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Correlation between Soluble Transferrin Receptor and Iron Status in Women with Gestational Diabetes

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Abstract. Soluble transferrin receptor (sTfR), a cleaved form of transferrin receptor 1 (TfR),serves as a marker of cellular iron demand and is largely unaffected by inflammatory responses. This makes it a potentially reliable indicator of iron status, even in the context of inflammation. Human soluble transferrin receptor (sTfR) concentrations were measured by ELISA in a group of 40 pregnant women with gestational diabetes mellitus (GDM) and a comparison group of 40 pregnant women without GDM. Iron-related parameters were also assessed in both groups using the Cobas Integra 400 Plus systems. Women with GDM exhibited significantly elevated sTfR levels compared to the control group. Ferritin levels were also increased among those with GDM.The results demonstrate elevated sTfR levels in pregnant women with GDM compared to those without the condition. Moreover, a positive association was identified between sTfR ferritin, and hepcidin levels. Elevated ferritin was also positively linked to increased GDM risk

Highlights:

1. Pregnant women with gestational diabetes showed significantly higher serum sTfR levels compared to controls.
2. Ferritin levels were markedly elevated in the GDM group, while serum iron and TIBC showed no significant differences.
3. sTfR demonstrated limited diagnostic accuracy for GDM, with only 55% sensitivity and 43% specificity.

Keywords: soluble transferrin receptor, Iron status, Gestational Diabetes , ELISA.

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Introduction

Diabetes encompasses a group of metabolic disorders marked by persistently elevated blood glucose levels (hyperglycemia), resulting from either a deficiency in insulin, resistance to its action, or both (1). Insulin, a hormone produced by pancreatic β-cells, facilitates glucose uptake by various tissues, supplying energy for daily functions and supporting numerous metabolic pathways (2,3).

Gestational diabetes mellitus (GDM) refers to a condition characterized by impaired glucose tolerance that is initially identified during the second or third trimester of pregnancythat does not meet the criteria for overt diabetes (4). It has become a significant global health concern and is one of the most frequent complications during pregnancy, often presenting as hyperglycemia that arises spontaneously during gestation (5).

Iron is a vital micronutrient that plays a key role in numerous physiological functions, such as ,the transport of oxygenantioxidant defense, and the mitochondrial electron transport chain in oxidative phosphorylation (6). As pregnancy progresses, both iron requirements and insulin resistance increase (7). Excess iron, particularly in the liver, can contribute to insulin resistance by disrupting insulin signaling and impairing hepatic insulin clearance (8). Emerging evidence suggests that iron can influence glucose metabolism even without iron overload. Increased iron levels can contribute to oxidative stress by promoting the formation of reactive oxygen species (ROS), damaging pancreatic β-cells and hindering insulin production (9,10).

Serum ferritin is commonly utilized as an indicator of the body's overall iron reserves and is frequently examined in studies exploring the link between iron status and gestational diabetes mellitus (GDM). Nonetheless, because ferritin is an acute-phase reactant, its levels can increase due to subclinical inflammation, a condition that is also linked to insulin resistance observed in .GDM)11(

Soluble transferrin receptor (sTfR) originates from the cleavage of transferrin receptor 1 TfR1)) particularly when it is unbound to iron-saturated transferrin. This cleavage occurs via a

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membrane-associated protease in erythroid cells. sTfR concentrations typically rise in iron deficiency and decline in states of iron excess (12,13).

Transferrin receptor is a membrane-bound protein that facilitates iron uptake from plasma into cells. Its soluble form, sTfR, reflects cellular demand for iron. The amount of sTfR in circulation correlates with the expression of transferrin receptors on cell surfaces and inversely with intracellular iron availability (14).

Compared to other iron-related markers, sTfR is considered more reliable for evaluating iron status, particularly because it is less affected by inflammation, though it may still be influenced by erythropoietic activity. Parameters such as serum hepcidin and sTfR may offer a more accurate assessment of iron status than ferritin or standard hematologic indices (15). Moreover, sTfR levels, which reflect tissue-level iron deficiency, remain relatively stable during inflammatory responses, making them potentially useful in assessing iron status even in inflammatory states (11).

Four prospective studies (16,17,18,19) have examined the association between sTfR concentrations and the risk of developing gestational diabetes mellitus (GDM). These studies consistently found no significant link between sTfR levels and GDM onset. In particular, a longitudinal study conducted in a multiethnic U.S. population reported no notable association between sTfR concentrations and GDM risk)19(.

This study is designed to investigate the iron status of pregnant womenwith GDM in comparison to healthy pregnant controls during the second and third trimesters. It evaluates serum sTfR concentrations in both groups and explores the correlations between sTfR and other iron parameters (Levels of serum iron, ferritin, and total iron-binding capacity (TIBC).

Materials and Methods

Study subjects

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Ethical clearance was obtained from the Research Ethics Committee, with authorization from both the Ministries of Higher Education (Environmental and Health sectors) and the Ministry of Scientific Research in Iraq.This case-control research was performed over the period from January to May 2019.Eighty pregnant women at second and third trimester between (16-40) weeks of gestation and average age between (20-40) years old were enrolled in this study. Patient group consist of forty pregnant women diagnosed with GDM depending on OGTT test. Forty apparently healthy pregnant women without GDM were involved as control group. Body mass index for both groups matched with gestational age. All pregnant woman with renal impairment ,thyroid dysfunction ,overt Diabetes either type 1 or 2, hypertension ,concurrent acute or chronic inflammation disease , post operation , inflammatory bowel disease ,malignancy, hypoprotenaemia and pregnant women taking therapeutic dose of iron were excluded from this study.

Method:

Eight milliliters of each sample was transferred to Test tube with separating gel in order to collect serum. The sample was allowed to stand at room temperature for 5 minutes before being centrifuged for 5min at 3000 round per minute (rpm). Serum was separated and divided to two plan tube as following:

1- Tow milliliters of serum were used to estimate Iron status (S.ferritin ,S.Total Iron Binding Capacity & S. Iron) and the analyze concentrations of each sample was calculated automatically.

2-Tow milliliters used to determine sTfR by ELISA technique (Enzyme Linked Immunosorbent Assay).All absorbance were taken at 450 nm.

Statistical analysis

Statistical analysis was conducted by using Microsoft excel 2013 and SPSS software version 20. The numerical data were presented as mean ± standard deviation (SD). To compare the average serum levels of sTfR and iron status between the patient and control groups in

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control, t-test was applied. All statistical tests were two tailed , with significance was set at P≤0.05. Additionally , a Receiver Operating Characteristics (ROC) curve was generated to assess the sensitivity , specificity and diagnostic performance of sTfR as biomarker.

Results

The mean and standard error of sTfR for pregnant women with GDM (29.32±2.90 ng/L) which was higher than that of control groups (21.69±1.34ng/L) and showed asignificant different in comparison with control group (P0. 02). (Table 1).

Table (1) :Comparison between serum sTfR concentrations in GDM woman (patients group) and control group

Mean±SE		P value
Patients group	Control group	
29.32±2.90	21.69±1.34	0.02

Regarding iron status (TIBC , s.iron and s.ferritin) showed the mean of iron values for pregnant with GDM (15.42±1.22) was more than that for control group (12.69±1.08) with no significant difference (P=0.09) while the mean of TIBC values for patients group (83.42 ±3.58)was less than that for control group (90.04 ±2.92)with no significant different(P=0.15) and the mean Ferritin values was significantly higher among cases with gestational diabetes(77.66 ±9.06) compared to controls(29.52 ±3.14)A highly significant difference was observed between the study groups (P < 0.001), as . .shown in Table 2

Table (2) : Comparison between biochemical parameters within study groups by using student t- test

Groups		**N**	**Mean**	**SE**	**P value**
Iron	Patients	40	15.42	1.22	NS

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	controls	40	12.69	1.08	
TIBC	Patients	40	83.42	3.58	NS
	controls	40	90.04	2.92	
Ferritin	Patients	40	77.66	9.06	0.001
	controls	40	29.52	3.14	

A significant positive correlation was found between sTfR and ferritin, while negative correlations were observed with serum iron and TIBC (Table 3).

Table (3): Correlation between iron status and **sTfR** by using Pearson correlation

R= Pearson correlation P= probability		STFR
Iron	R	-0.039
	P	0.810
TIBC	R	-0.007
	P	0.965
Ferritin	R	0.066
	P	0.684

The Analysis using the Receiver Operating Characteristic (ROC) curve showed that this test has limited accuracy and a low ability to differentiate cases of gestational diabetes. The determined cut-off value for serum sTfR concentration in pregnant women with GDM was greater than 21.23 ng/L, yielding a sensitivity of 55%, specificity of 43%, and an area under the curve (AUC) of 0.636 (Table 3).

Table (4) : Sensitivity and Specificity of **sTfR** ROC curve in pregnant woman with GDM

Cut-off value	Specificity	Sensitivity	Area under curve

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>21.23 ng/L	43%	55%	0.636

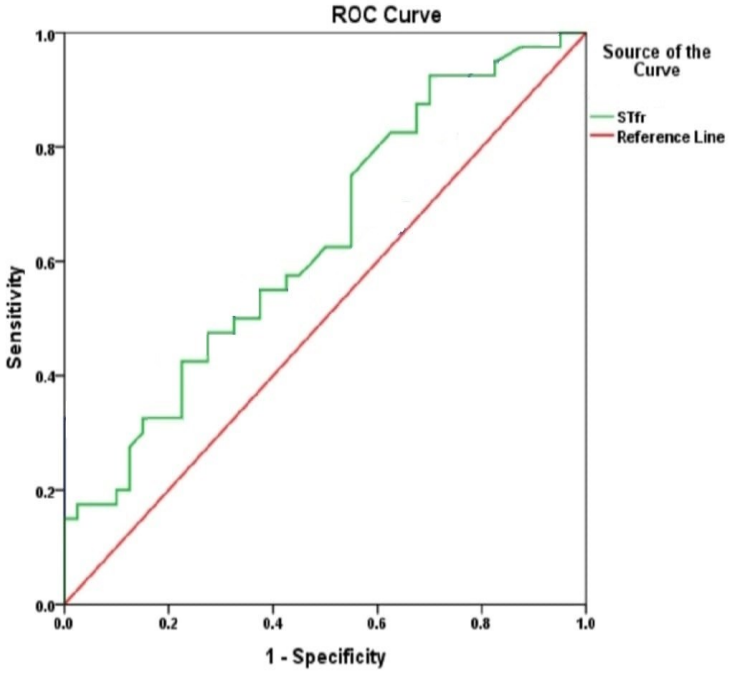

Figure 1: ROC curve for human **sTfR**

Discussion

GDM refers to a form of glucose intolerance first detected in mid to latepregnancy and does not meet the criteria for overt diabetes (5). It has become a widespread public health concern globally (20). As one of the most frequent complications in pregnancy, it involves the development of spontaneous hyperglycemia during gestation (21).

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Soluble transferrin receptor (sTfR), an indicator of tissue-level iron deficiency, has not been extensively investigated in relation to GDM risk. In the present study, sTfR concentrations were found to be significantly higher ($P < 0.05$) in pregnant women diagnosed with GDM compared to the control group.

This finding is consistent with research by Bowers et al. (2016) (18), who observed significantly elevated sTfR levels in GDM cases versus controls ($P = 0.002$), reporting a positive association between plasma sTfR concentrations and GDM.

Conversely, a study by Rawal et al. (2017) (19) found no meaningful variation in sTfR levels between women with and without GDM. Similar findings were reported by Khambalia et al. (2016) (17), where no significant variation in median sTfR levels was noticedbetween GDM and non-GDM groups ($P = 0.11$).

As a marker of the body's iron availability for red blood cell production, sTfR reflects functional iron status. In a study by Kataria et al. (2018) (22), No meaningful link was identified .between higher sTfR levels and the risk of developing GDM

In this study, the mean serum iron level was higher in the GDM group than in the control group; however, this difference did not reach statistical significance ($P = 0.09$). Similarly, although the average total iron-binding capacity (TIBC) was lower among women with GDM, the difference was not statistically significant ($P = 0.15$). In contrast, serum ferritin levels were notably elevated in the GDM group compared to the controls, with a statistically significant .difference ($P < 0.001$)

Similar outcomes were reported by Derbent et al. (2013) (23), who found significantly elevated levels of serum ferritin and iron in the GDM group ($P = 0.014$ and $P = 0.018$, respectively). Rawal et al. (2017) (19) also observed a strong positive relationship between ferritin concentrations and GDM risk during the second trimester.

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Supporting this, Khambalia et al. (2015) (17) reported increased odds of developing GDM in women with elevated ferritin levels. Kataria et al. (2018) (22) further confirmed that average serum iron and ferritin levels were higher in women with GDM, although no meaningful variationin in TIBC was noticedbetween the GDM and non-GDM groups.

Conclusion

In this study, women diagnosed with GDM exhibited higher serum sTfR levels relative to the control group. However, due to its limited diagnostic performance—demonstrated by sensitivity and specificity values of 55% and 43%, respectively,serum sTfR is not considered a reliable standalone biomarker for predicting GDM. Moreover, sTfR concentrations were significantly positively associated with ferritin, but inversely related to serum iron and TIBC.

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