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# High iron level in early pregnancy increased glucose intolerance

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ABSTRACT

High iron stores in pregnancy are essential in preventing negative outcomes for both infants and mothers; however the risk of gestational diabetes mellitus (GDM) might also be increased. We intend to study the relationship between increased iron stores in early pregnancy and the risk of glucose intolerance and GDM. This prospective, observational, single-hospital study involved 104 non-anemic pregnant women, divided into 4 groups based on the quartile values for ferritin at the first trimester of pregnancy. All participants were screened for GDM with 75-g oral glucose tolerance test (OGTT) at 24–28 weeks' gestation. We observed that ferritin levels at early pregnancy were significantly correlated to glucose level after OGTT at 1-h and 2-h (rho = 0.21, $p < 0.05$; rho = 0.43, $p < 0.001$ respectively). Furthermore, in the higher quartile for ferritin (>38.8 μg/L) glycemia at 2-h OGTT was significantly higher than in the others quartiles ($p = 0.002$). In multivariate regression analysis, serum ferritin was a significant determinant of glycemia at 2-h OGTT. Although we did not find a significant association in the incidence of GDM in women with higher serum ferritin levels, probably in reason to the limit power of our study, our data demonstrated that the role of iron excess is tightly involved in the pathogenesis of glucose intolerance. We report for the first time that high ferritin values in early pregnancy are predictors of impaired glucose tolerance in non-anemic women. Individual iron supplementation should be evaluated in order to minimize glucose impairment risk in women with high risk of diabetes.



## Introduction

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance resulting in hyperglycemia with onset or first recognition during pregnancy [1]. It is associated with an increased risk of perinatal complications and type 2 diabetes (T2D) later in life [2]. Most available evidence suggests that defects in the pathogenesis of GDM result from the same spectrum of causes that underlie hyperglycemia, including, reduced insulin secretion and insulin resistance [3].

Overweight, obesity and age at pregnancy are the major modifiable risk factors of GDM but, it is important to identify additional modifiable factors that might help to lower GDM risk [4]. Iron is as many others trace metals essential for cellular functions. Apart its vital role in oxygen transport and exchange, iron is a potent catalyst for the production of hydroxyl radicals from hydrogen peroxide through the Fenton chemistry, which can induce oxidative damage and apoptosis [5]. It is increasingly recognized that iron accumulation is associated with increased risk of type 1 diabetes and T2D, and has been proposed to be involved in the pathophysiological mechanism of T2D [6].

In pregnant women, an adequate iron level is important in preventing iron deficiency anemia as well as insuring an uncomplicated pregnancy, normal development of the fetus and maturity of the newborn child [7]. Pregnant women must enter pregnancy with iron stores ≥300–500 mg [8,9] if they are to meet their requirements fully. However, few studies suggest that iron stores are higher in GDM [10]. While in contrary, in a study iron-deficiency anemia is reported to have a reduced risk of GDM [11].

The objective of the present study is to examine the relationship between iron stores evaluated by ferritin in early pregnancy as a possible predictive factor of glucose intolerance and the associated risk for development of GDM in non-anemic Lebanese women.

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## Patients and methods

### Population and study design

This was a prospective observational study, conducted at Bahman hospital in Beirut between December 2012 and November 2013. The protocol was approved by the University Commission of Medical Ethic and Bioethics at Lebanese University and informed written consent form was obtained from each participant after explanation of the nature and purpose of the study.

Eligible participants were women with a single pregnancy, non-anemic with a hemoglobin (Hb) level ≥110 g/L according to World Health Organization (WHO) criteria [12], and who had their first prenatal visit before 12 weeks gestation. Women with preexisting anemia and chronic disease, such as diabetes mellitus, hypertension, dysthyroidism or inflammatory disease, were excluded. Among 150 women who met these criteria, 21 refused to participate, 11 had abortions before 24 weeks gestation and 14 were not submitted for assessment for GDM diagnosis. In the end, 104 pregnant women were included in the analysis.

Gestation duration was based upon gestation from the participants' last normal menstrual period and also confirmed by ultrasound. Detailed records of prenatal histories were gathered by research assistants. Questionnaires were obtained by interviews and completed from medical records of patients at the initial visit, and updated later between 24 and 28 weeks' gestation. Maternal data included socio-economic level, pre-pregnant weight, family history of diabetes, history of previous GDM, previous macrosomia, lifestyle, dietary habits and medication prescribed during pregnancy. Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. The total daily iron intake was obtained by an iron food frequency questionnaire and estimated according to the U.S. Department of Agriculture National Nutrient Database [13].

Participants were divided into four groups based on the quartile values for ferritin at the first trimester of pregnancy. All participants were screened for GDM between 24 and 28 weeks of gestation with 75-g oral glucose tolerance test (OGTT) using a 1 step approach as indicated by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) 2010 [14] and WHO 2013 [15] screening criteria. Glucose measurements were obtained at three times: at fasting and again twice after 1-h and 2-h glucose ingestion. Only one of the three values exceeding glucose thresholds was needed for GDM diagnosis (Fasting ≥ 92 mg/dL; 1-h ≥ 180 mg/dL and 2-h ≥ 153 mg/dL).

### Methods

Blood samples were collected at the beginning of the study and assayed for blood cell count, serum ferritin, fasting plasma glucose (FPG) and serum C-reactive protein (CRP). A second set of blood samples was taken between 24 and 28 weeks of gestation and assayed for blood count, serum ferritin, CRP, insulin, FPG, 1-h and 2-h plasma glucose. FPG was analyzed after an overnight fast of at least 8 h. The plasma glucose test was performed by enzymatic UV (hexokinase method). Serum CRP levels were measured by immunoturbidimetric assay using the Olympus AU 400 analyzer (Olympus Diagnostics, Germany). Serum ferritin was measured by chemiluminescence method automated on the Architect I (Abbott Diagnostics, USA). Insulin was assessed by radioimmunoassay (BI-Insulin IRMA kit, Cis bio International, Gif-sur-Yvette, France). Insulin sensitivity was calculated using the Homeostasis Model Assessment-insulin resistance (HOMA-IR) (Formula: fasting glucose (mg/dL) × fasting insulin μUI/mL/405) [16].

### Statistical analysis

Results are expressed as means ± standard deviation (SD) for continuous variables, and as percentages for categorical variables. The $Chi^2$ test was used for comparing categorical variables; when expected values within cells were <5, Fisher exact test was used. For quantitative variables with normal distribution, Student *t*-test and ANOVA were used to compare between two and multiple groups, respectively, in case of homogeneous variances. Correlation was evaluated by Spearman correlation coefficient (rho) for non-normally distributed variables. A multivariate logistic regression was used whenever the dependent variable was dichotomous, and the independent variables are those showing association in the bivariate analysis at *p*-value <0.2. In logistic regressions a non-significant Hosmer and Lemeshow test should be obtained to ensure an adequacy of the model. A multivariate logistic regression was conducted in our case to examine the influence of elevated ferritin (considered as the independent variable were group 1 (<13 μg/L) is referent) on the risk of GDM development (dependent variable). Subsequently, multiple linear regression was used whenever the dependent variable was continuous after ensuring residuals normality. It was applied to estimate the effect of ferritin on 2h-OGTT. Stratified analysis over "ferritin" was carried out to check if ferritin is a modifying factor that modifies the relationship between IR and GDM (or 2-h OGTT glucose values). Two strata were obtained one contains patients having ferritin level < 13 μg/L, and the other contains patients having ferritin level ≥ 38.5 μg/L. Statistical significance was defined as $p < 0.05$. Calculation was performed using a. computer package (Statistical Package for Social Sciences version 17; SPSS, Chicago, IL).

## Results

The characteristics of participants were tested according to womens' ferritin level at the beginning of the study (Table 1). Consequently, the participants were divided into four groups according to their baseline level of ferritin (G1: 8.98 ± 2.82 ($n = 27$); G2: 17.49 ± 2.64 ($n = 25$); G3: 29.88 ± 4.45 ($n = 26$) and G4: 56.55 ± 15.13 μg/L ($n = 26$); $p < 0.001$). There were no statistically significant differences in terms of age, BMI, other risk factors for GDM (familial history of diabetes, number of pregnancies, previous macrosomia, history of polycystic ovarian syndrome), lifestyle (smoking and physical activity), and gestational age at booking between the four groups. There were also no statistically significant differences in the baseline Hb, CRP and FPG. The dietary iron intake was significantly elevated in women in the higher quartile of ferritin level (11.4 ± 4.06 mg *vs* 9.81 ± 3.19; 9.47 ± 1.98; 8.75 ± 1.64 mg respectively in the first three groups; $p = 0.024$).

The results of blood sampling tests at the time of OGTT were represented in Table 2. Overall 16 (15.4%) patients developed GDM and no significant difference was found among the four quartiles (11.1%, 20%, 7.7%, and 23% respectively; $p = 0.381$). There was also no statistically significant difference in weeks of gestation, BMI, FPG, 1-h OGTT, whereas the difference was statistically significant in the 2-h OGTT (101.07 ± 21, 103.56 ± 22.8, 103.19 ± 25 mg/dL respectively in the first three groups *vs* 123.12 ± 21.7 mg/dL in the highest quartile; $p = 0.001$). In terms of iron status, the ferritin levels remain at 24–28 weeks' gestation statistically significantly higher in the highest ferritin group ($p = 0.019$), while Hb levels were similar between groups.

In addition, the characteristics of the patients were tested according to the 50th percentile for Hb values (125 g/L) at the entry of the study (Table 3), and the participants were divided into two groups ($n_1 = 56$ and $n_2 = 48$). There was no significant difference in weeks of gestation, age, BMI and family history of diabetes.