant women in their 24th to 28th week of gestation, consented to participate in this study. They were all comparable regarding the maternal age and gestational age as shown in Table 1

In our study, the fasting plasma glucose level was significantly lower in controls compared to those with gestational diabetes. Lipid profile also showed statistically significant difference between two groups with cholesterol (p<0.001) and triglycerides (<0.01) being higher and HDL cholesterol (p<0.001) being lower in cases compared to controls.(Table 1). We found statistically significant difference in the lipid profile, vit D and HbA1C levels in the two groups . (Table 1)

Mean HbA1C level of pregnant women with GDM was significantly higher than that of pregnant women without GDM (p<0.001). Mean serum 25 OH Vit D levels in both the groups were coming <30 ng/ml which indicates vitamin D insufficiency. Also there was significant difference between 25OH Vit D levels in cases compared to controls (<0.001) Table 2

Table 1: Demographic parameters,FPG and Lipid Profile in Study Population

Parameters	Pregnant women with GDM (cases, n=35) (mean±SD)	Pregnant women without GDM (controls, n=35) (mean±SD)	P Value
Maternal age (years)	24.40±3.77	25.38±3.83	0.107
Gestational age (weeks)	25.2±3	24.3±4.5	0.33
Fasting blood glucose (mg/dL)	93.76±7.15	76.50±4.20	<0.001***
Total Cholesterol (mg/dL)	142.40 ± 26.61	114.40 ± 25.80	<0.001***
Triglyceride (mg/dL)	126.43 ± 23.03	112.60 ± 13.34	<0.01**
HDL (mg/dL)	25.60 ± 4.95	30.77 ± 6.89	<0.001***

*p value ≤0.05 was considered statistically significant;**p<0.01was considered highly significant ;***p<0.001 was considered very highly significant

Table 2: 25 OH Vitamin D and HbA1c Levels in cases and controls

Parameters	Pregnant women with GDM (cases, n=35) (mean±SD)	Pregnant women without GDM (controls, n=35) (mean±SD)	P Value
25 OH Vit D (ng/mL)	14.19 ± 3.67	21.10 ± 5.88	<0.001*
HbA1C (%)	8.20± 0.89	5.32 ± 0.50	<0.001*

* p<0.001 was considered very highly significant

Pearson's correlation coefficient was calculated between 25 OH Vitamin D and Diabetic parameters (FPG and HbA1c). A significant inverse correlation was found between HbA1C and Vit D levels with (r = -0.499, p<0.001) in study group suggesting lower vit D levels in women with GDM have poor glycemic control compared to women without GDM. Also 25 OH Vitamin D and FPG showed negative correlation (r= -0.530 ,p<0.001)(Table 3)

Parameter	Correlation coefficient (r value)	P Value
25 OH Vitamin D and FPG	- 0.530	<0.001
25 OH Vitamin D and HbA1c	- 0.499	<0.001

Table 3: The correlation between 25 OH Vitamin D & FPG and HbA1c in the study group

*p value ≤0.001 was considered highly significant

DISCUSSION:

Vitamin D has been conventionally known to play a role in bone metabolism and mineral homeostasis. Recent data identified roles for the active form of vitamin D (1,25(OH)2D3) in many biological processes including regulation of cellular growth, differentiation and metabolic modulations [11]. Vitamin D insufficiency has a known effect on bone density, neonatal vitamin D and calcium status, and childhood rickets [12]. In several studies, the relation between low vitamin D levels, insulin resistance and impaired insulin secretion was clearly demonstrated [13]. Moreover, specific receptors for 1,25 (OH)2D3 were detected in pancreatic ß cells, denoting a probable effect of vitamin D on the insulin secretion process [14]. In recent years, vitamin D deficiency has been increasingly recognized as one potential contributor of GDM [15].

We noted that pregnant women in study population (cases & controls) were both having vitamin D levels less than the reference range .Also vitamin D levels were significantly lower in cases compared to controls although they were similar in age & gestational period

We found an inverse correlation between fasting blood glucose levels and vitamin D (r = -0.530). Our findings also support an independent inverse association between 25(OH)D and HbA1c in women with GDM, showing a potential interaction between 25(OH)D and poor blood glucose control in pregnancy.

The possible explanation for such relationship, between Vitamin D deficiency and the impaired glycemic control, found in our study could be made attributed to the defect in the important role that Vitamin D plays in glucose homeostasis, and via different mechanisms. The mechanism of action of vitamin D in type 2 diabetes is thought to be mediated not only through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, but it also improves insulin sensitivity of the target cells (liver, skeletal muscle, and adipose tissue). Additionally, Vitamin D enhances and improves β-cell function and protects them from detrimental immune attacks, directly by its action on β-cells, but also indirectly by acting on different immune cells, including inflammatory macrophages, dendritic cells, and a variety of T cells. Macrophages, dendritic cells, T lymphocytes, and B lymphocytes can synthesize Vitamin D, all contributing to the regulation of local immune responses [16].

This correlation between vitamin D and GDM were evaluated by various studies. Maghbooli et al demonstrated

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that maternal serum levels of 25(OH)D during 24-28 weeks of pregnancy were significantly lower in women with GDM compared with controls [17].

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 [18].

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 [19].

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 [20].

More recently meta-analysis, published in 2013, linked gestational diabetes with insufficient 25(OH)D levels, it correlated in addition vitamin D deficiency to preeclampsia, preterm birth and small for gestational age (SGA) babies [21]. In 2013, a randomized controlled study from a Turkish group, on 234 women with GDM and 168 controls, came to a more specific conclusion; they found a statistical significance, between glycemic control and vitamin D levels, only in women with severe deficiency of 25(OH)D levels. They also concluded that only this group (with severe vitamin D deficiency) is at a higher risk of GDM [3].

An important limitation of the present study is the small number of patients with vitamin D deficiency and the single measurement of 25(OH)D levels in the between 24th to 28th week of pregnancy. Other confounding factors included the heterogeneity of dietary habits and the differences in socioeconomic standards between the included pregnant women. This being a study with small sample size ,we would recommend population wide study of 25 OH Vit D in pregnancy to come to establish its role in GDM and its further inclusion in routine antenatal investigation.

CONCLUSION:

In our study, we found that 25 OH Vit D deficiency is significantly more in GDM than women without GDM during pregnancy. This study further highlights the complex interaction between Vit D deficiency and glucose intolerance in pregnancy. Considering this we suggest routine testing of all pregnant women, and treatment of women who are found to be vitamin D deficient.

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