

Association of Serum Ferritin with Gestational Diabetes Mellitus

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is the most common metabolic disorder during pregnancy and is associated with increased maternal and neonatal morbidity. There are many serum markers known to be associated with Gestational Diabetes Mellitus (GDM). High serum ferritin level has been associated with the risk of developing gestational diabetes mellitus. The aim of the study was to investigate the association of serum ferritin levels with GDM.

Materials and methods: This case control study was carried out in the Department of Obstetrics & Gynecology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh between February 2018 and January 2019. A total of 120 pregnant women between 18 and 35 years of age attending outdoor antenatal clinic in their second or third trimester of pregnancy were included in this study. Among them 60 diagnosed cases of GDM were consider as group A and rest 60 (Without GDM) were considered as group B. Serum ferritin concentration was measured in all of these patients. Statistical analysis of the results was obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-22).

Results: The mean serum ferritin level was 124.1±14.7 ng/ml and 87.4±18.9 ng/ml in group A and group B respectively.

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The difference was statistically significant ($p < 0.05$) between two groups. More than half (55.0%) patients had serum ferritin level > 120 ng/ml in group A and 15(25.0%) in group B. Serum ferritin level > 120 ng/ml had 3.67 (95.0% C.I. 1.58 to 8.60) times significantly ($p < 0.05$) increase to developed gestational diabetes mellitus. There was a significant positive correlation between serum ferritin and fasting plasma glucose ($r = 0.445$, $p = 0.001$) in GDM patients. Similarly, a significant positive correlation between serum ferritin and 2-h after plasma glucose level following 75g oral glucose ($r = 0.427$, $p = 0.001$) in GDM patients.

Conclusion: A significant positive association was found between GDM and maternal serum ferritin levels.

Key words: Ferritin; Gestational diabetes mellitus; Pregnancy.

Introduction

Gestational Diabetes Mellitus (GDM) is a common medical disorder during pregnancy. Hyperglycemia first detected at any time during pregnancy is classified as either: Diabetes Mellitus in Pregnancy (DIP) or Gestational Diabetes Mellitus (GDM). GDM is diagnosed when FBS is 5.1-6.9mmol/L or 2 hours plasma glucose is > 8.5 -11.0 mmol/L following a 75g oral glucose load.¹ Worldwide GDM affects 7% of all pregnancies and the prevalence of GDM ranges from 1 to 14% depending on the population sample and diagnostic criteria used.² The prevalence of GDM varies among different races and ethnic groups. In Bangladesh, the prevalence of GDM is 9.7%.³ Some women have risk factors for developing GDM. The risk factors are: age > 35 years, BMI > 30 kg/m² prior history of GDM, previous macrosomic baby (Weight > 4.5 kg), prior history of unexplained still birth, family history of diabetes (In 1st degree), and PCOS.² The hallmark of GDM is metabolic defect of β -cell dysfunction and insulin resistance. The physiologic result of insulin resistance is an increase of insulin secretion by the pancreatic β -cells. The progressive insulin resistance that occurs in normal pregnancy is associated with an increase insulin release by the β -cells in order to maintain glucose homeostasis. Women with GDM are unable to increase insulin production to compensate for the increased insulin resistance, resulting in β -cells deterioration and hyperglycemia.⁴

Ferritin, the major iron storage protein, plays a key role in iron metabolism. Serum ferritin concentration provides an indirect estimate of iron stores of body because it is highly correlated with bone marrow iron. Ferritin is also a positive acute-phase reactant and is increased in presence of various acute or chronic disease conditions.^{5,6} Recently the role of serum ferritin is being increasingly recognized. Iron overload and the associated oxidative stress contribute to the pathogenesis and increase risk of type 2 diabetes and other disorders. In iron overload, the accumulation interferes with the extraction, synthesis and secretion of insulin.⁷ Elevated serum ferritin concentration, which is associated with insulin resistance and diabetes in the general population, has also been recently described in GDM. High level of ferritin was found to be a risk factor for the development of Gestational Diabetes Mellitus (GDM) in pregnant women.⁸

In some studies, high iron level has been shown to be a harmful factor for the body via oxidative stress and free radicals.⁹ As GDM is associated with an increased serum C-reactive protein level, some authors suggest that GDM might be part of an inflammatory process.^{6,10} It has been previously reported that iron overload promotes inflammatory processes by inducing free radical formation through an oxidative mechanism.¹¹

GDM is a common pregnancy complication and is associated with increased maternal and neonatal morbidity. Identifying and treating women with risk for GDM is important to improve the outcome. So, if the association of elevated serum ferritin with GDM is established, it could be used as a tool for prediction, diagnosis and follow-up of GDM. This would help in taking preventive measures and early effective management of GDM to achieve better obstetric outcome, reduce maternal and neonatal morbidity and mortality. The aim of the study was to investigate the association of serum ferritin levels with GDM.

Materials and methods

This antegrade case control study was conducted in the Department of Obstetrics and Gynecology, BSMMU, Dhaka between 1st February 2018 and 31st January 2019. Ethical clearance for the study was taken from the institutional review board, BSMMU. Permission for the study was taken from the concerned departments where this study

was conducted. A total of 120 pregnant women, who attended the outdoor antenatal clinic of BSMMU at their 2nd and 3rd trimester (13-40 weeks) of pregnancy were enrolled for the study. Recruited pregnant women were divided into case and control groups. Case group consisted of 60 pregnant women who were diagnosed as GDM. Control group comprised of 60 apparently healthy pregnant women without GDM. Age range of all study subjects were within 18-35 years. Pregnant women with DM, severe anemia, hemoglobinopathies, acute and chronic infections, acute and chronic renal diseases, acute or chronic liver diseases, thyroid disorders were excluded from this study.

Purposive sampling was done according to the availability of the participants who had voluntarily joined this study. The purpose and procedure of study was discussed with the participants and informed written consent was taken. The study was anonymous and confidentiality of information was assured. An interviewer administered questionnaire was used for data collection. Detailed socio-demographic history, obstetric history, gestational age, family history and medical history were recorded in the predesigned data sheet. Their antenatal records, early ultrasound scans were reviewed to confirm the duration of gestation. Medical records of diagnosis of GDM were reviewed. Pregnant mothers who had undergone GDM screening, and diagnosed as GDM as per the WHO, with FBS 5.1 to 6.9mmol/L and 2 hours after 75g glucose of ≥ 8.5 to 11.0 mmol/L were recruited for the study as case group. Routine physical examination, anthropometric measurements (Height, weight) were taken and obstetric examination were conducted and recorded.

After selecting cases and controls, with all aseptic precaution 3ml antecubital venous blood sample was collected from each subject for measurement of serum ferritin. The blood sample was transferred into a clean, dry test tube, placed on ice immediately after collection and taken to the laboratory. Blood sample was allowed to clot and then centrifuged at 4000 revolutions per minute for 10 minutes. Whenever possible, the analysis was done immediately. When there was delay the samples were stored at 2-8^o Celsius for 7 days and if more delay, the samples were stored at -20^o Celsius till further analysis. Samples with calculated reactivity value > 120 ng/ml were considered positive.

Statistical analyses of the results were performed by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-22). In comparison of the baseline characteristics and outcomes between the two groups, student's t-test was used for continuous variables and chi-square tests for categorical variables, Odds Ratio (OR) with 95% confidence interval and Pearson's correlation test was utilized between serum ferritin (ng/ml) with fasting plasma glucose (mmol/L) and postprandial plasma. glucose (mmol/L) and p value < 0.05 was considered significant.

Results

Table I Distribution of the study patients by age and gestational age (n=120)

Age (In years)	Group A (n=60)		Group B (n=60)		p value
	n	%	n	%	
<20	0	0.0	3	5.0	
20-30	36	60.0	48	80.0	
>30	24	40.0	9	15.0	
Mean±SD	29.45	±3.91	28.15	±4.39	0.089 ^{ns}
Duration of gestation (week)	Group A (n=60)		Group B (n=60)		p value
	n	%	n	%	
≤28	43	71.7	46	76.7	
>28	17	28.3	14	23.3	
Mean±SD	27.27	±3.78	26.6	±3.8	0.337 ^{ns}

ns=not significant.

p value reached from Unpaired t-test.

Group A= Pregnant women with GDM.

Group B= Pregnant women without GDM.

Table I shows age distribution of the study patients. The difference was statistically not significant (p>0.05) between two groups. This table also shows gestational age of the study subjects. The difference was also not statistically significant (p>0.05) between two groups.

Table II Distribution of the study patients by parity (n=120)

Parity	Group A (n=60)		Group B (n=60)		p value
	n	%	n	%	
Nullipara	24	40.0	27	45.0	0.579 ^{ns}
Multipara	36	60.0	33	55.0	

ns=not significant.

p value reached from Chi-square test.

Table II shows the distribution of the study patients according to parity. It was observed that 60.0% patients were multipara in Group A and 55.0% in Group B. The difference was statistically not significant (p>0.05) between two groups.

Table III Serum ferritin concentration in study patients (n=120)

	Group A (n=60) Mean±SD	Group B (n=60) Mean±SD	p value
Serum Ferritin levels (ng/ml)	124.1±14.7	87.4±18.9	0.001 ^s

s=significant.

p value reached from Unpaired t-test.

Table III shows serum ferritin of the study patients and the difference was statistically significant (p<0.05) between two groups.

Table IV Association between elevated serum ferritin and GDM (n=120)

Serum Ferritin levels (ng/ml)	Group A (n=60)		Group B (n=60)		OR(95%CI)	p value
	n	%	n	%		
>120	33	55.0	15	25.0	3.67(1.58-8.60)	0.001 ^s
≤120	27	45.0	45	75.0		

s=significant.

p value reached from Chi-square test.

Table IV shows elevated serum ferritin and GDM, it was observed that 55.0 % patients had serum ferritin >120ng/ml in pregnant mothers with GDM, 25,0 % in normal pregnant group. The difference was statistically significant (p<0.05).

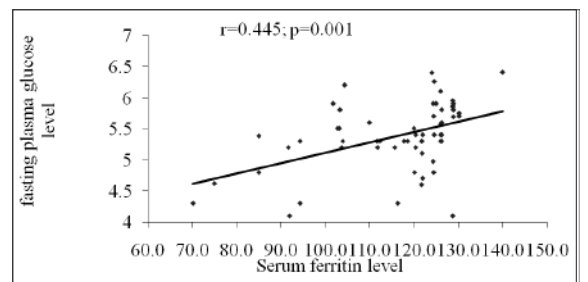


Figure 1 Scatter diagram showing positive significant correlation (r=0.445, p=0.001) between serum ferritin levels and fasting plasma glucose levels in GDM

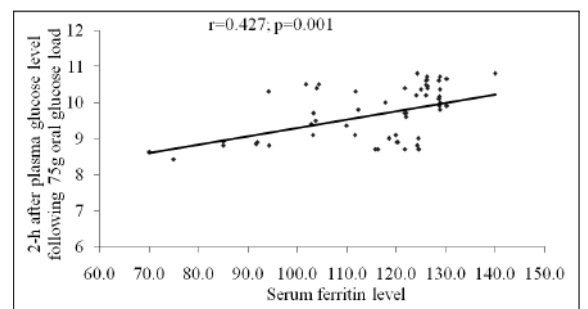


Figure 2 Scatter diagram showing positive significant correlation (r=0.427, p=0.001) between serum ferritin and 2-h after plasma glucose level following 75g oral glucose in GDM.

Discussion

It was observed that the difference in mean age was statistically not significant ($p>0.05$) between two groups. 60.0% patients were multipara in patients in Group A and 55.0% in Group B and the difference was statistically not significant ($p>0.05$) between two groups. A study conducted by Bowers and colleagues observed that 62.1% were multipara in GDM group whereas 48.4% were multipara in non GDM group.¹² Abu-Heija and colleagues conducted another similar type of study where they observed a steady increase in the incidences of GDM cases with increasing parity.¹³ The incidence of GDM increased steadily from 3.5% in nulliparous women to 14.6% in women with parity ≥ 4 . In another study Nielsen and colleagues reported that GDM is common in parity ≥ 4 .¹⁴ High serum ferritin levels have been demonstrated in many chronic disorders and vascular inflammation.^{15,16} Some studies revealed that elevated serum ferritin concentration is associated with insulin resistance and type 2 diabetes.^{9,17} In this present study, it was observed that the mean serum ferritin levels were 124.1 ± 14.7 ng/ml in Group A and 87.4 ± 18.9 ng/ml in Group B, which is significantly ($p<0.05$) elevated in Group A. Soheilykhah and colleagues observed in their study that in pregnant women with gestational diabetes, the serum ferritin level was found to be higher (41 ± 35 in GDM and 35.5 ± 30.7 in non GDM) in comparison with healthy pregnant women and the difference was statistically significant ($p<0.05$).⁹ In addition, Jiang and colleagues revealed that risk of type 2 diabetes is increased when the level of ferritin is elevated and this association is independent of other diabetes risk factors in healthy women.¹⁸ Chen and colleagues showed a 3.5 folds increase risk of GDM in obese women that had higher level of serum ferritin.¹⁹ Serum ferritin levels were significantly elevated in GDM with compared to non GDM group also observed by many investigators, including Yadav and colleagues, Bowers and colleagues, Javadian and colleagues, Islam and colleagues, Sharifi and colleagues.^{20,12,21,22,17}

In this present study, it was observed that 55.0% patients had serum ferritin level >120 ng/ml in patients with GDM Group, whereas 25.0% had high serum ferritin in patients without GDM Group. Serum ferritin level >120 ng/ml had 3.67

(95.0% C.I. 1.58 to 8.60) times significantly ($p<0.05$) increased to developed gestational diabetes mellitus with compared to healthy pregnant women. Soheilykhah and colleagues conducted a similar type of study where it was observed that the risk of having GDM with high level of ferritin to be 1.4 fold higher than the subjects with lower ferritin concentrations having OR 1.4 with 95% CI= 1-1.87 ($p<0.05$).⁹ Amiri and colleagues also conducted similar type of study where they showed that the risk of gestational diabetes increased upto 2.4-fold with 95% CI= 0.83-6.9 ($p<0.05$).²³ in patients having high ferritin levels. The risk of having GDM to be more than two fold higher than the risk for those with lower concentrations of ferritin were also observed by another study conducted by Bowers and colleagues, Sharifi and colleagues and Soubasi and colleagues.^{12,17,24} The above findings are closely resembled with the present study.

In this study significant positive correlation ($r=0.445$, $p=0.001$) was found between serum ferritin and fasting plasma glucose level in GDM. Similarly a significant positive correlation ($r=0.427$, $p=0.001$) was also found between serum ferritin and 2-h after plasma glucose level following 75g oral glucose load in GDM. A study conducted by Sharifi and colleagues which showed a linear relationship between serum ferritin with mid-pregnancy fasting plasma glucose ($r=0.241$, $p=0.05$).¹⁷ Wang and colleagues conducted another study where it was observed that in case of low level of serum ferritin, there was a weak positive correlation between ferritin and fasting plasma glucose, but at a high level of serum ferritin, the correlation between ferritin and fasting plasma glucose was remarkably strengthened, suggesting the strong association of a high level of serum ferritin with GDM, where they found significant positive correlation between the levels of serum ferritin and fasting plasma glucose ($r = 0.461$, $p<0.05$).²⁵ Therefore, the current study suggests that there is a clear evidence depicts the increasing serum ferritin levels with GDM.

Limitations

The present study was conducted within a short period of time. The study population was selected from one selected hospital, so that the results of the study may not be reflect the exact picture of

the country. Small sample size with purposive sampling was also a limitation of the present study. All the GDM cases were diagnosed before the measurement of ferritin levels and so it cannot be determined whether the observed elevation in ferritin preceded the development of GDM.

Conclusion

This study was undertaken to investigate serum ferritin levels and its association with GDM. It concluded that serum ferritin level is significantly higher in pregnant women with gestational diabetes mellitus when compared with non GDM pregnant women. Thus high serum ferritin may be considered as a risk factor for the development of GDM.

Recommendations

Our study suggests, Ferritin is significantly associated with GDM. Further study with larger sample size in multiple centers with long duration may strengthen the outcome of this study result. It may give more information if other cofactors related to GDM should also be evaluated and if association of serum ferritin would be seen with maternal and fetal outcome in GDM.

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Contribution of authors

KD-Conception, data collection, drafting & final approval.

FH-Design, interpretation data, critical revision & final approval.

NH-Data analysis, critical revision & final approval.

FI-Data collection, drafting & final approval.

BR-Data analysis, drafting & final approval.

RHS-Interpretation of data, drafting & final approval.

SH-Data analysis, critical revision & final approval.

TAA-Design, critical revision & final approval.

Disclosure

All the authors declared no conflict of interest.

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