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ORIGINAL ARTICLE

Association of Serum Ferritin Level in Early Second Trimester of Pregnancy with Development of Gestational Diabetes Mellitus: A Prospective Observational Study

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Abstract

Background Gestational diabetes mellitus (GDM) is associated with various maternal and perinatal morbidities. Serum ferritin is a major storage protein of iron and also acts as acute phase reactant which is increased in inflammatory conditions. GDM is a state of insulin resistance and associated with inflammation. The aim of this study was to find the correlation between serum ferritin and development of GDM.

Objectives To determine the serum ferritin concentration in nonanemic pregnant women and its correlation with subsequent development of GDM.

Methodology In this prospective observational study, 302 nonanemic pregnant women with singleton gestation between 14 and 20 weeks, attending antenatal OPD, were enrolled. Serum ferritin was measured at the time of enrolment, and they were followed till 24–28 weeks of gestation and subjected to blood glucose test by DIPSI method. A total of 92 women had blood glucose level ≥ 140 mg/dl and were labeled as GDM, and 210 pregnant women with blood glucose level < 140 mg/dl were labeled as non-GDM.

Result Mean serum ferritin level of women with GDM (56.44 ± 19.19 ng/ml) was found to be higher as compared to non-GDM (27.62 ± 12.11 ng/ml), and this difference was found to be statistically significant ($p < 0.001$). The cutoff value of serum ferritin > 37.55 ng/ml was found to be 85.9% sensitive and 81.9% specific.

Conclusion We can infer that serum ferritin is associated with development of GDM. Based on the findings of the current study, serum ferritin level can be used a predictive marker for the development of GDM.

Keywords Serum ferritin · GDM

Introduction

Gestational diabetes mellitus is a public healthcare problem which affects a large proportion of females till delivery as well as after delivery. It has both short- and long-term consequences for both fetus and mother. Importance of GDM is that two generations are at risk of potential development of diabetes in future.

According to WHO, gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy [1].

Diabetes is a serious disease, and its complications can be devastating. But despite this, with early recognition and treatment of diabetes those complications and disease itself can be prevented or delayed. India, one of the populous country globally, incidence of GDM, is likely to increase to 20%, i.e., one in every 5 pregnant women is likely to have GDM [2]. This high occurrence of GDM among Indian population requests early diagnosis and treatment.

There are no biochemical tests so far available that can forecast the risk of development of GDM. In current time, considerable evidence has suggested that certain serum biomarkers like serum ferritin, SHBG, CRP and adiponectin may serve to foretell the risk of GDM [3].

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Serum ferritin serves as a major storage protein of iron. It is also an acute phase reactant which tends to increase in inflammatory conditions [4]. Studies have shown positive association of concentration of serum ferritin with risk of development of cardiovascular events, risk of insulin resistance syndrome and type 2 DM [5].

GDM is a state of insulin resistance associated with increased level of human placental lactogen, estrogen, progesterone and other placental hormones [6]. The significance of a low-grade inflammatory condition in the pathogenesis of insulin resistance has in recent times turn to evident [7]. Proinflammatory cytokines are related to both impair insulin signaling and reduce insulin release from β-cells of pancreas [8]. These causes lead to insulin resistance [10]. So in this way linkage of serum ferritin with GDM has seen.

Material Method

This study was conducted in the Department of Obstetrics and Gynaecology, in collaboration with Department of pathology, King George's Medical University, Lucknow. It was a prospective observational study, conducted over one year (June 2019–May 2020). Singleton pregnant women with 14–20 weeks of gestation were included in the study. Women with anemia (Hb less than 11 gm/dl), women who diagnose GDM before 20 weeks of pregnancy, type 1or 2 diabetes, hematological disorders (hemoglobinopathy, sickle cell anemia, thalassemia), autoimmune disorders, seizure disorder, malignancies, acute or chronic inflammatory or infective diseases, acute or chronic liver disease or any medical disorder complicating pregnancy, were excluded from the study.

Sample Size Calculation

Sample size is calculated on the basis of comparing proportion of high serum ferritin level (> 60 units) among GDM and non-GDM cases using the formula

$$n = \frac{\left(z_\alpha + z_\beta\right)^2}{[\ln(1-e)]^2}\left[\frac{1-p_1}{p_1} + \frac{1-p_2}{p_2}\right]$$

where $p_1 = 0.063$ (6.3%) the proportion of high serum ferritin level in non-GDM group; $p_2 = 0.649$ (64.9%) the proportion of high serum ferritin level in GDM group.

Coefficient difference $e = 0.6$, considered to be clinically significant.

Type I error, $\alpha = 5\%$

Type II error $\beta = 10\%$ for setting power of study 90%

The sample size was calculated to be $n = 120$ [9]. (Although sample size was 120 but due to availability of patient and time, we took more patients).

After obtaining informed consent, all enrolled women were subjected to detailed history, examination and routine ANC investigations including blood sugar screening.

Two milliliters of blood sample of women was taken in plain vial for serum ferritin measurement. Serum ferritin was measured by ARCHITECT ferritin assay. The ARCHITECT ferritin assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of ferritin in human serum and plasma. Serum Ferritin levels were done by department of Pathology of our University.

All enrolled pregnant women were followed and subjected to blood glucose test by DIPSI (Diabetes In Pregnancy Study Group of India) method between 24 and 28 weeks of gestation (in this test, women has to be given 75gm oral glucose load irrespective of fasting status and after 2 h blood glucose level to be measured).

Enrolled pregnant women with blood glucose level ≥ 140 mg/dl were labeled as GDM, and other pregnant women with blood glucose level < 140 mg/dl were labeled as normal glucose tolerant pregnant women (non-GDM). The statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 21.0 statistical analysis software.

Results

A total of 302 pregnant women were enrolled in the study who fulfilled the inclusion criteria. Out of these, 92 (i.e., 30.5%) women whose blood glucose level ≥ 140 mg/dl were noted as GDM and rest 210 (i.e., 69.5%) pregnant women with blood glucose level < 140 mg/dl were noted as normal glucose tolerant pregnant women/non-GDM. The demographic profiles of study population were noted and are illustrated in Table 1. No difference in maternal age, habitat, educational status, socioeconomic status and dietary habits was observed between the two groups. There were significantly higher proportions of females with GDM as compared to those of non-GDM fall in category of overweight and obese. Mean BMI (pre-pregnant BMI) of Group I (26.59 ± 3.86 kg/m^2) was found to be significantly higher than that of Group II (24.16 ± 2.16 kg/m^2) ($p < 0.001$). In non-GDM women, proportions of nulliparous females were higher as compared to GDM in which higher proportions of primiparous and multiparous were seen. Difference in parity of both the groups was found to be significant ($p = 0.008$) (Figs. 1 and 2).

Level of serum ferritin in study population ranged from 4 to 102 ng/ml. Mean serum ferritin level of Group I (56.44 ± 19.19 ng/ml) was found to be significantly higher ($p < 0.001$) than that of Group II (27.62 ± 12.11 ng/ml) (Table 2).

Table 1 Distribution of groups according to demographic profile

Sn	Variable	GDM ($n=92$)		Non-GDM ($n=210$)		Total = 302	
		No	%	No	%	No	%
1	Age (years)						
	Mean age ± SD (Range)	28.26 ± 4.27		27.33 ± 4.06		27.62 ± 4.14	
	$\chi^2 = 2.202$ (df = 3); $p = 0.532$						
2	Habitat						
	Rural	11	12	27	12.9	38	12.5
	Urban	81	88	183	87.1	264	87.4
	$\chi^2 = 0.047$ (df = 1); $p = 0.828$						
3	Socioeconomic status						
	Lower	17	18.5	28	13.3	45	14.9
	Middle	62	67.4	157	74.8	219	72.5
	Upper	13	14.1	25	11.9	38	12.5
	$\chi^2 = 1.868$ (df = 2); $p = 0.393$						
4	Dietary habits						
	Nonveg	34	37	55	26.2	89	29.4
	Veg	58	63	155	73.8	213	70.5
	$\chi^2 = 3.567$ (df = 1); $p = 0.059$						
5	Nutritional status (BMI kg/m^2)						
	Mean BMI ± SD (Range) kg/m^2	26.59 ± 3.86		24.16 ± 2.16		24.90 ± 3.00	
	't' = 6.962; $p < 0.001$						
6	Parity						
	Nullipara	43	46.7	138	65.7	181	59.9
	Primipara	33	35.9	51	24.3	84	27.8
	Multipara	16	17.4	21	10.0	37	12.2
	$\chi^2 = 9.782$ (df = 2); $p = 0.008$						
7	Educational status						
	Primary	4	4.3	9	4.3	13	4.3
	Middle	1	1.1	4	1.9	5	1.6
	High school	21	22.8	52	24.8	73	24.1

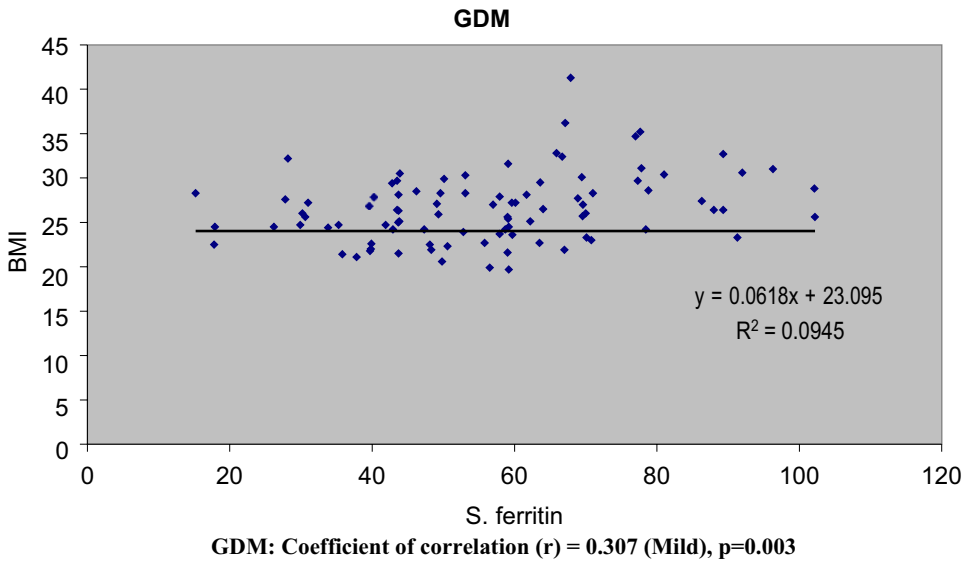

Fig. 1 Correlation between BMI and GDM. GDM: coefficient of correlation (r) = 0.307 (mild), $p = 0.003$

GDM: Coefficient of correlation (r) = 0.307 (Mild), p=0.003

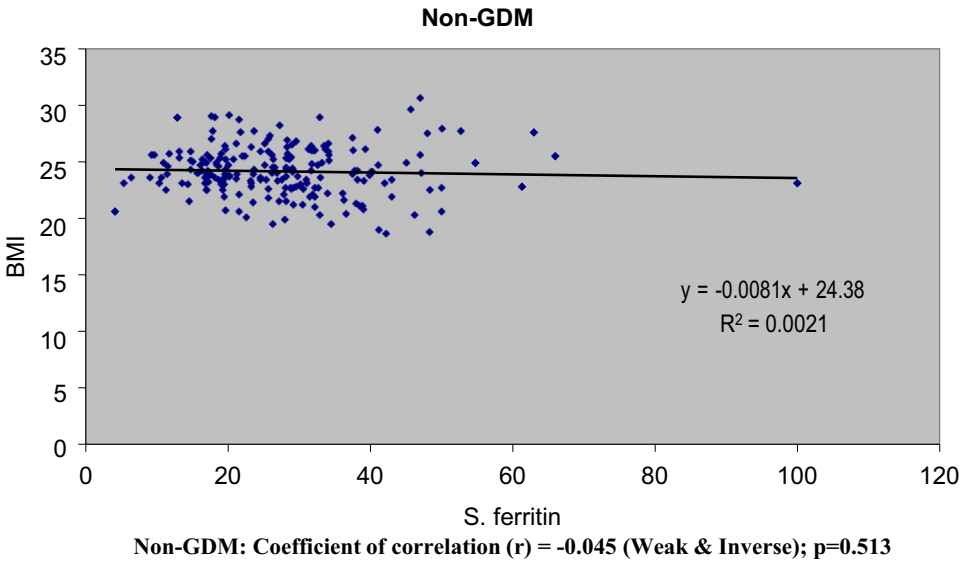

Fig. 2 Correlation between BMI and non-GDM. Non-GDM: coefficient of correlation (r) = −0.045 (weak and inverse); p = 0.513

Table 2 Levels of serum ferritin (ng/ml) in two groups

Group	No. of cases (n = 302)	Min S. Ferritin	Max. S. Ferritin	Mean S. Ferritin	S.D
GDM	92	14	102	56.44	19.19
Non-GDM	210	4	100	27.62	12.11

't' = 15.768; p < 0.001

Linear relationship between serum ferritin level and level of blood glucose (DIPSI method) were observed; i.e., with increasing level of blood glucose, level of serum ferritin is increasing. Serum ferritin level of females with blood sugar 120–139 mg/dl (DIPSI), i.e., with gestational glucose intolerance, was found to be significantly higher (p = 0.015) than those having blood sugar < 120 mg/dl (DIPSI) (Table 3).

In the present study, no significant correlation of serum ferritin with age and dietary habits was found, whereas a significant correlation of serum ferritin with BMI of women with GDM was found (p = 0.002) (Table 4).

In the present study, the predictive accuracy of serum ferritin as a marker for GDM was determined by the ROC (receiver operator curve) analysis (area under curve: 0.904, with 95% confidence interval ranging from 0.865 to 0.944). The value of serum ferritin > 37.55 ng/ml was found to be 85.9% sensitive and 81.9% specific. At this cutoff value, calculated positive predictive value and negative predictive values are 67.5 and 93.0%, respectively (Fig. 3).

Discussion

The mean age of participants with GDM was 28.26 ± 4.27 years and in group of non-GDM was 27.33 ± 4.06 years, and difference was not found to be statistically significant. Most of the women have sedentary lifestyle nowadays, and this may be the reason why GDM is more prevalent between 25 and 30 years in the present study.

Majority of the study population (n = 264; 87.4%) as well as women with GDM (88.0%) and women with non-GDM (87.15%) belong to urban areas; rest of the women were from rural areas. Proportions were almost equal in both of the group; no significant difference was found in terms of habitat.

Table 3 Correlation of serum ferritin level (ng/ml) with blood sugar level

Blood sugar (mg/dl)	No. of cases (n = 302)	Min. S. Ferritin	Max. S. Ferritin	Mean S. Ferritin	S.D
< 120 mg/dl	75	4.11	50.00	24.91	9.66
120–139 mg/dl	135	5.42	100.00	29.12	13.07
140–159 mg/dl	50	15.20	89.30	49.86	16.99
160–179 mg/dl	25	27.80	102.20	61.39	20.56
> 180 mg/dl	17	35.80	102.10	68.54	15.71

F = 75.845 (ANOVA); p < 0.001

Table 4 Association of serum ferritin with demographic profile in both the groups

Sn	Variable	GDM (n = 92)		Non-GDM (n = 210)		Total	
		No	Mean ± SD (S. Ferritin)	no	Mean ± SD (S. Ferritin)	'*t*'	'*p*'
1	Age (years)						
	≤ 20 yrs	3	39.03 + 7.32 (95%CI: 20.86–57.21)	10	29.72 ± 8.15 (95%CI: 23.89–35.54)	1.769	0.105
	21–25 yrs	24	53.09 ± 18.95 (95%CI: 45.08–61.09)	63	25.39 ± 9.56 (95% CI: 22.9–27.79)	9.020	< 0.001
	26–30 yrs	39	58.84 ± 18.84 (95%CI: 52.73–64.96)	93	29.43 ± 14.34 (95%CI: 26.48–32.39)	9.761	< 0.001
	≥ 31 yrs	26	57.96 ± 20.18 (95%CI: 49.81–66.11)	44	26.49 ± 10.49 (95%CI: 23.30–29.68)	8.591	< 0.001
	Within group comparison	$F = 1.340$; $p = 0.267$		$F = 1.655$; $p = 0.178$			
2	BMI						
	Normal	34	49.60 ± 16.27 (95% CI: 43.92–55.28)	140	27.58 ± 12.29 (95% CI: 25.52–29.63)	8.761	< 0.001
	Overweight	42	57.00 ± 19.58 (95% CI: 50.90–63.10)	69	27.41 ± 11.67 (95% CI: 24.61–30.21)	9.986	< 0.001
	Obese	16	69.52 ± 17.72 (95% CI: 60.08–78.97)	1	47.00	1.233	0.236
	Within group comparison	$F = 6.626 =$; $p = 0.002$		$F = 1.296$; $p = 0.276$			
3	Dietary habits						
	Nonveg	34	56.34 ± 17.76 (95%CI: 50.15–62.54)	55	28.62 ± 11.67 (25.47–31.78)	8.891	< 0.001
	Veg	58	56.50 ± 20.13 (95%CI: 51.21–61.79)	155	27.26 ± 12.28 (25.31–29.20)	12.825	< 0.001
	Within group comparison	'*t*' 0.038 =; $p = 0.970$		'*t*' = 0.718; $p = 0.474$			

Proportion of pregnant women with normal BMI was found to be higher among non-GDM women as compared to GDM (66.7% vs. 37.0%) while proportion of overweight and obese were higher in women with GDM as compared to non-GDM. Difference in BMI of pregnant women enrolled in both group was found to be statistically significant ($p < 0.001$). Mean body mass index (BMI) of pregnant women with GDM (26.59 ± 3.86 kg/m^2) was found to be significantly higher as compared to that of non-GDM (24.16 ± 2.17 kg/m^2).

Galal et al. [10] found the mean BMI in women with GDM (28.54 ± 1.26 kg/m^2) as compared to non-GDM (24.50 ± 2.00 kg/m^2, < 0.001). BMI can be used as a predictive factor for GDM. A healthy diet and recommended levels of physical activity can be implemented to prevent overweight and obesity and subsequent development of GDM. In this study, 92 women found to be GDM out of 302, representing 30.5% of women. Level of serum ferritin at 14–20 weeks of gestation ranged from 4 to 102 ng/ml with overall mean serum ferritin level was 36.40 ± 19.74 ng/ml. Mean serum ferritin level of women with GDM (56.44 ± 19.19 ng/ml) was found to be significantly higher as compared to non-GDM women (27.62 ± 12.11 ng/ml), ($p < 0.001$). Although serum ferritin level was found to be lower than other studies, difference between two groups was statistically significant. Similar results were found in study done by Galal et al. [10] and concluded that there was statistically significant increase in level of serum ferritin in pregnant women who developed GDM when compared to pregnant women who did not develop GDM (140.77 ± 8.17 ng/ml vs. 82.56 ± 29.64 ng/ml), respectively($P < 0.001$).

Das et al. [11] conducted a case–control study at the Department of Obstetrics and Gynecology, a tertiary care in a south Indian hospital. They had taken 85 cases of GDM and 85 controls and found that mean serum ferritin level was higher in cases 55.06 ng/ml than in control 31.26 ng/ml. This difference in serum ferritin between cases and control was statically significant ($p < 0.001$).

Sharon et al. [12] did study over 124 GDM and 124 healthy noncomplicated pregnancies that served as controls. The mean serum ferritin levels in GDM were 68. 14 ng/ml ± 15. 63 ng/ml which was significantly higher as

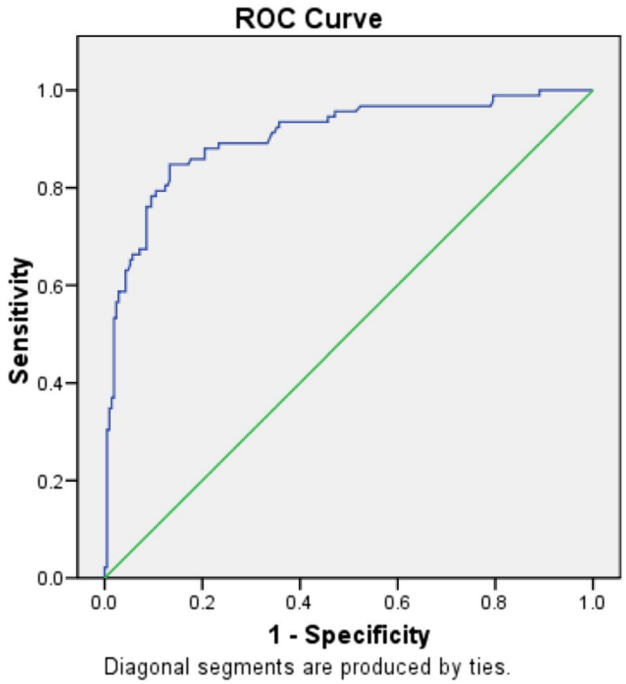

Fig. 3 ROC curve depicting sensitivity and specificity of S. ferritin. Correlation of BMI and S. ferritin levels in GDM cases was found to be of mild level and statistically significant while for non-GDM cases correlation of BMI and S. ferritin was weak and inverse but statistically nonsignificant

compared to that of non-GDM (30. 18 ng/ml ± 06. 02 ng/ml) ($p = 0.0001$). Cheng et al. [13] conducted a prospective, observational study. In this study total, 851 pregnant women between 10 and 20 weeks of gestation took part. The women were divided into four groups by quartiles of serum ferritin levels (Q1–4) and were followed up with a 75-g oral glucose tolerance test at 24–28 weeks of gestation. The participants had an average serum ferritin concentration of 65.67 µg/L. GDM prevalence within each serum ferritin quartile was 9.4, 14.6, 18.8, and 19.3%, respectively ($P = 0.016$). They concluded that elevated serum ferritin concentrations in early gestation are associated with an increased risk of GDM.

GDM is related to increased number of adipose tissue macrophages (ATM) which secrete proinflammatory cytokines that include TNF-α, IL-6, and IL-1β. The significance of a low-grade inflammatory condition in the pathogenesis of insulin resistance has in recent times turn to evident. Proinflammatory cytokines are related to both impair insulin signaling and reduce insulin release from β-cells of pancreas. These causes lead to insulin resistance [7].

Ferritin is an acute phase reactant whose concentration increases during inflammation and is an important component of insulin resistance as well. GDM being an insulin resistance state as well as inflammatory state can be linked with increased serum ferritin levels.

Thus, serum ferritin apart from iron storage action can be used as a marker for prediction of gestational diabetes mellitus. As in early gestation, elevated level of serum ferritin is associated with increased risk of developing GDM, so level of serum ferritin can be monitored in antenatal visits for prediction of development of GDM in pregnancy.

In the present study, level of serum ferritin was found to be significantly higher among pregnant women with blood sugar level (DIPSI) 160–179 mg/dl and > 180 mg/dl (61.39 ± 20.56 and 68.54 ± 15.71 ng/ml, respectively) as compared to those with blood sugar level < 120 mg/dl and 120–139 mg/dl (24.91 ± 9.66 and 29.12 ± 13.07 ng/ml, respectively). It implies that the value of serum ferritin can predict severity of derangement in blood sugar level in pregnant women as well.

Early diagnosis by serum markers, which can predict the risk of developing GDM, should be widely used. Serum ferritin in this study has a significant correlation with development of GDM. High ferritin range women are at risk of GDM. Routine use of monitoring of serum ferritin levels, during the antenatal visit in the early second trimester, can be carried out, for early prediction of developing GDM, so that early intervention in terms of dietary changes and lifestyle modifications can be done.

In our study, the cutoff of serum ferritin is > 37.55 ng/ml. At this cutoff, calculated positive predictive value and negative predictive values are 67.5 and 93.0%, respectively. So we can conclude that with measurement of serum ferritin level we can predict the risk of development of GDM even before its development.

Conclusion

After doing a comprehensive analysis of all the above observations, the final conclusion that can be drawn from the present study is that the GDM women have higher level of serum ferritin as compared to normal glucose tolerant pregnant women. Because of its association, it can be used as a biomarker in early gestation for the prediction of development of GDM later in pregnancy. Serum ferritin is an economical and feasible option as early prediction of GDM, which helps us to intervene early in the form of dietary modification and lifestyle changes and protect pregnant women from diabetes-related morbidities and perinatal morbidities.

We propose that further studies are required to establish the role of serum ferritin as a predictor of gestational diabetes mellitus in early pregnancy.

Being a tertiary care center, most of the pregnant women visit to hospital are high-risk pregnancies or being referred patients, probably that is the cause that prevalence of GDM is high as compared to national standards.

Author Contributions US contributed to concept and design of study. RP contributed to data collection. VS contributed to layout of study and writing. SM contributed to formal analysis of study.

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Declarations

Conflict of interest There are no conflicts of interest in the study.

Ethical Approval Institutional ethical committee clearance was obtained for study number 96th ECM IIB /P49 dated 27/05/19 (attached below). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from every individual participant included in the study.

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