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Original Research Article

Serum ferritin level and its association with gestational diabetes mellitus in pregnancy

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ABSTRACT

Background: Short term as well as long term effects of GDM on both the mother and the child are preventable if screening and diagnosis are done at an early stage. Efforts have been made to try and identify clinical and biochemical markers that could predict GDM. Ferritin, an acute phase reactant is one such protein. This study was undertaken to know if there is an association between serum ferritin level and GDM in pregnancy.
Methods: A prospective study conducted in the Department of OBG, ESIC-MC-PGIMSR from January 2020 to June 2021. 388 gravid women satisfying the inclusion criteria were enrolled for the study after obtaining an informed written consent and maternal serum ferritin was assayed between 24 to 28 weeks of gestation and was statistically analysed.
Results: Both group demographic characters were matched and they were also matched for Hb% thereby eliminating anaemia, a confounding factor for the study. The mean serum ferritin level in GDM group was 46.4 ng/ml and in non-GDM group was 37.3 ng/ml ($p<0.001$). With ROC (Receiver operator characteristics curve) the cut off value of serum ferritin is 34.7 ng/ml with 95% CI, with sensitivity of 71% and specificity of 63%.
Conclusions: In this study S. ferritin value of >34.7 ng/ml at 24-28 weeks of gestation, there is 63% risk of developing GDM. Thus, we conclude that elevated serum ferritin level could be used as a biochemical marker for prediction of GDM.

Keywords: Gestational diabetes, Serum ferritin, Haemoglobin, Inflammation, Acute phase reactant

INTRODUCTION

Gestational diabetes mellitus (GDM) is 'any degree of glucose intolerance that either starts during pregnancy or is newly diagnosed in pregnancy' according to ACOG (American college of obstetrics and gynaecology) and The International association of diabetes and pregnancy study groups (IADPSG).[1] It is also defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy, according to WHO guidelines. It also includes women, whose glucose tolerance becomes normal after pregnancy and those with type 2 diabetes with persistent glucose intolerance developed later.

The incidence of GDM is increasing globally and presently it is 20-27% of all pregnancies. Modern lifestyle, changes in diet, increased obesity, reduced physical activity, increased prevalence of metabolic syndrome, older age at child birth lead to increased GDM incidence. History of diabetes in family and Indian ethnicity are additional risk factors.[2] Gestational diabetes mellitus is an important cause of perinatal morbidity and mortality. Short term as well as long term effects on the health of both mother and the child due to GDM is preventable if screening and

diagnosis are done at an early stage.[2] There is no specific biochemical test that can predict the risk of developing GDM other than blood sugars tests which can screen and diagnose GDM like oral glucose challenge test (OGCT)/Oral glucose tolerance test (OGTT). Despite years of research, there is still no agreement regarding optimal GDM screening.[3] Recent studies have shown a positive correlation between elevated serum ferritin concentration with insulin resistance and diabetes, and its association has also been described in gestational diabetes mellitus (GDM).[4] Thus, the present study was to evaluate association between serum ferritin level and GDM in pregnant women.

METHODS

Study design, sample size and source of data

Current study is a prospective study, 388 pregnant women attending antenatal clinic in the department of obstetrics and gynaecology, ESIC-MC-PGIMSR, Rajajinagar, Bangalore, between January 2020 to June 2021(18 Months) were enrolled in the study.

Inclusion criteria

Pregnant women willing to give informed written consent, Gestational age 24 to 28 weeks as calculated by LMP and dating scan

Exclusion criteria

Pregnant women with Anaemia (Hb <11gm/dl), pre-eclampsia, type 1 and type 2 diabetes, haematological disorders (sickle cell anaemia, hemoglobinopathies, thalassemia), liver disorders (haemochromatosis, hepatitis), any local and systemic infections, autoimmune disorder (SLE, rheumatoid arthritis).

Method of collection of data

All patients satisfying the inclusion criteria were enrolled for the study. Each participant was clinically evaluated with detailed obstetric, menstrual and medical history. General physical examination, systemic examination and obstetric examination were performed and accurate gestational age was assessed by noting the last menstrual date and confirmed by early trimester dating scan. All of them underwent serum ferritin estimation and oral glucose tolerance test (OGTT) at 24-28 weeks.

Serum ferritin estimation

Venous blood samples were obtained from the subjects enrolled for the study between 24-28 weeks gestation to measure serum ferritin level by chemi-luminescent immune-assay (CLIA) on ACCESS TWO with Beckman Coulter. It was done in fully automated analyser. The serum ferritin was measured in ng/ml.

Screening for GDM

All pregnant women enrolled for the study, irrespective of their last meal were given 75 gm anhydrous glucose dissolved in 300 ml water to be consumed orally at one time or within 5-10 minutes. A plasma standardised glucometer was used to evaluate blood sugar 2 hours after the oral glucose load. The threshold blood sugar level of more than or equal to 140 mg/dl was taken as cut off for diagnosis of GDM as per diabetes in pregnancy society of India (DIPSI) criteria. All patients received antepartum and intrapartum care as per the institutional protocol. All of them subsequently underwent repeat screening test for GDM at 32 to 34 weeks. Patients diagnosed as GDM was advised and prepared for frequent prenatal care visits, metabolic control requiring Medical Nutritional Therapy (MNT), self-monitoring of blood glucose and Insulin therapy and counselled regarding the risk of potential fetal and neonatal complications and the need for routine surveillance of fetal well-being. All the data were entered in a pretested proforma and analysed using SPSS software.

RESULTS

In the present study 388 gravid women, whose serum ferritin level was estimated at 24 to 28 weeks were followed up with repeat screening for GDM in third trimester, among them 77 (19.7%) were diagnosed with GDM during the follow up period.

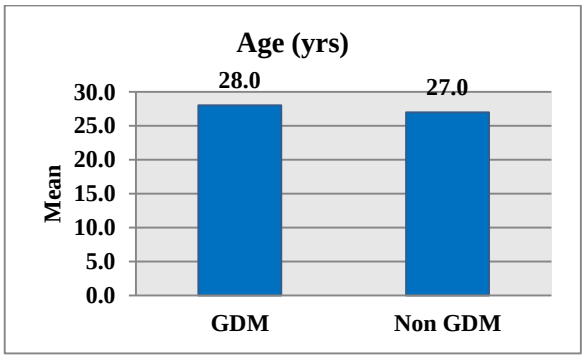

Figure 1: Mean age distribution among study groups.

Age distribution

The mean age of patients in GDM group was 28.0 years and in non-GDM group was 27.0 years. The p value being 0.087, statistically insignificant. Hence both groups were comparable with respect to maternal age.

Parity distribution

Number of primigravida's in GDM group and in non-GDM group were 33.8% and 44.7% respectively. Multigravidas were 66.2% in GDM and 55.3% in non-GDM, p value is 0.082, statistically insignificant, therefore the parity distribution was comparable in both groups.

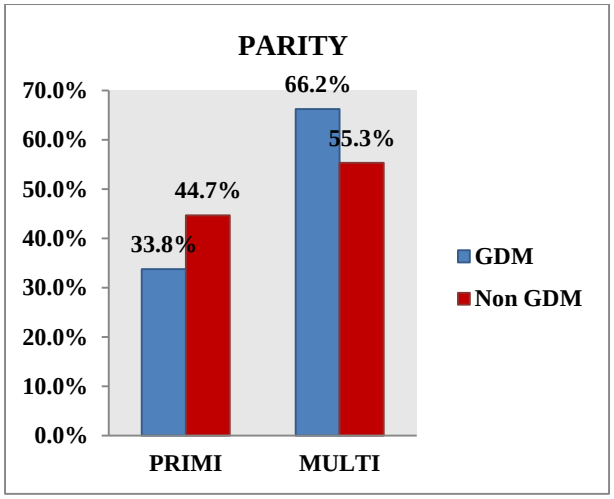

Figure 2: Distribution of parity among study groups.

Gestational age

The mean gestation age for serum ferritin assay in both GDM and non-GDM group was 27.1 years and 25.1 years respectively (p=0.277), infers that both the groups were matched for GA.

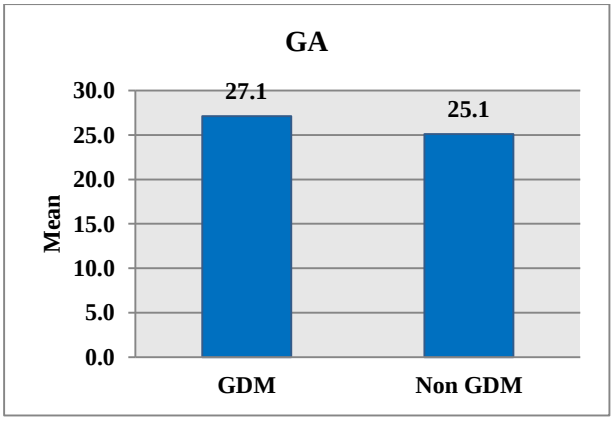

Figure 3: Mean gestational age at the time of serum ferritin assay.

Hemoglobin

The mean Hb in both GDM and non-GDM group were 12.2 gm% and 11.7 gm% (p=0.665). Infers that both the groups were matched for Hb %.

Serum ferritin distribution

The mean serum ferritin level of patients in GDM group was 46.4 and in non-GDM group was 37.3. The p value being 0.001, statistically significant. Hence serum ferritin is a risk factor for GDM.

In comparison with proportions of serum ferritin level <30 ng/dl, 148 (85.5%) were non-GDM and 25 (14.5%) were GDM, between 30-60 ng/dl, 88 (79.3%) were non-GDM and 23 (20.7%) were GDM, between 60-90 ng/dl 68 (76.4%) were non-GDM and 21 (23.6%) were GDM and with S. Ferritin level of >90 ng/dl, 7 (46.7%) were non-GDM and 8 (53.3%) were GDM. P value being (<0.001) statistically significant, it infers that higher the serum ferritin level greater the risk for development of GDM.

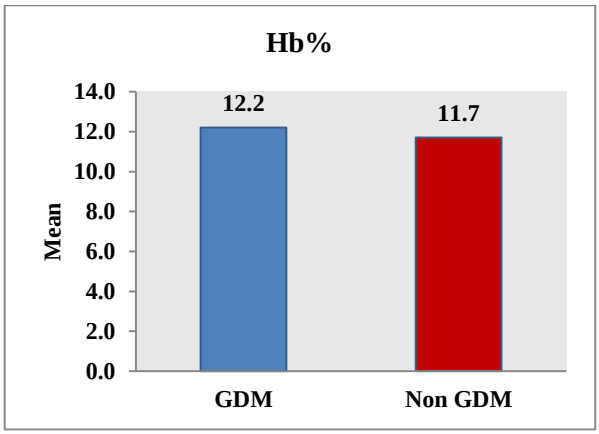

Figure 4: Mean Hb distribution.

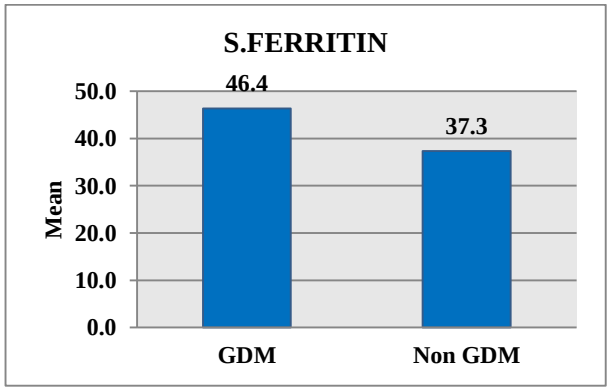

Figure 5: Mean serum ferritin distribution among study groups.

Table 1: Comparison of proportions of serum ferritin with GDM.

Outcome	S. Ferritin								P value
	<30		30-60		60-90		>90		
	N	%	N	%	N	%	N	%	
Non GDM	148	85.5%	88	79.3%	68	76.4%	7	46.7%	<0.001*
GDM	25	14.5%	23	20.7%	21	23.6%	8	53.3%	
Total	173	100.0%	111	100.0%	89	100.0%	15	100.0%	

Note: p value* significant at 5% level of significance (p<0.05).

Table 2: ROC analysis.

Parameters	AUC	Std. Error	P value	95% CI	
				Lower	Upper
S. ferritin	0.595	0.038	0.01*	0.52	0.669

*p value significant at 5% level of significance (p<0.05)

Table 3: Specificity and sensitivity determined through ROC analysis.

Parameters	Cut-off value	Sensitivity	Specificity
S. ferritin	34.7	71%	63%

The AUC for serum ferritin is 60% (p<0.01). The cut-off value to predict GDM among pregnant women is >34.7 ng/ml with sensitivity of 71% and specificity of 63%. This infers that in pregnant women with serum ferritin value of >34.7 ng/ml there is 63% chance that they will develop gestational diabetes.

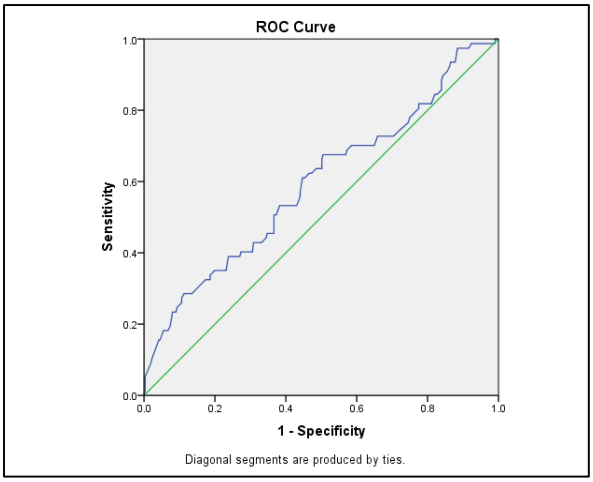

Figure 6: ROC distribution curve.

Table 4: Baseline demographic characteristics in the present study.

Variables		GDM	Non GDM	P value
N		77	311	NA
Age (years) Mean±SD		28.0±5.2	27.0±4.4	0.087
Parity (%)	**Primi**	33.8	44.7	0.082
	Multi	66.2	55.3	
Gestational age		27.1	25.1	0.277
Haemoglobin (gm%)		12.2	11.7	0.665

DISCUSSION

Insulin is responsible for redistribution of transferrin receptors to cell surface, which in turn causes insulin dependent GLUT and IGF II to co-localise on adipocytes. Insulin action in the liver is inhibited by Increased iron levels, which causes hyperinsulinemia. This hyperinsulinemia glycates transferrin receptors, thereby causing increases free iron, in-turn there is overall increase in ferritin synthesis. Hyperinsulinemia adds to this oxidative stress by causing increased iron levels.[13] Glycated transferrin in diabetic state is unable to bind iron, which leads to storage of elevated free iron in the form of ferritin. Ferritin production is triggered by the presence of iron. As serum ferritin levels are increased in the states of insulin resistance and hyperinsulinemia, GDM which is associated with insulin resistance, should have the possibility of elevated serum ferritin levels. This increase in serum ferritin levels manifests even before the symptoms of insulin resistance develops and GDM manifests. So, measuring serum ferritin levels early in the pregnancy just before the period of development of GDM, could guide us to a better awareness about the possibility of developing GDM.[14] Thereby reducing the morbidity concerned with GDM. This study included 388 gravid women attending the antenatal clinic, meeting the inclusion criteria. serum ferritin level and OGTT were done at 24-28 weeks of gestation, antenatal follow-up of patients done, with 77 (19.8%) were diagnosed with GDM in the current pregnancy. 44 (57%) were on medical nutrition therapy and 33 (43%) were on insulin.

The demographic characteristics of both the groups were well matched. In present study there was no statistical significance in Hb values (p=0.665) between 2 groups, which is similar to studies done by Soheilykhah et al (p= 0.70) and Islam et al (p=0.222).[6,15] This eliminated anemia as a confounding factor, minimizing the error and strengthening the present study. The mean serum ferritin concentration in GDM and non-GDM groups were 46.4 ng/mL and 37.3 ng/ml (p<0.001). Serum ferritin levels are significantly elevated in GDM group which was similar to studies done by Sumathy et al (p<0.001), Soheilykhah et al (p=0.01) and Islam et al (p<0.001).[3,6,15] ROC (Receiver operator characteristics curve) obtained in our study with the cut off value for serum ferritin as marker of development of GDM is 34.7 ng/ml with 95% CI. The sensitivity and specificity being 71% and 63% respectively. This infers that in pregnant women with serum ferritin value of >34.7 ng/ml there is 63% chance that they will develop Gestational diabetes (2 out of 3 women with serum ferritin level of >34.7 can develop GDM). Among these 388 pregnant women in this study, 77 were diagnosed with GDM in the current pregnancy. 44 were on medical nutrition therapy and 33 were on insulin therapy. out of 77 who developed GDM, about 21 had S. ferritin values between 60-90 ng/ml, and 8 had values above 90 ng/ml and in these 8 women with serum ferritin >90, 6 were started on insulin. This implies that high serum ferritin levels had required the need of insulin for their blood sugar control. Among 21 who had serum ferritin level 60-90ng/ml, about 12 had the need of insulin and remaining 9 just needed MNT for their adequate blood sugar control. The p value of this association is <0.001, which was significant.

Limitations

Limitations of current study were, our study being a time bound study with smaller sample size, the future research is required with adequate sample size to conclude that if serum ferritin level could be used as a biochemical marker for prediction of GDM.

CONCLUSION

In the present study with cut-off for serum ferritin level being 34.7ng/ml with 95% CI, sensitivity of 71% and specificity of 63%, we conclude that elevated serum ferritin level is associated with development of GDM. It is advantageous as it is cost effective and widely done biochemical test in most laboratories.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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