

Gestational diabetes and serum ferritin concentration in Iraqi pregnant women

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ABSTRACT

Background. A strong connection between elevated ferritin levels and diabetes incidence was noted as diabetes mellitus (DM) in pregnant women.

Objective. The aim of this study was to examine the effect of elevated ferritin levels on the development of gestational diabetes mellitus GDM in early pregnancy.

Materials and methods. Thirty expecting women with a gestational age of 12-16 weeks and 30 age-matched healthy pregnant women were enrolled in this study. Blood measurement of ferritin was collected in the first trimester. Glucose tolerance test was done to diagnose GDM at the period (24-28) weeks.

Results. Highly significant differences in the levels of HbA1C, R.B.S, and ferritin were found between control and patients ($p=0.0001$), respectively. There was positive correlation in the ferritin level with HbA1c ($r=0.9033$), RBS ($r=0.24$) and with iron ($r=0.002$).

Conclusion. Serum ferritin can be used as a diagnostic marker for gestational diabetes mellitus in the first and second trimesters of pregnancy, and to determine the appropriate regular supplementation and dosage relationship for both anemic and non-anemic pregnant women.

Keywords: ferritin, gestational diabetes, HbA1C, insulin resistance, iron

INTRODUCTION

One of the consequences of pregnancy is gestational diabetes mellitus (GDM), a condition in which blood glucose levels rise on their own throughout the gestation period [1]. Nearly 18-million births are affected annually due to 14% of pregnancies worldwide with GDM as the International Diabetes Federation (IDF) reports [2].

During pregnancy, many changes happen according to its conditions including changes in the sensitivity of insulin. Throughout early gestation, insulin sensitivity increases, boosting glucose entry into adipose tissues to ensure increasing energy needs for pregnancy [3].

Nevertheless, proceeding pregnancy may cause a surge of hormones, like estrogen, progesterone, leptin, cortisol, placental lactogenic, and placental growth hormone, enhancing in turn insulin resistance [4].

This results in blood glucose elevating, and being easily transported across the placenta to provide a fuel that is needed for fetus growth. Subsequently, this promotes endogenous glucose production and the breakdown of fat stores, leading to the production of high concentrations of blood glucose and free fatty acid (FFA) [5]. In animal patterns, there is data suggests that to keep glucose homeostasis, pregnant women counter these changes through pancreatic β -cells hypertrophy, hyperplasia, and boosting glucose-stimulated insulin secretion (GSIS) [6]. Within a few days of delivery, the placental hormones will return the maternal insulin sensitivity to pre-pregnancy levels [7]. For some reason, the normal metabolic adaptations to pregnancy do not adequately occur in all pregnancies, resulting in GDM.

In a healthy pregnancy, the mother's body goes through several physiological changes to meet the needs of the developing child. Insulin sensitivity is one important metabolic adaptation that is almost accom-

panied by other alterations to the cardiovascular, respiratory, renal, hematologic and metabolic systems.

GDM is formally classified as “diabetes first diagnosed in the second or third trimester of pregnancy that is not either previously existing type 1 or type 2 diabetes” [1]. Nevertheless, due to a lack of consensus amongst health professionals on the precise threshold for a GDM diagnosis depending on the criterion used, some societies advised following criteria of the International Association of Diabetes and Pregnancy Study Group (IADPSG) in the diagnosis of GDM [8].

METHODS

This case-control study included 30 pregnant women (25-38 years) with gestational diabetes and 30 pregnant healthy women, same age. Both groups were joined consecutively at 24–28 weeks of pregnancy at Baghdad private clinic, from October 2022 to March 2023. All contributors were told about the purpose of the trial in detail and signed informed consent at registration. Eligible participants were women of a normal pregnancy; mid-trimester (24–28 weeks) diagnosed with GDM, according to the International Association of the Diabetes and Pregnancy Study Groups, using a 75-gram oral glucose tolerance test (OGTT). IADPSG [9] were investigating serum iron, and ferritin. Pregnant women with iron deficiency anemia, a history of malignancy, acute or chronic inflammatory or infective diseases, seizure disorders, DM, renal disease, liver disease, and alcohol or drug abuse, were excluded.

BMI was calculated as a pre-pregnant weight in kilograms per square of height in meters.

Serum ferritin of both groups was measured and compared. The glucose oxidase peroxidase method was used to estimate plasma glucose. Two-site sandwich immunoassay using direct chemiluminometric technology to evaluate serum ferritin and measuring glycosylated hemoglobin (HbA1c) by ion exchange chromatography with DS5.

A two-step method was used for the diagnosis of GDM. Initially, the plasma glucose concentration was estimated by (a 75-gram oral glucose tolerance test) between weeks 24 and 28 of gestation, and this diagnostic test was performed on the subgroup of women having plasma glucose concentrations over the glucose threshold value (>140 mg/dL).

Statistical analysis

For analysis, SPSS version 20 software was employed. The information was displayed as mean± standard deviation. Group means were matched using the Student’s t-test and analysis of variance (ANOVA). The Pearson correlation statistic was used to investigate the connection between high serum ferritin and BMI, HbA1c, RBS, and serum iron.

RESULTS

No significant difference was found in the BMI and iron levels between patients and control groups (p=0.29, 0.8) respectively. Whereas, there were highly significant differences in the levels of HbA1C, R.B.S, and ferritin) between control and patients (p= 0.0001), respectively (Table 1).

TABLE 1. Frequency - Table of age

	Mean ± SD of CONTROL	Mean ± SD of PATIENTS	P
BMI	29.3 + 4.4	30.9 + 5.08	0.29
HbA1C	4.93 + 0.49	7.37 + 0.88	0.0001
R.B.S	97.14 + 14.3	191.7 + 36.7	0.0001
FERTINE	86.7 + 47.7	193.85 + 64.9	0.0001
IRON	77.4 + 36.08	79.1 + 26.9	0.8

From the results in Table 2, there is a positive correlation in the ferritin level with HbA1c r = 0.33, RBS r=(0.24), and iron r=(0.002). On the other hand, a negative correlation was found in the level of ferritin with BMI r=(-0.0059).

TABLE 2. Correlation of ferritin level with the other measured parameters

Ferritin	
HbA1c	0.33
R.B.S	0.24
IRON	0.002
BMI	-0.0059

DISCUSSION

In this study, the mean HbA1c was observed to differ significantly between the patient and control groups. (7.37±0.88, 4.93±0.49) respectively with p-value=0.0001 and there was a positive correlation between the mean of HbA1c and the mean of ferritin (0.33). Similar results in other studies were found, where most of them showed a pre-diabetic range of HbAc1, while the control group was within the range [10]. Likewise, another study found that the prediction of pregnancy complications depends on first-trimester HbA1c of pregnancy, but it can’t be used for the diagnosis of GDM due to the physiological changes occurring during pregnancy [11]. However, it could be considered a biomarker in predicting type 2 DM occurrence in women with GDM. Also, similar findings from other studies mentioned that the mean HbA1c level in normal pregnant women was significantly lower than in GDM women [12].

As it is known, obesity causes a state of sub-clinical inflammation, the stored fat causes hypoxia by

compression of adipocytes leading to the release of inflammatory cytokines and chemokines. In our study, obesity's effect can be neglected because no significant difference ($p=0.29$) was found in the mean of BMI in the control and patient group (29.3 ± 4.4 , 30.9 ± 5.08) respectively. The mean of BMI falls within the overweight so a negative correlation was found between the mean of BMI and ferritin (-0.0059). However, many studies showed that obesity can activate leukocytes, macrophages, and lymphocytes to release pro-inflammatory mediators [13,14]. Moreover, other studies showed that a positive correlation was found between high levels of ferritin with the possibility of obesity, metabolic syndrome, and inflammatory marker CRP [15,16]. A study found that in overweight and obese people, ferritin strongly indicates the occurrence of inflammation rather than iron stores [17]. Surprisingly, a study indicates that elevated serum ferritin and hepcidin aren't associated with dietary intake but are associated with excessive adiposity [18].

For iron levels, no significant difference was found in the mean of Iron levels ($p=0.8$) between the patient and control groups (79.1 ± 26.9 , 77.4 ± 36.08), respectively. However, there is a positive correlation between the mean of iron levels and ferritin (0.002). According to a study, the origin of ferritin could be from an injured cell, liberating most of its iron in the form of a highly reactive free radical by the Fenton reaction (hydroxyl radicals) [19]. These free ions of ferrous (Fe^{2+}) can cause lipid peroxidation and produce ROS to trigger ferroptosis. Subsequently, low expression of antioxidant enzymes in pancreatic beta-cells makes them more susceptible to ferroptotic cell death. Undeniably, experiments on induced ferroptosis pharmacologically have impaired human pancreatic islets' function and viability [20]. Feng et al. also found similar results [21].

Ferritin has been the most iron biomarkers often investigated concerning GDM. However, the majority of earlier research was cross-sectional and only measured ferritin once, at the time of GDM diagnosis [22-24]. Although concentrations of peripherally circulating ferritin are thought to be a reliable indicator of body iron reserves, the ferritin levels can also increase when one has an acute-phase reactant, with systemic inflammation that is subclinical and linked to insulin resistance in GDM [25]. Therefore, prospec-

tive investigations evaluating iron status fit before to GDM diagnosis are necessary to distinguish GDM from the puzzling inflammation brought on by insulin resistance. Nevertheless, the results of prospective studies that have looked at the relationship between ferritin and the risk of GDM may be few and erratic [26,27]. One research conducted in Lebanon, for example, found a strong correlation between elevated ferritin levels in the early stages of pregnancy and poor glucose tolerance, but not with the prevalence of GDM. However, the study's small sample size of 16 GDM-afflicted women may have contributed to this finding [26].

Also, a growing body of research from epidemiological and biological investigations suggests that elevated body iron levels are linked to a higher risk of type 1 and type 2 diabetes [28,29]. Moreover, Induction of iron depletion has improved insulin sensitivity tests in those who are intolerant to carbohydrates [30,31]. According to other research, having a large amount of iron stored in the liver might impair insulin signaling by increasing insulin resistance and decreasing the liver's ability to absorb insulin. Alternatively, too much iron buildup in the muscles might increase the oxidation of non-esterified fatty acids (NEFAs) and obstruct the absorption or excretion of glucose. Additionally, iron buildup may hinder insulin's effectiveness and obstruct adipocytes' ability to transport glucose under the influence of insulin [32, 33]. In our study, small sample size and didn't using inflammatory marker could limit the obtained results, so more distinguish marker should be used in future to support our results.

CONCLUSIONS

From the results, serum ferritin can be used as a diagnostic marker for gestational diabetes mellitus in the first and second trimesters of pregnancy, and it plays a major role in the development of the disease. These results are crucial for clinical and public health settings to prevent the development of GDM and to determine the appropriate regular supplementation and dosage relationship for both anemic and non-anemic pregnant women. We need a novel iron biomarker to distinguish between inflammatory or dietary increases in ferritin levels in pregnant women.

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