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Full Length Research Paper

Early pregnancy Serum Ferritin and Risk of Gestational Diabetes Mellitus

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Abstract
Elevated serum ferritin concentration is associated with insulin resistance and diabetes. Recently it has also been described in gestational diabetes mellitus (GDM). A prospective study was done to determine whether there was a relationship between serum ferritin concentration in early pregnancy and the risk of GDM. A study was performed on 100 pregnant women with gestational age of 10-12 weeks. A blood sample was obtained for measurement of ferritin in the first trimester. Diagnosis of GDM was done by 75 gr oral glucose tolerance test between 24-28 wk. Women who developed GDM had a higher concentration of serum ferritin than women who did not develop GDM (<0.001). A ferritin concentration of 130 ng/ml was calculated to be the 75th percentile for healthy pregnant women. Considering this level 100% in the GDM group and 15.9 % of normal subjects exhibited high ferritin levels (p0<.001). The risk of GDM with these high levels of ferritin was higher than that for subjects with lower concentrations. High serum ferritin can be regarded as a significant predictor for the development of gestational diabetes.

Key words: *Ferritin, Gestational Diabetes.*

Introduction

Diabetes is the most common metabolic disorder to affect pregnancy and is associated with increased maternal and neonatal morbidity (Sutton et al., 2017). The prevalence of diabetes in pregnancy has increased substantially over the last 20 years because of the obesity epidemic and improved DM screening (Selvin et al., 2014). Maternal insulin resistance begins in the second trimester and peaks in the third trimester. This is the result of increasing secretion of diabetogenic hormones such as human placental lactogen, growth hormone, progesterone, cortisol and prolactin. These hormones cause a decrease in insulin sensitivity in the peripheral tissues such as adipocytes and skeletal muscle by interfering with insulin receptor signaling (Newbern and Freemark 2011). As a result, maternal glucose use declines and gluconeogenesis increases maximizing the availability of glucose to the fetus (Rodney et al., 2003). Ferritin, the major iron storage protein, play role in iron metabolism. Serum ferritin concentration provides an indirect estimation of body iron stores because it is highly correlated with bone marrow iron. Ferritin is also a positive acute phase reactant and increase in the presence of various acute and chronic disease conditions (Tori and Tori 2002). Ferritin is the cellular storage protein for iron. It is present in small concentrations in blood, and the serum ferritin concentration normally correlates well with total-body iron stores, making its measurement important in the diagnosis of disorders of iron metabolism (Bull, 2010). Several prospective studies in the general population have reported an increase in the risk of type2 diabetes among those with higher levels of iron markers mainly ferritin (Podmore et al., 2016). These data lend support to a significant role of iron metabolism in the development of type 2 diabetes even within its normal range. Studies have also shown that pregnant women who develop GDM have higher levels of serum ferritin or Hb than women who do not develop GDM (Helen et al ., 2012). The goal of this observational prospective study was to determine the relationship between serum ferritin concentration and risk of GDM.

Patients and methods

This an observational prospective study will be conducted in the department of Obstetrics and gynecology Al-Azhar university (New Damietta) between October 2016 to October 2017 and included 110 pregnant women. and applied after oral and informed consent with the following criteria:

Inclusion criteria: singleton pregnancy and first trimester pregnancy. All women with any of the following were excluded: Pre-gestational or history of gestational diabetes in the previous pregnancy, multiple pregnancy, sever iron deficiency anemia, haemoglobinopathies, late pregnancy after13 week, acute or chronic Inflammatory or infective disease, history of malignancy, any

medical disorder as, cardiac, hepatic and renal disease and age more than35 years. All Patients eligible for the study undergo the following: General information including personal, obstetric and medical history, Gestational age determination based on the date of last menstrual period confirmed by an early first trimester ultrasound scan, BMI was obtained (weight in Kilogram divided by the square of height in meters). Routine and special investigation as: ABO-RH typing, CBC, glucose and serum ferritin. Assessment of gestational diabetes was done by 75 gr oral glucose tolerance test between 24-28 wks of Oral glucose tolerance test (OGTT) was carried out between 24 and 28 weeks of gestation in the morning after overnight fast of ≥ 8 hours, using 1- step 75g as indicated by American Diabetes Association (ADA, 2015). GDM was diagnosed if plasma glucose Fasting ≥ 92 mg/dl; 1-h ≥ 180 mg/dl and 2-h ≥ 153 mg/dl). According to the result the pregnant women lies into two categories:

1-Normal Glucose Tolerance (NGT).

2-Gestatonal Diabetes Mellitus (GDM).

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using statistical package for social sciences (SPSS) version 22 (SPSS Inc, Chicago, USA), running on IBM compatible computer. For qualitative data, frequency and percent distributions were calculated. For quantitative data, mean, standard deviation (SD), minimum and maximum were calculated. The ROC curve was performed to discriminate diseased cases from normal cases. $P < 0.05$ was considered to be statistically significant.

Results:

Among 110 pregnant women who met inclusion criteria of the study, five had aborted before 24 weeks gestation and rolled out of the study. Five were not submitted for assessment for GDM diagnosis. At the end, 100 pregnant women continued in the study. The characteristics of participants are shown in two groups (Table I). Women who developed gestational diabetes GDM during pregnancy (18%) were older (p< 0.001*) and had higher pregnancy BMIs (p<0. 001) and higher serum ferritin concentrations than women who did not develop GDM (Table I). The serum level of hemoglobin and HCT was not significantly different between the two groups.

Table (1): Demographic characters of studied pregnant women.

Characters		Normal	GDM	P value
Age		25.51±2.44	29.22±2.21	< 0.001*
BMI		24.50±2.00	28.54±1.26	< 0.001*
Parity		1.50±0.59	1.72±0.57	0.15(ns)
GA at sample collection for serum ferritin		11.15±0.69	11.00±0.84	0.40(ns)
Family history of diabetes	Positive	19(23.2%)	6(33.3%)	0.36(ns)
	Negative	63(76.8%)	12(66.7%)	
Serum ferritin		82.56±29.64	140.77±8.17	<0.001*
Hct %		37.49±1.13	37.83±2.25	0.35(ns)
Hemoglobin		12.47±0.28	12.56±0.46	0.33(ns)
Pre-pregnancy HTN	Positive	9(11.0%)	6(33.3%)	*0.016
	Negative	73(89.0%)	12(66.7%)	

In the present work, Age of studied pregnant women ranged from 21 to 32 years and there was statistically significant increase in pregnant women developed GDM when compared to normal (29.22±2.21 vs 25.51±2.44 years respectively) (Table2).

Table (2): Demographic characters of studied pregnant women in relation to development of GDM as regard to age

	Mean	SD	Minimum	Maximum	T	P
GDM	29.22	2.21	24.00	32.00		
Normal	25.51	2.44	21.00	31.00	5.92	<0.001*
Total	26.18	2.79	21.00	32.00		

In the present study BMI ranged from 19 to 30.11 and there was statistically significant increase of BMI in GDM group when compared to normal group (28.54±1.26 vs 24.50±2.00) (Table 3).

Table (3): BMI of studied pregnant women in relation to development of GDM

	Mean	SD	Minimum	Maximum	T	P
GDM	28.54	1.26	26.40	30.11		
Normal	24.50	2.00	19.00	29.00	8.18	<0.001*
Total	25.23	2.44	19.00	30.11		

As regard to pre-pregnancy hypertension in studied pregnant women, it was encountered in 15% of all studied pregnant women and there was statistically significant increase in GDM when compared to normal groups (33.3% vs 11.0% respectively. (Table 4).

Table (4): Pre-pregnancy hypertension in studied pregnant women in relation to development of GDM

	GDM		Normal		Total	
	n	%	N	%	N	%

Hypertension	Positive	6	33.3%	9	11.0%	15	15.0%
	Negative	12	66.7%	73	89.0%	85	85.0%
Statistics			X^2= 5.87, ρ = 0.016*				

Serum ferritin ranged from 43 to 158 ng\ml and there was statistically significant increase in pregnant women developed GDM when compared to normal group (140.77±8.17 vs 82.56±29.64 respectively) (Table 5).

Table (5): Serum ferritin in studied pregnant women in relation to development of GDM

	Mean	SD	Minimum	Maximum	T	P
GDM	140.77	8.17	131.00	158.00		
Normal	82.56	29.64	43.00	141.00	8.23	<0.001*
Total	93.04	35.15	43.00	158.00		

As regard to results of 75 gm oral glucose tolerance test, there were statically significant increase of fasting serum glucose levels and levels at 1, 2 hours in pregnant women who developed GDM when compared to normal group (Table 6).

Table (6): Results of 75 gm oral glucose tolerance test in studied pregnant women in relation to development of GDM

		Mean	S. D	Min.	Max.	t	P
Fating glucose	GDM	97.16	2.74	93.00	103.00		
	Normal	84.89	3.07	79.00	91.00	15.59	<0.001*
	Total	87.10	5.61	79.00	103.00		
Glucose at 1 hour	GDM	192.83	4.92	183.00	201.00		
	Normal	166.98	5.16	154.00	178.00	19.37	<0.001*
	Total	171.64	11.20	154.00	201.00		
Glucose at 2 hours	GDM	160.44	4.18	154.00	167.00		
	Normal	132.91	3.71	124.00	139.00	27.38	<0.001*
	Total	137.87	11.28	124.00	167.00		

In the present study Running receiver operation characteristic curve, serum ferritin was found to be a good predictor test for gestational diabetes mellitus; as the area under the curve was 0.95; the best cutoff point was >130, that yielded sensitivity of 100.0% and specificity of 84.15% (Table7).

Table (7): Sensitivity of serum ferritin in prediction of GDM in studied pregnant women

	Value	95% CI
Area under the curve	0.95	0.88- 0.98
Cutoff	>130ng\ml	
Sensitivity	100.0%	81.5-100
Specificity	84.15%	74.4-91.3

Running regression analysis for variables found significant in analysis, results revealed that oral glucose tolerance test and serum ferritin remain significant in diagnosis or prediction of GDM (Table 8).

Table (8): Predictability of GDM by serum ferritin and other significant variables

	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
Age	-.004	.004	-.028	-.927	.356
BMI	-.003	.005	-.019	-.545	.587
Fasting OGTT	-.011	.003	-.155	-3.295	.001*
OGTT 1hour	-.009	.002	-.265	-5.264	.000*
OGTT 2hour	-.017	.002	-.508	-8.827	.000*
Ferritin	-.001	.000	-.104	-3.144	.002*
Hypertension	-.003	.029	-.003	-.095	.924

Discussion

With the increased prevalence of diabetic pregnancies, it is necessary to develop simple reliable method for screening of GDM. serum Ferritin is being an easy, cheap and available method as it yielded sensitivity of 100.0% and specificity of 84.15%. In the present study GDM was developed in 18 pregnant females out of 100 representing 18% and this is in agreement with Zein et al. (2015) who reported in longitudinal prospective study that incidence of GDM is 15.4%.also in cross-sectional study by Pan et al .(2013) at Singapore reported that incidence of GDM is 17.3%. The present study demonstrated that pregnant women with elevated serum ferritin concentration in early pregnancy had a higher rate of gestational diabetes. Shimin and colleagues in a systematic review revealed that increased risk of GDM is significantly associated with greater levels of ferritin (Shimin et al., 2016). In the present study, serum ferritin ranged from 43 to 158ng/ml and there was statistically significant increase in pregnant

women who developed GDM when compared to pregnant women who did not develop GDM (140.77±8.17 vs 82.56±29.64 respectively P<0.001). The best cutoff point was >130 ng/ml that yielded sensitivity of 100.0% and specificity of 84.15%. Scholl showed that over ten years, women with high ferritin levels are more vulnerable to type II diabetes (nearly three times more) (Scholl, 2005). In the present study there was statistically significant increase in age and BMI of pregnant women who developed GDM when compared to those not develop GDM (29.22±2.21 vs 25.51±2.44 years; 28.54±1.26 vs 24.50±2.00) P <0.001 respectively). Matching with our result Soheilykhah et al. (2016) reported that Women who developed GDM during pregnancy (22.1%) were older than those not develop GDM (29.4±5.4 vs 27.1±4.5) (p<0.0001). and had higher pre-pregnancy BMIs (26.4±5vs 24.7±4.4) (p<0.0001). Our result showed no significant difference was observed regarding of the parity (P 0.15), gestational age (P 0.40) and family history (p >0.05) of diabetes between pregnant females who developed GDM and normal pregnant women. This is in agreement with Rawal et al. (2016) who reported in longitudinal prospective study that no difference in parity (P 1) and family history between GDM cases and normal pregnant women. In the present study We did not find any association between high hemoglobin level and the risk of GDM (P 0.33).our result were in concordance with Soheilykhah et al. (2016) they did not find any association between high hemoglobin level and risk of GDM with OR=1.19 (95% CI 0.88-1.6) (p=0.27). Regarding pre-pregnancy hypertension in studied females, it was encountered in 15% of all studied females and there was statistically significant increase in GDM when compared to non GDM groups (33.3% vs 11.0% respectively) p = 0.016.

Matching with our result Khambalia et al. (2015) reported that women with GDM more likely to have hypertensive disorder of pregnancy (P 0.009). In the present study, as regard to results of oral glucose tolerance test, there was statically significant increase of fasting serum glucose levels and levels at 1, 2 hours in females who developed GDM when compared to females who did not develop GDM (p<0.001). Zein and co- workers in a prospective observational study on 104 pregnant women, observed that ferritin level in early pregnancy was significantly correlated to glucose level after OGTT at 1-h and 2-h (Zein et al., 2015).

In the present study When searching for correlation between serum ferritin levels and other studied variables, the results revealed that serum ferritin was mildly and significantly correlated with patient age (r 0.233-P 0.019). In addition, serum ferritin was moderately and significantly correlated with each of BMI (r 0.492 –P<0.001), Fasting (r 0.45 -P<0.001), 1hour (r 0.55 -P <0.001) and 2hours (r 0.60 -P<0.001) serum glucose levels. However, there was no significant correlation with parity (r 0.12 –P 0.22), gestational age (r 0.13 –R 0.21) or hemoglobin (r 0.19 –P 0.06). A study by Chen et al. (2006) agree with our study that reported Linear relationships between serum ferritin with maternal age (P < 0.0001) and prepregnant BMI (P <0.0002) were observed, but Hb and HCT levels were not significantly different. The highest quintile of serum ferritin at entry was associated with a twofold increased risk of developing GDM. Our study revealed that oral glucose tolerance test and serum ferritin remains significant in diagnosis or prediction of GDM.

Conclusion

This study showed association between elevated serum ferritin levels during early gestation and the risk of development of GDM. Therefore, high ferritin can be regarded as a significant good predictor for the development of GDM with 100% sensitivity and high specificity. Further studies are required to confirm these results, especially taking into consideration measurement of serum ferritin more than one time in the first trimesters of pregnancy.

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