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Research Article

Prediction of Postpartum Diabetes Mellitus in Gestational Diabetes Mellitus Patients by Serum Ferritin

Belal S[1]*, Adaroas AS[2] and Nassar NEHA[2]

[1]Department of Obstetrics and Gynecology, El Sahel Teaching Hospital, Egypt

[2]Department of Clinical and Chemical Pathology, El Sahel Teaching Hospital, Egypt

***Corresponding author:** Shimaa Belal, Department of Obstetrics and Gynecology, El Sahel Teaching Hospital, Egypt

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Abstract

Objectives: The aim of this study is to determine the possible role of ferritin in predicting early development (eight week after delivery) of postpartum glucose intolerance and diabetes mellitus in patient with gestational diabetes mellitus.

Methodology: 50 pregnant women diagnosed as GDM, their gestational ages ranging from 24 to 37 weeks, were selected for this study. History was obtained, general examination was done, and Body Mass Index (BMI) was determined for all participants, as well as laboratory analysis of their serum for ferritin 8 weeks after delivery, and was evaluated for DM, based on the standard oral glucose tolerance test with 75g glucose.

Results: 10 cases developed postpartum DM, and 5 cases developed IGT/IFG. The mean interquartile serum ferritin was insignificantly higher in the diabetic group when compared to the normal group ($P > 0.05$). The serum ferritin level was a poor predictor for development of postpartum DM, ($P > 0.05$). The serum ferritin level was a poor predictor for development of postpartum IGT or DM ($P < 0.05$).

Conclusion: Serum ferritin was insignificantly higher in diabetic group when compared to normal group. Serum ferritin was a poor predictor of postpartum development of DM or IGT.

Keywords: Gestational diabetes mellitus; Ferritin

Introduction

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus defined Gestational Diabetes Mellitus (GDM) as the new onset or new diagnosis of glucose intolerance during pregnancy, complicates 4% of pregnancies [1].

Women with a history of Gestational Diabetes Mellitus (GDM) are characterized by a high risk of Type 2 Diabetes Mellitus (T2DM) 7 fold, metabolic syndrome 2 to 5 fold and Cardiovascular Diseases (CVD) 1,7 fold. Women with lesser degrees of glucose intolerance share the same risks. Type 2 diabetes mellitus may occur from post-partum (5 to 14%) to several years later, up to 25 years [2].

Serum ferritin is sensitive to body stores of iron and is currently the most reliable non-invasive marker of iron status in pregnancy [3].

Because it is an acute phase protein, Serum Ferritin (SF) is increased independent of iron status by acute or chronic inflammation [2].

It was stated that in pregnant women, higher hemoglobin (Hb) (>13g/dl) was an independent risk for GDM and that women with iron deficiency anemia had a reduced risk of GDM [4].

A few studies found that high serum ferritin and C Reactive Protein (CRP) levels are independent risk factors for type 2 diabetes [5].

Iron stores, expressed as serum ferritin concentration, have been proposed to be a component of the insulin-resistance syndrome. Indeed, the concentration of circulating ferritin was significantly associated with centrally distributed body fatness as well as with several other measurements of obesity. In gestational diabetes, both Body Mass Index (BMI) and serum ferritin levels were found to be independent predictors of 2-h glucose during an oral glucose tolerance test [6].

In humans, elevated iron stores during pregnancy have been associated with maternal and neonatal morbidity. Women with raised ferritin levels in the third trimester of pregnancy have a greatly increased risk of preeclampsia, Intrauterine Growth Retardation (IUGR) and preterm delivery [7].

Subjects and Methods

This cohort study was conducted at Al Sahel Teaching hospital from Jan 2017 to July 2017. Patients were recruited from outpatients' clinics and those who were admitted in hospitals. 50 pregnant women were diagnosed as gestational diabetes mellitus, their gestational ages ranged from 24 to 37 weeks were selected for this study.

Justification of the sample size

With the assumption that 12.5% will develop DM and 35% will develop either DM or impaired glucose tolerance (IGT), and AUC (Area under the curve) =80% with 15% margin of error and with alpha =0.05 and power of 80% the following sample size will be needed: 50 to differentiate between normal and any (DM or IGT), PASS power analysis and sample size, NCSS.www.ncss.com.

Inclusion criteria

Pregnant women diagnosed as gestational diabetes mellitus.

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Gestational age 24-37 weeks.

Exclusion criteri

Anaemia (hemoglobin ≤10.5gm/dl.

Acute or chronic inflammatory or infective diseases.

Pregestational diabetes mellitus.

Acute or chronic liver disease.

Acute or chronic renal disease and malignancy.

History of malignancy, seizure disorder, drug or alcohol abuse.

All patients enrolled in this study were subjected to the following:

- Informed written consent was obtained from the patients who were included in the study.

- To confirm exclusion and inclusion criteria complete history was taken; including: personal history, present history, past history, menstrual history, obstetric history, medical history and family history.

- General examination: vital signs, body mass index (BMI) [weight (kg)/height (m^2)] below 25kg/m^2 was defined as normal, while 25-29.9 kg/m^2 was perceived as overweight and above 30 was considered as obese.

- For each patient a blood sample was collected for laboratory investigations (serum ferritin, C-reactive protein, insulin, glycosylated hemoglobin (HbA1c), and hemoglobin levels).

Method of blood samples collection

Venous blood sample of 5ml was collected from each subject using a disposable plastic syringe after sterilization of skin with iso propyl alcohol (70%) swabs.

Blood samples were collected in disposable plastic tubes and left for half an hour to allow clotting of the blood and separation of the serum.

The specimens were centrifuged immediately thereafter for 5 minutes at 4.000rpm, and the supernatant serum was transferred into another dry, clean, non contaminated tube and immediately frozen and stored at -20C. Serum ferritin level was measured using Enzyme-Linked Immunosorbent Assay (ELISA).

- Pregnancy outcomes were recorded in all subjects including weight of the baby.

- A diagnostic Oral Glucose Tolerance Test (OGTT) was performed eight weeks after delivery.

Measurements of OGTT

Diagnoses of type 2DM, Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) were made with 75 gram OGTT based on the suggestions of the World Health Organization (WHO) 2006. The patients were divided into 3 groups according to their final diagnoses following 75 gram glucose loading test: Normal Glucose Tolerance (NGT) group (Patients with Fasting Plasma Glucose (FPG) of <110 mg/dl and the second hour the plasma glucose was ≤ 140. IGT/IFG group (Patients with an FPG value of between 110-125 mg/dl and following the loading, when at the second hour the plasma glucose was between 140-199 mg/dl. Type 2 DM group (Patients with FPG of ≥126mg/dl or following the loading, when at the second hour the plasma glucose was ≥ 200mg/dl. Plasma glucose concentrations were measured using the standard glucose oxidize method from venous plasma samples.

Table 1: The Characteristics of the whole study population (Numerical variables).

Variable	Mean	SD	1st quart.	Median	3rd quart.
Age, years	31.4	5.9	26	31	37
Weight, kilogram	94.2	18.1	80	90	101.8
Height, meter	1.59	0.55	1.59	1.6	1.6
BMI, kg/m^2	37.3	7.7	32.3	35.5	40.5
Gestational age GDM diagnosed, months	6.4	1.6	5	7	8
CRP, mg/l	14.1	23.8	0	6	12
HbA1c, %	6.1	1.4	5.1	5.9	6.9
Serum insulin, pmol/l	35.8	28.9	10.6	27	60
Serum ferritin, ng/ml	63.7	127	13.8	32.3	64.5
Weight of baby, kg	3.4	0.9	3	3.2	4

Statistical methods

Statistical analysis was done on a personal computer using IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY) and MedCelc© version 11.4 (MedCalc© Software bvba, Ostend, Belgium).

Normality of numerical data distribution was tested using The Komogorov-Smirnov and the Shapiro-Wilk tests. Normally distributed numerical data were presented as mean and standard deviation and differences among the groups were compared parametrically using one-way analysis of variance (ANOVA) with application the Turkey Honstly Significant Difference (HSD) test for post hoc pair wise comparisons if ANOVA revealed a statistically significant difference among the group.

Skewed data are presented as quartiles and intergroup differences are compared non-parametrically using the Kruskal Wallis test. The Mann-Whitney U test was employed for post hoc pair wise comparisons if the Kruskal Wallis test revealed a statistically significant difference among the group.

Categorical data were presented as number and percentage and between-group differences are compared using the Pearson chi square test or the chi square test for trends for nominal or ordinal data, respectively. Fisher's exact test is used in place of the chi square test if >20% of cells in any contingency table had an expected count of <5.

Receiver-Operating Characteristic (ROC) curve analysis was used to examine the value of continuous variables for prediction of binary outcomes. The DeLong method was used to compare the Areas Under the Curve (AUC) for any pair of ROC curves.

Multiple logistic regressions were used to determine independent predictors for binary outcomes.

All P values are two-sided. The Bonferroni method was used to correct for multiple pair wise comparisons with the U test. This indicated that to maintain a final type I error of 0.05, significance should be set at the P < 0.017 level for pair wise comparisons with

Table 2: The Characteristics of the whole study population (Categorical data).

		Percent
Parity	P0	20
	P1	25.5
	P2	24.5
	P3	15.5
	P4 or higher	14.5
History of GDM	Irrelevant	86.4
	Relevant	13.6
Family history of GDM	Irrelevant	28.2
	Relevant	71.8
Treatment with insulin	Non-insulin-treated	4.5
	Insulin-treated	95.5
Postpartum diabetic status	Normal	70.9
	IGT/IFG	10
	DM	19.1

The serum ferritin level was a poor predictor for development of DM (Area under the ROC Curve (AUC) = 0.635, (P= 0.0661) criterion >46, sensitivity = 61.9 with 95% confidence interval = 38.4 - 81.9, Specificity= 71.91 with 95% confidence interval = 61.4 - 80.9) (Table 3).

the U test. Otherwise, $P < 0.05$ is considered statistically significant.

Results

Table 1 and 2 show characteristics of the included women.

Discussion

Women with GDM have an increased risk of developing type 2 diabetes, with estimates of the lifetime risk ranging from 2.6% to 70%, depending on the study population and length of follow-up. Several studies from North America have reported postpartum diabetes rates from 3 to 38% within 1 year after delivery [8].

It was found 20% prevalence of glucose intolerance early postpartum in Chinese women with GDM [9]. While others reported that the incidences of postpartum prediabetes and diabetes at 6 to 12 wk follow-up in Korean women with GDM were 44.8% and 5.2% [10].

In our study 50 women with gestational diabetes participated in this study, from them we reported 10 cases (20%) developed postpartum diabetes mellitus and 5 cases (10%) developed impaired glucose tolerance.

In contrary, Jang examined 311 participants between 6 and 8 weeks postpartum, from them 119 (38.3%) women were found to have persistent glucose intolerance; 47 (15.1%) had diabetes and 72 (23.2%) had IGT [11].

In our study we screened for postpartum development of type 2 diabetes mellitus by two-hour oral glucose tolerance test with 75g of glucose at eight weeks after delivery.

The American College of Obstetricians and Gynecologists recommend that women whose pregnancy was complicated by GDM be screened for persistent glucose abnormality at 6 to 12 weeks postpartum with either a Fasting Plasma Glucose (FPG) test alone or with a fasting 75-g, 2-hour Oral Glucose Tolerance Test (OGTT) [12].

Table 3: Receiver-Operating Characteristic (ROC) curve analysis for the value of serum ferritin the prediction of postpartum DM.

Sample size	50
Disease prevalence (%)	19.1
Area under the ROC curve (AUC)	0.635
Standard Error	0.0734
95% Confidence Interval	0.538 to 0.725
z statistic	1.838
Significance level P (Area=0.5)	0.0661
Criterion	>46
Sensitivity	61.9
95% CI	38.4 - 81.9
Specificity	71.91
95% CI	61.4 - 80.9
+LR	2.2
95% CI	1.5 - 3.2
-LR	0.53
95% CI	0.3 - 1.0
+PV	34.2
95% CI	19.6 - 51.4
-PV	88.9
95% CI	79.3 - 95.1

The OGTT is more sensitive, with reported sensitivities of 100% compared with 67% for FPG [13].

National Institute for health and Clinical Excellence (NICE) guideline recommended that women who were diagnosed with gestational diabetes should be offered lifestyle advice (including weight control, diet and exercise) and offered a fasting plasma glucose measurement (but not an oral glucose tolerance test) at the 6-week postnatal check and annually thereafter [14].

In another approach, women with a history of GDM with a normal postpartum screening be rescreened every 3 years, and women with IFG or IGT or both (prediabetes) should be rescreened annually [13].

Golden mentioned that the studies with the longest follow-up-screening for T2DM up to 12 years after delivery had similar results compared with those in which screening was conducted earlier [15].

In our study, serum ferritin was insignificantly higher in diabetic and IGT/IFG groups when compared to euglycemic women after delivery (P= 0.061).

Serum iron concentration is significantly higher in cases with abnormal glucose tolerance when compared with cases of normal glucose tolerance [16].

High iron load and disorders of iron metabolism have been associated with an increased risk of disturbances in glucose metabolism. High iron intake might be a factor, which increases the risk of GDM especially in women with already good iron stores [17].

The study of Bansal showed a significant association between serum ferritin levels and type II diabetes mellitus in 200 Indian male [18].

Dietary heme iron intake was positively and significantly associated with GDM risk after adjusting for age, BMI, and other risk factors [19].

The study of [16] showed that elevated serum iron levels correlates with the development of Gestational Diabetes Mellitus.

High serum ferritin levels have been linked with type 2 diabetes and the development of Gestational Diabetes Mellitus (GDM) in pregnant women [20]. There is a twofold increase in GDM risk in women in the highest quartile of serum ferritin [21].

Lao results indicated that maternal HBsAg carriage could explain in part the association between increased serum ferritin concentration with gestational diabetes in Hong Kong Chinese women, and that HBsAg carrier status is an independent risk factor for gestational diabetes [22].

Soubasi concluded that elevated maternal ferritin is not a reflection of excess iron stores, but is related to an increased risk of GDM or IUGR. Also, maternal ferritin levels are not associated with either neonatal iron status or neonatal outcomes [20].

Using receiver-operating characteristic (ROC) curve analysis, our findings showed that serum ferritin was poor predictor for postpartum development of DM or IGT (AUC) = 0.635, (P= 0.0661).

This is similar to the results of Sharifi who concluded that ferritin levels in GDM cannot be used as an indicator to predict subsequent glucose concentration in early postpartum oral glucose tolerance test [23].

However, Forouhi have shown prospectively that even modestly elevated ferritin, below levels diagnostic of haemochromatosis or other iron-storage disorders, predicts incident diabetes independently of known risk factors and confounders [24].

In the present study the correlation between serum ferritin and CRP was insignificant (P= 0.094).

Sharifi reported that Serum ferritin levels were increased in women with Polycystic Ovary Syndrome (PCOS) irrespective of their BMI, CRP and insulin resistance [23]. However, Oh found a significant relationship between the increase of serum ferritin and high sensitivity C-reactive protein in healthy women [25].

Ferritin is considered an inflammatory marker. Therefore serum level of CRP, another inflammatory marker was measured in these women to assess the potential confounding effect of chronic inflammation on the observed increase in ferritin levels [23].

Conclusion

The prevalence of postpartum DM or IGT in this study was 29.1%. Serum ferritin was insignificantly higher in diabetic group when compared to normal group. Serum ferritin was a poor predictor of postpartum development of DM or IGT.

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