The Association of Gestational Diabetes with Serum Ferritin

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ABSTRACT:

BACKGROUND:

Serum ferritin is the standard measurement for the body iron stores, and is the most reliable marker for iron status. During pregnancy, there is a gradual decline in serum ferritin level. However, elevated maternal serum ferritin was notified in women with gestational diabetes mellitus (GDM).

OBJECTIVE:

To investigate the association between maternal serum ferritin level and gestational diabetes.

METHODS:

A prospective case control study of 50 women with singleton pregnancy that had gestational diabetes compared to 50 healthy pregnant women. The study was performed in Baghdad teaching hospital for one year period from June 2010 through June 2011. Serum iron, total iron binding capacity, and serum ferritin level were assayed. Mean serum ferritin was elevated (95.6027±99 ng/ml) in women with gestational diabetes, compared to that in the control group (31.7213±42ng/ml).

RESULTS:

There was a statistically significant elevation of serum ferritin in women with gestational diabetes.

CONCLUSION:

We concluded that there is a positive association between the elevated serum ferritin and gestational diabetes.

KEY WORDS: serum ferritin, gestational diabetes, serum iron, total iron binding capacity

INTRODUCTION:

Ferritin is an intracellular protein and the major iron store in the human body [(1).] Serum ferritin is the standard marker of body iron stores [(1, 2, and 3).] An extensive body of data suggests that higher iron stores and increased serum ferritin in non-pregnant subjects are positively associated with elements of the insulin resistance syndrome such as elevated blood glucose. Elevated serum ferritin has been observed in patients with type 2 diabetes [(1, 4, 5, 6, 7, 8, 9, 10, 11)].

Epidemiological studies support the positive relation of elevated iron stores with the increased risk of insulin resistance, and type 2 diabetes mellitus [(9, 12, and13)]. Moreover, serum ferritin was found to be elevated in men and women with high total cholesterol, elevated serum uric acid, and high blood pressure, and high BMI [(5,13)]. This may predispose to the development of long term complications of diabetes, both microvascular and macrovascular diseases. Elevated iron stores may induce diabetes through a variety of mechanisms, including oxidative damage to pancreatic beta cells, and interference with insulin's ability to suppress hepatic glucose production [(14)].

In healthy volunteers, frequent blood donation lead to decreased iron stores, with reduction in post-prandial hyperinsulinemia and improvement in insulin sensitivity [(8,12)]. Venesection demonstrated improved glycaemic control and insulin sensitivity in a group of patients with high ferritin level [(6)], while depletion of iron stores improves insulin resistance. On the other hand, blood donation and phlebotomy are followed by drop in postprandial hyperinsulinemia, and serum glucose [(12,13,15)].

There is a positive association between elevated serum ferritin and chronic inflammation –related diseases, e.g. cardiovascular diseases, insulin resistance syndrome, and risk of type 2 diabetes [(7, 13, 16)].

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Gestational diabetes mellitus (GDM) is the most common metabolic disorder during pregnancy, and affects 1-14% of pregnancies in different populations [3,15,17]. There is evidence that elevated serum ferritin during pregnancy predicts the incidence of impaired fasting glucose, and gestational diabetes mellitus [3]. Many studies correlated the elevation of serum ferritin levels with GDM and intrauterine growth restriction (IUGR) [3]. A decrease in iron stores, serum ferritin with reduced iron concentrations in liver, heart and brain levels has been found in infants of diabetic mothers [18]. GDM has been related to prenatal death, macrosomia, birth trauma such as maternal lacerations and neonatal shoulder dystocia, blood loss and increased caesarean births [15]. Therefore, diagnosis of gestational diabetes mellitus is important to identify maternal and fetal adverse outcomes.

There is now accumulated evidence in the literature that women with a history of gestational diabetes have higher risk for subsequent development of type 2 diabetes mellitus [19]. In Theresa Scholl study, women with high levels of ferritin (more than 107ng/mL) were nearly three times more likely to develop type 2 diabetes over a 10-y interval, independent of other risk factors such as body mass index BMI, age, and ethnicity [10].

Thus, the aim of this case-control study was to determine whether there is a relationship between serum ferritin level and the risk of GDM among Iraqi women.

PATIENTS AND METHODS:

The study was conducted at the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital for the period between June 2010 through June 2011. The study included 100 pregnant women admitted to the obstetric ward, fifty healthy pregnant control group, and fifty with gestational diabetes. They were selected according to clinical signs, symptoms and investigations. Inclusion criteria were; singleton pregnancy, maternal age 15-40 years, gestational age 20 weeks relying upon the last menstrual cycle LMP or early sonography. Women were diagnosed to have diabetes by single random blood sugar > 200 then referred to our ward for sugar profile and for the control the blood sugar. Women with anemia (Hb < 10.5g/dl), iron overload state Hb >14g/dl), pre-existing infectious disease, multiple pregnancy, polyhydramnios, preterm labor, pre-eclampsia, eclampsia and/or pregnancy induced hypertension, and women with liver and renal diseases were excluded.

Verbal consent, medical history, past and present, menstrual, obstetric and family history was taken from women included in the study. Abdominal and pelvic examinations were performed when needed. Hematological investigations including Hb%, PCV,TIBC, and serum iron, in addition to abdominal ultrasound for the determination of gestational age and exclusion of congenital anomalies. Serum ferritin was assayed by UBI Magiweltm-United Biotech ferritin quantitative test system, a solid phase enzyme-linked immunosorbent assay (ELISA) kit, according to the manufacturer instructions. Serum iron and total iron binding capacity (TIBC) were estimated by standard method recommended by the International Committee for Standardization Hematology. Data were collected and subjected to statistical analysis using the SPSS-18 "PASW" statistics 18 "statistical package for social sciences". Data were presented in simple measures of frequency, percentage, mean standard deviation, standard error of the mean, and range. Analysis of variance ANOVA was used for more than two groups, student t-test was for the difference between two means, and Pearson Chi-square (x^2) test for different percentages were used. Statistical significance was considered when the p value was less than 0.05

RESULTS:

In our study, the maternal age of the two groups of patients were comparable, the mean maternal age for diabetic women was (28.28 -± 6.40) ranging from 17 - 40 years , while the mean age of control group was (28.28 ± 6.40) ranging from 17- 41. There was no statistically significant difference in mean maternal age, p value 0.867.

The mean parity for diabetic women was (2.8± 1.53), while the mean parity of control group (2.04 ± 1.46). There was no statistically significant difference in parity in between two groups, p value was 0.423.

The mean gestational age of diabetic women was (34.20 ± 2.41) ranging from 30-40 years, and the control group had a mean gestational age of (34.82± 2.52) ranging from 28-40 years. There was no statistically significant difference in gestational

age between the studied groups, *p* value 0.21.
Serum ferritin level, serum iron, and total iron binding capacity (TIBC) were measured. Serum ferritin level (mean and SD, median, mode, range, percentile) for both groups are shown in table 1.

Mean serum ferritin level in diabetic women was (95.60± 27.99) ng / ml, in control group the mean serum ferritin was (31.72± 13.42) ng/ml. There was a highly significant difference in mean serum ferritin, *p* value 0.0001(Figures 1, 2).

Table 1:Serum ferritin (ng/ml) distribution between studied groups.

Serum Ferritin (ng/ml)	GDM	Controls
Mean±SD	95.60±27.99	31.72±13.42
Standard Error of the Mean	3.96	1.90
Mode	112.00	30.00
Range	10-140	11-60
Percentile 05th	50.00	13.00
50th (Median)	98.00	30.00
P value	0.0001*	

*T-test for two independent means is significant at the 0.05

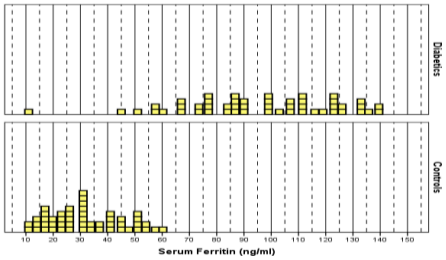

Figure1: Distribution of serum ferritin in two different groups

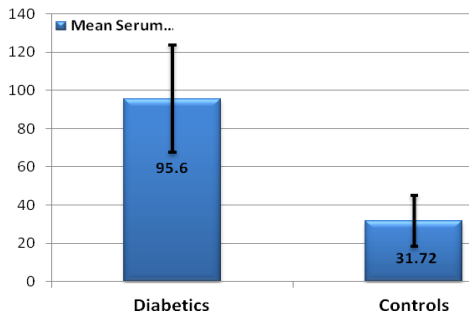

Figure 2: Mean serum ferritin level (ng/ml) in the two different studied groups.

Serum iron level; (mean, and SD, median, mode, range, percentile) for both groups are shown in table 2 and figures 3, 4. Mean serum iron level in women with gestational diabetes was 97.22±21.47µg/dl and in control group serum iron level was 105.52±64µg /dl, there was no significant difference between the two studied groups, *p* value0.076 (Figures 3, 4).

Table 2: Serum iron level (µg /dl) in the two studied groups.

Serum Iron (µg/dL)	GDM	Controls
Mean±SD	97.22±21.47	105.52±24.64
Standard Error of Mean	3.04	3.49
Mode	96.00	74.00
Range	60-134	60-144
Percentile 05th	62.00	62.00
50th (Median)	97.00	105.50
P value	0.076	

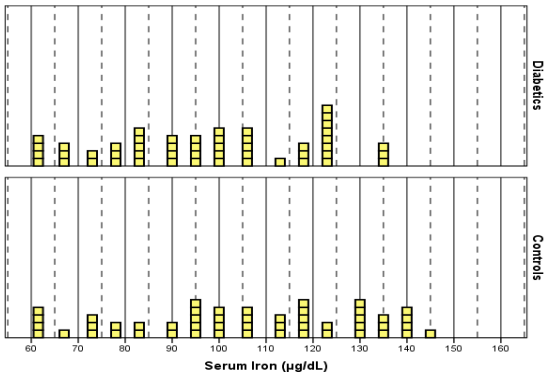

Figure3: Distribution of serum iron in two different groups

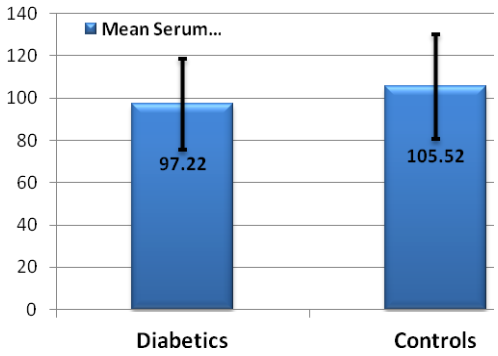

Figure 4: Demonstrate mean serum iron level in the two studied groups.

Regarding TIBC ferritin level the (mean and SD, median, mode, range, percentile) for both groups are shown in table 3 and figure 5. The mean level of TIBC for women with gestational diabetes was 326.90±45.39µg/dl and mean level of TIBC in control group was 312.16±40.48, there was no significant difference in between those group; and *p* value 0.090 (Figures 5, 6).

Table 3: TIBC level (µg /dl) in two studied groups.

TIBC (µg/dL)	GDM	Controls
Mean±SD	326.90±45.39	312.16±40.48
Standard Error of Mean	6.42	5.72
Mode	285.00	289.00
Range	249-411	249-389
Percentile 05th	252.00	253.00
50th (Median)	322.50	303.00
P value	0.090	

No significant difference in mean as *p* value <0.05

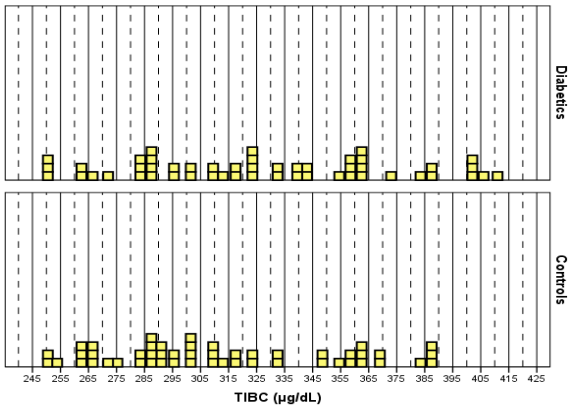

Figure 5: Distribution of TIBC in two different groups.

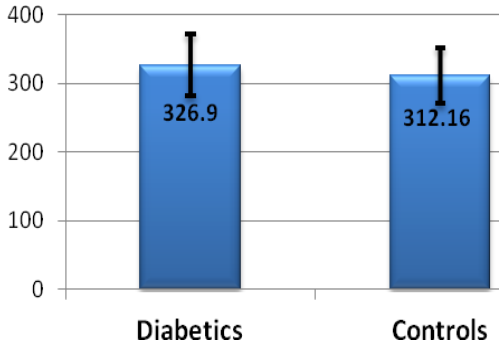

Figure 6: Demonstrate mean TIBC in two difference groups.

Table 4: Association of serum ferritin with different variables.

Age (years)	Diabetics		Controls	
	Serum Ferritin (ng/ml)		Serum Ferritin (ng/ml)	
	No	Mean±SD	No	Mean±SD
<20	3	87.67±30.53	4	32.25±6.55
20—24	8	81.88±34.97	13	34.15±15.81
25—29	16	90.31±26.15	10	29.10±12.86
30—34	18	104.72±25.91	15	34.53±14.05
=>35	5	106.40±22.82	8	25.50±11.17
P value		0.252		0.542
Parity				
Primi	7	104.29±22.43	10	34.70±10.99
Para1	10	98.90±24.52	7	32.29±13.43
Para2	12	103.75±26.80	15	27.80±12.43
Para3	8	85.13±30.61	10	36.90±13.03
Para4 & more	13	87.31±32.02	8	28.38±18.09
P value		0.405		0.451
Gestational age (weeks)				
<32	6	79.00±26.40	3	22.33±7.77
32-33	13	101.85±30.27	11	31.64±14.87
34—35	17	87.35±26.42	15	33.53±13.21
36—37	10	109.30±22.47	14	29.29±14.74
=>38	4	101.00±31.09	7	36.86±10.40
P value		0.144		0.536

*Significant difference among means using ANOVA test at 0.05 level of significance.

In table 4 serum ferritin increases with the increase of maternal age in women with gestational diabetes; at age of 20 it was (81.88±34.97) increasing to (106.40±22.82) at age 35, without significant difference from control group (*p* value was 0.542). Concerning serum ferritin to parity, we found that serum ferritin was decreasing as parity increases; the mean serum ferritin in para 1 women was (104.29±22.43) compared to (87.31±32.02) in para 4 women. Serum ferritin level in para 4 women was similar to that in the control group (*p* value0.405). Serum ferritin was elevated with the increase of gestational age, the mean serum ferritin when women at 32 weeks gestation was (79.00±26.40) and (101.00±31.09) and no significant difference from control group (*p* value 0.144).

Table 5: Serum ferritin in relation to the type of treatment.

GDM treatment	Serum Ferritin (ng/ml)	
	Count	Mean±SD
Diet	15	64.87±20.05
Insulin	35	108.77±19.20
P value		0.0001*

We measured serum ferritin in women with gestational diabetes who need insulin and in women on diet; the mean values of serum ferritin was (64.87±20.05) and (108.77±19.20) for women on diet and women who need insulin respectively. We found significant difference in the mean serum ferritin level between the two groups (*p* value was 0.0001) as shown in table 5 and figure 7.

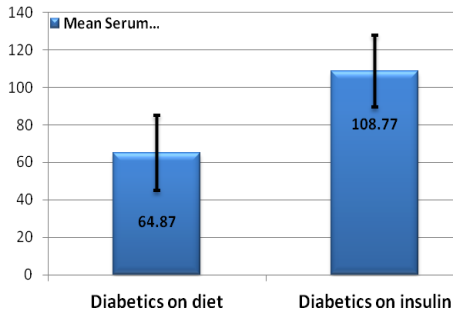

Figure 7: Distribution of serum ferritin in relation to type of treatment
*Significant difference among means using ANOVA test at 0.05 level of significance.

Table 6: Correlation of diabetes with different values.

Correlations of G. diabetics				
		Serum Ferritin (ng/ml)	Serum Iron (µg/dL)	TIBC (µg/dL)
Age (years)	r	0.255	-0.266	-0.002
	P	0.073	0.062	0.987
Parity	r	-0.248	-0.124	-0.124
	P	0.083	0.391	0.392
Gestational age (weeks)	r	0.200	0.095	-0.076
	P	0.163	0.513	0.600
Serum Ferritin (ng/ml)	r		-0.069	-0.142
	P		0.632	0.326
Serum Iron (µg/dL)	r			0.234
	P			0.103

Table 7: Correlations of controls with different values.

Correlations of controls				
		Serum Ferritin (ng/ml)	Serum Iron (µg/dL)	TIBC (µg/dL)
Age (years)	r	-0.116	0.083	-0.062
	P	0.424	0.567	0.670
Parity	r	-0.087	-0.205	-0.018
	P	0.547	0.154	0.903
Gestational age (weeks)	r	0.113	0.059	0.198
	P	0.434	0.684	0.168
Serum Ferritin (ng/ml)	r		-0.086	0.064
	P		0.555	0.660
Serum Iron (µg/dL)	r			0.120
	P			0.405

When we studied the correlation of serum ferritin, serum iron and TIBC with different values in both groups as shown in above tables, the result showed variable weak correlation whether –ve or +ve

DISCUSSION:

This is a case-control study which was designed to assess the association between elevated serum ferritin level and other hematological parameters in 50 pregnant women with gestational diabetes compared to 50 pregnant normal women. Both groups were at the same gestational age, parity, and maternal age. Serum ferritin was assessed above 20 weeks of gestation. We found significant statistical difference between the two groups; serum ferritin was markedly higher in women with GDM compared to the control group.

Our findings were consistent with the data published by the Camden study who found that ferritin levels were significantly increased in patients with GDM compared to those without GDM [(1)]. It was observed by Soubasi *et al* that pregnant women with higher serum ferritin levels in early gestation had a twofold increased risk of GDM [(7)]. Elevated serum ferritin was recognized by Sharifi *et al* in their study among women with GDM compared to healthy non-diabetic pregnant women [(16)]. These findings were consistent with the findings revealed by Afkhami-Ardekani in a case-control study among 34 normal pregnant women compared to 34 women with GDM at 24-28 weeks of pregnancy [(20)]. Similar investigation done by Fatemeh Nasiri Amiri *et al*, have shown that serum ferritin was noticeably higher in women with GDM in comparison to normal pregnant women [(19)].

Serum iron was not significantly elevated among our studied group, the same findings were reported by Nasiri Amiri as well [(19)]. On the other hand, Prasad *et al* in their study among Indian Pregnant women concluded that serum iron level is positively related to GDM. While serum phosphorus and hemoglobin concentration have not shown any significant variation [(21)]. These findings were in concordance with Mohammed Afkhami who observed significantly different levels of serum iron between the two studied groups, perhaps due to the high iron supplementation given to the diabetic women [(20)].

We observed an elevation in TIBC level among women in GDM in comparison to the control group. These findings were consistent with the findings of Afkhami; he showed that TIBC was significantly higher in GDM group compared to the control group, while Fatemeh Amiri did not find any significant difference between the two groups [(19, 20)].

Lao *et al* in his report observed that serum ferritin was significantly higher in the third trimester of pregnancy than the first trimester [8]. Similar results were observed in our study groups; serum ferritin was higher at 38 weeks than that at 31 weeks of gestation. In addition, we noticed that serum ferritin increases with the increasing maternal age, Xinhua chen supported that and found a linear relationship between serum ferritin and maternal age [1]. In our studied population, serum ferritin level was decreasing with the increase in parity among the women with GDM, these findings were observed by Milman N who found an inverse relationship between serum ferritin and parity [22].

CONCLUSION:

Our study found a significant association between elevated serum ferritin level and gestational diabetes. Moreover, serum ferritin level could be a useful marker for the development of GDM in high risk patients.

Recommendations

1. Further studies are required to investigate the pathophysiological mechanism of increased serum ferritin levels during pregnancy
2. The assessment of serum ferritin level could be a good tool for the diagnosis of GDM

REFERENCES:

1. Chen X, Scholl T.O., Stein P.: Association of elevated serum ferritin levels and the risk of gestational diabetes mellitus in pregnant women (The Camden Study). *Diabetes Care*, May 2006; Vol. 29, Number 5, pp 1077-1082
2. Fernandez-Real J.M., Penarroja G., Castro A., Garcia-Bragado F., Hernandez-Aguado I., Ricart W. : Blood letting in high ferritin type2 diabetes Effect on insulin sensitivity and □-cell function. Diabetes, April 2002; Vol. 51, 1000-1004
3. Watanabe H., Association of elevated serum ferritin concentration and risk of gestational diabetes mellitus (Ch. 7) in: Ferritin Functions, da Lima G. S.(Editors) Nova Science Publishers, Inc. 2012.
4. Pramiladevi R., Umakanth Boke, Sheeram Kora: Serum ferritin levels in type II diabetes mellitus. Scholars Journal of applied Medical Sciences (SJAMS) Sch. J. App. Med. Sci. 2013; 1(5):472-475.
5. Wrede C E, Buettner R, Bollheimer L C, Scholmerich J, K-D Palitzsch and C Hellerbrand: Association between serum ferritin and insulin resistance syndrome in a representative population. European Journal of Endocrinology 2006; 154: 333-340
6. Jiang L., Wang A., Molyneaux L., Constantino M. I. and Yue D.K.: The long-term impact of ferritin level on treatment and complications of type II diabetes (A letter to the editor). Diabetes, Obesity and Metabolism, 2008; 10, 514-522
7. Soubasi V., Petridou S., Sarafidis K., Tsantali Ch., Diamanti E., Buonocore G., Drossou-Agakidou V.: Association of increased maternal ferritin levels with gestational diabetes and intra-uterine growth retardation. Diabetes and Metabolism, 2010; 36: 58-63
8. Terence T. Lao, Ka-Yu Tse, Louis Y. Chan, Kar-Fai Tam, Lai-Fong Ho: HBsAg Carrier Status and the Association Between Gestational Diabetes With Increased Serum Ferritin Concentration in Chinese Women. Diabetes Care 2003; 26: 3011–3016.
9. Chunfang Qiu, Cuilin Zhang, Bizu Gelaye, Daniel A. Enquobahrie, Ihunnaya O. Frederick, Michelle A. Williams: Gestational Diabetes Mellitus in Relation to Maternal Dietary Heme Iron and Nonheme Iron Intake. DIABETES CARE, July 2011; Volume 34, 1564-1569
10. Scholl T.O.: Iron status during pregnancy: setting the stage for mother and infant. The American Journal of Clinical Nutrition, 2005; 81(suppl): 1218S-22S
11. Uzma Zafar, Hamid Javaid Qureshi, Asima Karim: Insulin resistance and serum parameters of iron statusin type 2 diabetics. Pak J Physiol 2011; 7(2)
12. Sumeet Smotra, V.R.Tandon, Sanjay Sharma, R. P. Kudyar: Serum Ferritin and Type-2 Diabetes Mellitus. October-December 2007; Vol. 9, No. 4,
13. Sumeet Smotra, R.P. Kudyar: Relationship between serum ferritin and type-2 diabetes mellitus. J K Science. Oct-Dec 2008; Vol. 10, No. 4, 170-174.

14. Sumesh Raj, G.V.Rajan: Correlation between elevated serum ferritin and HbA1c in type 2 diabetes mellitus. International Journal of Research in Medical Sciences. 2013 Feb;1(1):12-15

15. Helin A, Tarja Inkeri Kinnunen, Jani Raitanen, Suvi Ahonen, Suvi M Virtanen, Riitta Luoto: Iron intake, haemoglobin and risk of gestational diabetes: a prospective cohort study. BMJ 2012; 2: 001730.

16. Sharifi F., Amir Ziaee, Abdolamir Feizi, Nouraddin Mousavinasab, Afagh Anjomshoaa, Pooran Mokhtari: Serum ferritin concentration in gestational diabetes mellitus and risk of subsequent development of early postpartum diabetes mellitus. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2010; 3: 413–419

17. Katherine Bowers, Deirdre K Tobias, Edwina Yeung, Frank B Hu, and Cuilin Zhang: A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes Am J Clin Nutr. 2012 Feb; 95(2): 446–453. Published online 2012 Jan 4.

18. Terence T. Lao, Kar-Fai Tam: Maternal Serum Ferritin and Gestational Impaired Glucose Tolerance. Diabetes Care, September 1997; Volume 20, No. 9

19. Fatemeh Nasiri Amiri, Zahra Basirat, Shabnam Omidvar, Majid Sharbatdaran, Karimollah Hajian Tilaki, and Mahdi Pouramir: Comparison of the serum iron, ferritin levels and total iron-binding capacity between pregnant women with and without gestational diabetes. J Nat Sci Biol Med. 2013 Jul-Dec; 4(2): 302–305.

20. Mohammad Afkhami-Ardekani, Maryam Rashidi: Iron status in women with and without gestational diabetes mellitus. Journal of Diabetes and Its Complications 2009; 23: 194–198

21. Prasad DKV, Sheela P, Kumar AN, Kumar NL, Deedi MK and Madhulatha D: Iron Levels Increased in Serum from Gestational Diabetes Mellitus Mothers in Coastal Area of Andhra Pradesh. J Diabetes Metab 2013; 4:5.

22. Milman N: Serum ferritin in Danes: studies of iron status from infancy to old age, during blood donation and pregnancy. Int J Hematol. 1996 ; 63:103-35.