

Serum Ferritin and Gestational Diabetes Mellitus: A Case Control Study

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Summary:

Background: Gestational diabetes mellitus (GDM) has been observed to be associated with increased perinatal morbidity and mortality. Increased serum ferritin, among others, has been identified as a risk factor for GDM.

Objectives: The present case-control study was conducted to determine the association between plasma ferritin level and risk of GDM.

Methods: The study was carried out in the Department of Obstetrics and Gynaecology, Department of Biochemistry and Clinical Pathology, Bangabandhu Sheikh Mujib Medical University Hospital from January 2008 to December 2009. Pregnant women 24-28 weeks onwards if exhibited a plasma glucose level fasting ≤ 6.1 mmol/L or blood sugar 2 hour after 75gm glucose > 7.8 mmol/L were included as cases.

Result: The mean serum ferritin was significantly higher in study group than in control group (36.4 ± 2.5 vs. $17.3 \pm$

1.0 , $p < 0.001$). A significantly linear correlation was observed between serum ferritin and 2 hours postprandial glucose. More than 90% of the women having GDM exhibited elevated serum ferritin (> 12 ng/ml) compared to 70% without GDM. The likelihood of having GDM is 5 times higher among those patients having high serum ferritin (> 12 ng/ml) than that in low or normal serum ferritin.

Conclusion: The study concludes that elevated serum ferritin is associated with increased risk of GDM and serves as an early predictor of diabetes in pregnancy. High maternal ferritin (> 12 ng/ml) at third trimester might be a risk factor for GDM and the caring obstetricians should, therefore, be cautious enough in prescribing iron to the pregnant women.

Key words: serum ferritin, GDM

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Introduction:

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. It occurs in 5 and 10%

of all pregnancies. The hallmark of GDM is increased insulin resistance.¹ Classical risk factors for developing gestational diabetes are maternal age (older than 35 years of age), history of type 2 diabetes in first degree relatives, a previous diagnosis of gestational diabetes or pre-diabetes or impaired glucose tolerance or overweight and obesity, a previous pregnancy which resulted in a child with a high birth weight ($> 90^{\text{th}}$ percentile, or > 4 kg).¹

GDM of any severity increases the risk of fetal macrosomia, neonatal hypoglycemia, jaundice, polycythemia, and hypocalcemia may complicate GDM as well. GDM is associated with an increased frequency of maternal hypertensive disorders and the need for cesarean delivery. The latter complication may result from fetal growth disorders and/or alterations in obstetric management due to the knowledge that the mother has GDM,² while presaging a long-term risk of development of type-2 diabetes for the mother.^{2,3} In Chinese pregnant women, serum ferritin concentration was higher in women with impaired glucose tolerance and GDM.⁴ In a large cohort study in New Jersey⁵, it was found that women

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who developed GDM had higher concentration of serum ferritin than women who did not develop GDM which persisted after adjustment for confounding variables like age and BMI. Elevated serum ferritin levels were associated with greater than two-fold increased risk of developing type-2 diabetes in the Finnish population.⁶ A strong association between higher serum ferritin concentration and newly diagnosed type-2 diabetes was observed among a US population as well.⁷

In our country maternal ferritin concentration in last trimester of pregnancy has never been categorically labeled as a risk factor for gestational diabetes mellitus (GDM). The present study was contemplated to address the hypothesis that high level of serum ferritin might be associated with gestational diabetes mellitus. The data generated from the study is likely to provide evidence on justification of the random use of iron in pregnancy which could be extrapolated to avert the chance of Gestational Diabetes Mellitus by avoiding routine iron supplementation in non-anaemic pregnant women.

Materials and Methods:

The present case-control study was conducted in the Department of Obstetrics and Gynaecology in collaboration with Department of Biochemistry and Clinical pathology, Bangabandhu Sheikh Mujib Medical University Hospital between January 2008 to December 2009 to determine the association between plasma ferritin level and risk of gestational diabetes mellitus (GDM). Pregnant women after 24-28 weeks of gestation whose fasting plasma glucose level ≥ 6.1 mmol/L or 2 hours postprandial glucose (after ingestion of 75 gm of glucose) > 7.8 mmol/L were included as cases, while women with normal pregnancy were included as controls. Pregnant women with age > 35 years, multiple pregnancy, severe iron deficiency anaemia (Hb% < 6 gm/dl), hemoglobinopathies & recent H/O injectable iron therapy were excluded from the study. A total 50 cases and 50 controls who met the respective eligibility criteria were included as sample. Serum ferritin level > 12 ng/ml was considered as high level and ≤ 12 ng/ml was considered as normal or low level of serum ferritin. Hb% < 10 gm/dl considered as anemia. Data were analysed using SPSS version 11.5 and the test statistics used to

analyse the data were Chi-square (χ^2) Test, Fishers' Exact Test, Student's t-Test, Mann Whitney Test, Odds Ratio (OR) with 95% confidence interval and Spearman correlation. Level of significance was set at 0.05 and p-value < 0.05 was considered significant.

Results:

The mean ages of cases (27.4 ± 3.0 years) and controls (26.6 ± 3.0 years) were almost similar ($p = 0.166$). Family history of diabetes was found significantly higher in case group than in control group (40% vs. 20%; $p = 0.029$) (Table I).

The incidence of anaemia in cases was significantly lower (8%) than that in control (20%) ($p = 0.016$). Oedema was found significantly higher in case group (52%) compared to control group ($p = 0.001$) (Table II).

Past obstetrics history was applicable for multigravidae only (number of cases 23 and number of control 21). Over half (52.2%) had history of gestational diabetes mellitus (GDM), 43.5% macrosomic baby and 17.4% stillborn baby or IUD. Only 9.5% of the controls had past history of still born or IUD (Table III).

The serum ferritin was significantly higher in case group than that in control group (36.4 ± 2.5 vs. 17.3 ± 1.0 ng/ml, $p < 0.001$). A low haemoglobin level was observed in control group compared to case group, although the difference between the groups was not statistically significant ($p = 0.222$) (Table IV).

High serum ferritin was significantly common in women who developed GDM than those who did not develop the disease ($p < 0.05$). The risk of developing GDM among the subjects who had elevated serum ferritin (> 12 ng/ml) at third trimester of pregnancy was nearly 5 times higher (95% CI = 1.3 – 14.7) than those who did not have elevated serum ferritin ($p = 0.009$) (Table V).

A linear correlation was observed between serum ferritin and fasting plasma glucose level, though the correlation was not statistically significant ($r = 0.131$, $p = 0.193$). However, a significantly linear correlation was evident between serum ferritin and serum plasma glucose 2 hours after 75 g of glucose ingestion ($r = 0.392$, $p < 0.001$) (Fig.1 & 2).

Table-I

<i>Comparison of demographics between cases and controls</i>			
	Case (GDM) (n = 50)	Control (Non GDM) (n = 50)	P value
Age (yrs) [#] < 25	9(18.0)	12(24.0)	
25 – 30	25(50.0)	28(56.0)	
e” 30	16(32.0)	10(20.0)	
Mean ± SD	27.4 ± 3.0	26.6 ± 3.0	0.166
Family history of diabetes*	20(40.0)	10(20.0)	0.029

[#]Data were analysed using Student’s t-Test; *Chi-square (c²) Test was done to analyse the data; Figures in the parentheses indicate corresponding percentage.

Table-II

<i>Current clinical characteristics between case and control</i>			
Clinical characteristics	Case (GDM) (n = 50)	Control (Non GDM) (n = 50)	P value
Anaemia*	4(8.0)	10(20.0)	0.016
Oedema [#]	26(52.0)	10(20.0)	0.001

[#]Chi-square (c²) Test was done to analyse the data; *Fisher’s Exact Test was done to analyse the data; figures in the parentheses denote corresponding percentage.

Table-III

<i>Comparison of past obstetric history between groups</i>			
Past obstetric history	Case (GDM) (n = 23)	Control (Non GDM) (n = 21)	P value
History of GDM [#]	12(52.2)	00	<0.001
History of macrosomic baby [#]	10(43.5)	00	0.001
H/O still-born/IUD*	4(17.4)	2(9.5)	0.165

[#]c² Test was done to analyse the data. *Fisher Exact Test was employed to analyse the data.

Table-IV

<i>Comparison of biochemical parameters between groups</i>			
Biochemical parameters	Case (GDM) (n = 50)	Control (Non GDM) (n = 50)	P value
Haemoglobin [#] (g/dl)	12.1 ± 0.8	10.7 ± 0.9	0.222
Serum ferritin [¶] (ng/ml)	36.4 ± 2.5	17.3± 1.0	<0.001

[#] Data were analysed using Student’s t-Test and were presented as mean ± SD.

[¶]Data were analysed using Mann Whitney Test and were presented as median ± SEM.

Table-V

<i>Association between elevated serum ferritin and GDM</i>				
S. ferritin (ng/ml)	Case (GDM) (n = 50)	Control (Non GDM) (n = 50)	P value	Odds ratio (95% CI)
> 12	46(92.0)	35(70.0)	0.009	4.7(1.3 – 14.7)
<12	4(8.0)	15(30.0)		

Data were analysed using χ^2 Test; *Odds Ratio estimates the risk of developing GDM.

Figures in the parentheses denote corresponding percentage.

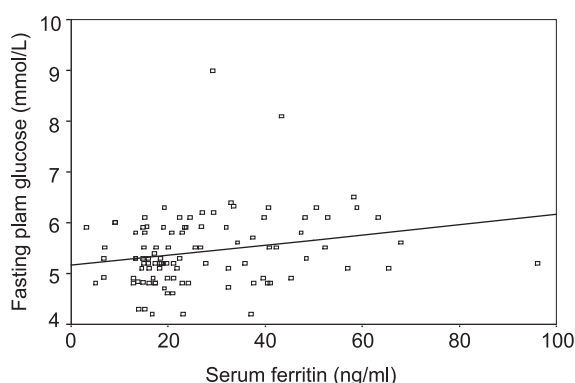


Fig.-1: Correlation between serum ferritin and fasting plasma glucose

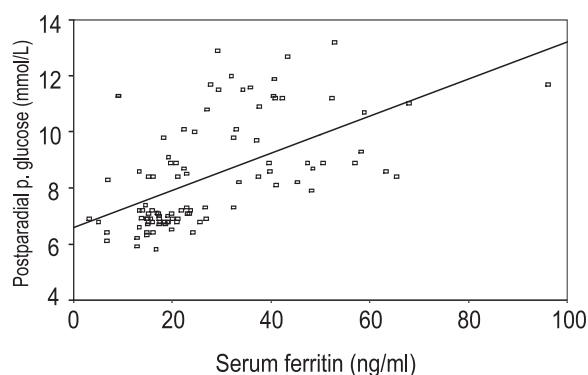


Fig.-2: Correlation between serum ferritin and postprandial plasma glucose

Discussion:

In the result we have already observed that cases and controls were almost similar in terms of age, gestational age and parity, although pregnant women with GDM had a significantly higher incidence of family history of diabetes than the control group women. In the present study more than 90% of the pregnant women having GDM exhibited elevated serum ferritin (> 12 ng/ml) compared to 70% of pregnant women without GDM. The likelihood having GDM is 5 fold higher (95% CI = 1.3 – 14.7) in pregnant women with high serum ferritin than that in low or normal serum ferritin ($p = 0.009$). In a prospective observational study of 1,456 healthy pregnant women, serum ferritin and anthropometric measurements were determined in early pregnancy.⁸ Of them who subsequently developed GDM had a higher concentration of serum ferritin than women who did not develop GDM ($p < 0.001$). Women in the highest quintile of serum ferritin had a 2-fold increased risk of

developing GDM adjusted for skin-fold thickness and prepregnant BMI. This study bears consistency with findings of the present study. Jiang and associates⁹ in a nested case-control study demonstrated that the mean concentration of serum ferritin among cases of incident diabetes was significantly higher compared with control subjects, and the relationship persisted after correction for various other risk factors for diabetes, including markers of obesity and inflammation. Similarly, high iron stores have been linked to insulin resistance, metabolic syndrome, and gestational diabetes.¹⁰ Besides these, there are some indirect evidences that increased serum ferritin concentrations or iron stores may be linked with gestational diabetes mellitus.

In a prospective observational study¹¹, 762 non-diabetic Chinese women with singleton pregnancies whose initial visit hemoglobin concentration 10 g/dL or more were recruited at 28-30 weeks gestation. The women were categorized by their initial visit haemoglobin

concentration into quartiles and the incidence of GDM was analyzed together with the maternal characteristics and iron status. Compared with rest, the group in the highest hemoglobin quartile (> 13 g/dL) had a significantly higher incidence of GDM (18.7% versus 10.9%, $p = 0.007$) After adjustment for the age, weight, serum ferritin and iron concentrations, advanced age and hemoglobin in the highest quartile were found to be the significant predictors of GDM (odds ratio 3.79 and 1.73 respectively). This study suggests that a high maternal hemoglobin (reflecting a high serum ferritin as well) early in pregnancy is an independent risk factor for GDM. The idea gleaned from these studies led to the testing of another hypothesis that iron deficiency anemia then may be an inhibiting factor for development of GDM in pregnant women. Accordingly in a retrospective case-control study,¹² 242 women with iron deficiency anemia (Hb <10 g/dl with features of iron deficiency) were compared with 484 non-anemic women matched for age, maternal demographics and infant outcome. The findings showed that the anaemic group was less likely to develop GDM than their non-anaemic counterpart (odds ratio = 0.52, 95% CI 0.27-0.97) and the prevalence of GDM was observed to be significantly reduced with the increase in duration of anaemia ($p = 0.045$). Multiple logistic regression analysis was performed adjusting for the effects of multiparity and BMI, and anemia emerged as significant predictor for decreased prevalence of GDM (adjusted OR = 0.46, 95% CI 0.23-0.90). These findings warn us that indiscriminate prescribing of iron in pregnant mothers without assessing their level of haemoglobin or too much consumption of iron-rich food by the pregnant women themselves may predispose to the development of GDM by increasing the load of serum iron. However, there is dispute over the association between serum iron status and GDM as to whether serum iron is a cause or consequence of insulin resistance. From Swaminathan et al¹⁰ reported that modest elevations in ferritin levels observed in diabetes may be a consequence or marker rather than the cause of impending insulin resistance and that elevated ferritin may not reflect elevated body iron store or an intracellular labile iron pool that participates in oxidant injury.

Offspring of diabetic mothers have a higher rate of infant morbidity compared to those born to non-diabetic mothers¹³, and this is characterized by excess macrosomia and operative delivery.¹⁴ Perinatal mortality was also shown to be higher in the offspring of the diabetic mothers compared to those without diabetes.¹⁵ These findings indicate that control of GDM is must to reduce the perinatal morbidity and mortality.

Conclusion:

The study concludes that high level of serum ferritin serves as a predictor of gestational diabetes mellitus. As high level of haemoglobin corresponds to high serum ferritin and results from additional intake of iron, indiscriminate prescribing of iron without assessing the level of haemoglobin or serum ferritin may cause more harm than good. The study suggests that elevated serum ferritin (>12 ng/ml) at third trimester of pregnancy might be a risk factor for gestational diabetes mellitus.

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