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Original Article

The effect of oral iron supplementation on glucose metabolism in non-anemic pregnant women who are in the risk group for gestational diabetes mellitus

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ABSTRACT

Objective: There are opinions about the negative effects of the increase in iron storages or plasma iron levels during pregnancy on glucose metabolism. We aimed to investigate the effects of oral iron supplementation on glucose metabolism in non-anemic pregnant women who are in the risk group for gestational diabetes mellitus.

Materials and methods: While oral iron supplementation of 40 mg/day was givento 41 pregnant women in the study group (Group I) for eight weeks, oral iron supplementation was not givento 35 pregnant women in the control group (Group II). 100 g oral glucose tolerance test (OGTT) was applied for the diagnosis of GDM in pregnant women whose 50 g OGTT results were positive. Analyzing the results between groups.

Results: There was no significant difference between the two groups in terms of mean fasting plasma glucose (FPG) value (p: 0.185), GDM (p:0.292) and mean results of 50gr OGLT (p: 0.109).A total of 26 pregnant women with 50 gr OGLT positive were applied 100 gr OGTT for diagnostic purposes.

Conclusion: It was concluded that 40 mg/day oral iron supplement used from the first trimester in pregnant women in the risk group for GDM did not have a significant negative effect on glucose metabolism and did not cause an increase in the risk of GDM.

Keywords: anemia; pregnancy; iron supplementation; gestational diabetes mellitus

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Introduction

Pregnancy is a process in which profound changes occur in almost all organ systems to adapt to the growing and developing fetoplacental unit. The first of the hematological adaptive changes is an increased in plasma volume and physiological anemia. The development of the fetal brain and placenta during pregnancy and the increase in the amount of maternal red cells increase the need for iron. Iron deficiency is the most common single nutrient deficiency worldwide [1, 2]. Worldwide, 41.8% of pregnant women are anemic, and at least half of them are due to iron deficiency. The World Health Organization (WHO) recommends 30-60 mg of elemental iron supplementation daily for pregnant women [3]. Gestational diabetes mellitus (GDM) has been defined as a diabetes condition with no known history of diabetes and first appearing in the second or third trimester of pregnancy [4, 5]. The global prevalence of Gestational Diabetes Mellitus is estimated to be 17% [6]. Risk factors for GDM include obesity, previous diabetes history, family history, hypertension, hyperlipidemia, macrosomic fetus, sedentary lifestyle [4, 5].

Early diagnosis in pregnant women enables to reduce feto-maternal risks and possible financial burden to the health system. There are studies reporting a significant association between plasma iron levels during pregnancy and the risk of gestational diabetes [7-11]. Hepcidin is one of the main targets of the pathophysiological processes occurring in patients with type II diabetes. Hepcidin is a peptide hormone that is synthesized from the liver and plays an essential regulatory role in iron metabolism. It regulates the absorption of iron from the intestines, its cycle in macrophages and its release from hepatic stores. Hepcidin synthesis increases with iron loading but decreases in anemia and hypoxia states. Therefore, it is thought that increased plasma iron level may lead to Type II diabetes by causing an increase in hepcidin levels [12, 13]. Due to the diabetogenic environment that occurs during pregnancy, the potential risks of routine iron use should be taken into account as well as the benefits.

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Iron supplementation given to pregnant women without anemia may increase the risk of gestational glucose intolerance due to iatrogenic iron increase. In our study, we aimed to prospectively investigate the effect of oral iron supplementation on glucose metabolism in pregnant women at risk for GDM.

Material and methods

In this prospective study, 88 pregnant women, who were at 15-17 weeks of gestation and were in the risk group for GDM, who applied to the Izmir Tepecik Training and Research Hospital pregnancy polyclinic between December 2010 and September 2011 were included. Necessary approvals were obtained from the hospital management for our study. Local Ethical Board committee approval was obtained and in the design and implementation of the study, the articles of the Helsinki Convention were adhered to. A total of 12 pregnant women, seven of whom did not attend regular follow-ups, and five who did not use iron supplements regularly, were excluded from the study. Pregnant women who were not in the risk group for GDM, multiple pregnancies and anemic pregnant with an initial hemoglobin value below 10 g/dL were not included in our study. The study was continued with 76 pregnant women who were in the risk group for GDM. Gestational week determination was calculated by confirming with ultrasound examination and old ultrasound reports.

Pregnant women who had at least one of the following conditions were evaluated in the increased risk group for GDM; having a BMI ≥25 kg/m2 but a diagnosis of GDM in previous pregnancies, having an HbA1c ≥5.7% or impaired glucose tolerance or fasting blood glucose in previous tests, having a first-degree relative with a diagnosis of diabetes, a history of cardiovascular disease, hypertension presence, low HDL cholesterol (<35 mg/dL) or high triglyceride (>250 mg/dL), history of polycystic ovary syndrome, sedentary life, signs of insulin resistance (acanthosis nigricans or severe obesity), and history of macrosomic birth (≥4000 grams) [4, 5].

While 40 mg/day oral iron supplement was given to 41 pregnant women in the study group for eight weeks, oral iron supplementation was not given to 35 pregnant women in the control group. Hemogram and plasma ferritin values of all pregnant women were measured before the study. All pregnant women were called for control 8 weeks after they were included in the study. In the control examination, plasma ferritin value, fasting blood glucose and 50 g oral glucose challenge test (OGTT) were performed. Venous blood glucose value was measured 1 hour after oral ingestion of a standard solution containing 50 g glucose, which was prepared beforehand for 50 g OGTT. The test was considered positive in pregnant women with a glucose level of ≥135 mg/dL [5]. 100gr oral glucose tolerance test (OGTT) was applied to the pregnant women who were positive for 50gr OGTT as a GDM diagnostic test. For 100gr OGTT, pregnant women were asked to eat a diet with a low glycemic index at night and to come to the outpatient clinic on an empty stomach in the morning. After measuring fasting blood glucose, venous glucose values were measured again in the first, second and third hours of the pregnant women who received oral standard solutions containing 100 g glucose. For 100gr OGTT, 0., 1., 2. and 3. hour blood glucose threshold values were accepted as 95, 180, 155 and 140, respectively, and pregnant women were diagnosed with GDM if at least two values were high [14].

Statistically Analysis

In this text, the SPSS 21.0 program was used for statistical analysis. The mean and standard deviation values were used for descriptive statistics, and the distribution of variables was checked using the Kolmogorov-Smirnov test. For the analysis of quantitative data, the independent sample t-test and Mann-Whitney u-test were used, and the chi-square test was used for the analysis of qualitative data. In cases where the conditions for the chi-square test could not be met, the Fisher test was used.

Results

76 pregnant women who were in the risk group for GDM were included in our study. While 54% (n: 41) of the pregnant women were given 40mg/day oral iron supplementation for eight weeks (Group I-study group), 46% (n: 35) were not given iron supplementation (Group II-control group). There was no difference between the groups in terms of age, education level, smoking-alcohol use and body mass index (BMI) (Table 1).

Table 1. Comparison of groups in terms of age, education level, smoking and alcohol use, and BMI

		Group I (n:41)		Group II (n:35)		p
Age		40,25±48,19		33,53±7,31		0,974
Education Level	Preliminary	26	63,40%	25	71,50%	0,444
	Middle school	4	10,00%	4	11,40%	
	High school	9	21,60%	4	11,40%	
	University and higher	2	5,00%	2	5,70%	
Smoking		6	14,60%	4	11,40%	0,685
Alcohol use		0	0,00%	0	0,00%	-
BMI		27,53±4,67		28,46±5,40		0,432

Ferritin value was used to monitor the iron stores of the pregnant women included in the study. At the beginning of the study, no statistical difference was observed between the ferritin levels of both groups. At the end of the study, there was a significant increase of 2.46 ± 6.22 units in the mean ferritin value in pregnant women given iron supplementation (p:0.000), while a decrease of 1.33.± 4.79 units in the mean ferritin value was found in the control group (p: 0.059). At the end of the study, a significant difference was found in the mean ferritin value between the groups (p<0.005) (Table 2).

Table 2. Comparison of the mean initial and final ferritin levels of the groups

		Group I	Group II	p
Ferritin level	Initial measurement	14,33.± 6,48	13,52.± 5,94	0,58
	Final measurement	16,79.± 6,66	12,20.± 5,63	0,002
	Change	2,46.± 6,22	-1,33.± 4,79	0,000
P value		0,000	0,059	

In the evaluation made after eight weeks of follow-up, no significant difference was found between the group given iron supplementation and the group not given iron supplementation in terms of mean fasting blood glucose (FG) value (p: 0.185). There was no statistically significant difference between the groups in terms of 50gr OGTT mean results (p:0.109). In 41.5% (n: 17) of group

I pregnant and 25.7% (n:9) of group II pregnant, their tests were considered positive by measuring glucose value ≥135 mg/dL as a result of 50 g OGTT. There was no significant difference between the groups in terms of 50 g OGYT positivity (p:0.150). A total of 26 pregnant women with 50 gr OGYT positive were applied 100 gr OGTT for diagnostic purposes. 12.2% (n:5) of pregnant women in group I and 2.85% (n:1) of pregnant women in group II were diagnosed with GDM, and no significant difference was found between the groups in terms of GDM (p:0.292) (Table 3).

Table 3. Comparison of the groups in terms of the rates of fasting blood sugar, 50 gr OGTT, and gestational diabetes mellitus

		Group I		Group II		p
FBS		88,03±14,07		83,65±12,54		0,185
50 gr OGLT		137,25±18,01		127,79±31,2		0,109
50 gr OGLT	Normal	24	58,50%	26	74,3%	0,15
	Positive	17	41,50%	9	25,7%	
100 gr OGTT	Normal	12	70,60%	8	88,9%	0,209
	Positive	5	29,40%	1	11,1%	

Discussion

Experimental studies have shown that higher-than-normal serum iron concentrations cause dysfunction in pancreatic β-cells and impair glucose metabolism [8]. In addition, there are studies reporting that increased serum iron causes an increase in hepcidin levels and this increase impairs glucose metabolism [11-13]. In the literature review conducted during the writing of our study, many studies evaluating increased iron stores and GDM risk during early pregnancy were identified, but no similar study examining only the population with risk factors for GDM was found. In our study, it was found that although routine oral iron supplementation caused a significant increase in serum ferritin levels in pregnant women in the risk group for GDM, it did not make a significant difference in the results of fasting blood glucose, postprandial blood glucose, 50 g OGTT and 100 g OGTT, and did not increase the risk of GDM (p> 0.05). Although there are many articles in the literature showing a significant relationship between high iron stores and GDM risk, there are also publications that reject this relationship. Guo et al. reported that high iron concentration and increased ferritin values detected in early pregnancy (12th week) significantly increase the incidence of GDM and can be used predictively for GDM [7]. In the study conducted by Bowers et al. from Denmark and comparing 350 GDM pregnants and 349 non-GDM pregnant women, it was reported that plasma ferritin level measured in early pregnancy was significantly and positively associated with GDM risk [8]. According to a meta-analysis of 11 articles investigating the relationship between serum hemoglobin and ferritin levels and GDM risk, it has been reported that high hemoglobin values cause a more than 50% (OR = 1.52; 95% CI: 1.23-1.88) risk of GDM, and high ferritin levels cause a two-fold (OR = 2.09; 95% CI: 1.48-2.96) increase in the risk of GDM [9]. Lao et al., on the other hand, did not find a significant relationship between GDM risk and hemoglobin values, but reported that the increase in iron stores (transferrin saturation, serum iron or ferritin level) detected in the early stages of non-anemic pregnant women was significantly associated with increased glucose intolerance in the third trimester [10]. In the studies of Rawal et al. evaluating the relationship between GDM and hepcidin, it was reported that the mean hepcidin concentration measured between the 15th and 26th weeks of pregnancy was 16% higher in pregnant women with GDM than in the control group, and high hepcidin caused a significant increase in the risk of GDM. It has been mentioned that routine iron supplementation in non-anemic pregnant women raises potential concerns [11]. In the meta-analysis of 33 original articles published by Kataria et al., it was reported that no difference was found between women with and without GDM in terms of total iron binding capacity or transferrin concentration. It has also been reported that increased iron intake or iron supplementation does not increase the risk of GDM [15]. Renz et al., in their study evaluating 231 pregnant women, concluded that iron supplementation in non-anemic pregnant women did not affect HbA1c levels [16]. Liu et al. reported that iron supplementation does not increase the risk of GDM in singleton pregnancies and may even benefit both the pregnant woman and the newborn [17]. In our study, it was determined that oral iron supplementation significantly increased the serum ferritin value in pregnant women who were in the risk group for GDM. There was no significant difference between the mean values of fasting blood glucose and postprandial blood glucose measured at the end of the second trimester of the pregnant women who took iron supplementation and the mean values of the control group pregnant women who did not receive iron supplementation. The 50-gr OGTT tests were positive in 41.5% (n: 17) of the pregnant women who took iron supplementation and in 25.7% (n:9) of the pregnant women who did not take iron supplementation. There was no significant difference between the groups in terms of 50 g OGTT positivity (p:0.150). In our study, 100 g OGTT was applied for diagnostic purposes to pregnant women who were positive for 50 g OGTT. GDM was detected in 12.2% (n:5) of our pregnant women who received iron supplementation and 2.85% (n:1) of our pregnant women who were not given iron supplements, and there was no statistically significant difference between the groups. In summary, contrary to the general opinion in the literature, it was concluded in our study that oral iron supplementation, which was started during early pregnancy, did not impair glucose metabolism even in the presence of a risk factor for GDM. The fact that it is a prospective study and the absence of similar studies evaluating pregnant women in the risk group for GDM in the literature increases the strength of our article. The small number of patients can be considered as the weakness of our article. Lin et al. have shown that anemia in pregnancy is associated with poor obstetric outcomes, such as preterm birth, hypertensive disease, low birth weight fetus, and neonatal intensive care admission [18]. In this context, we attach importance to oral iron supplementation, which is used in the early stages of pregnancy, because it does not increase the risk of GDM, but reduces poor obstetric outcomes.

Conclusion

It was concluded that 40mg/day oral iron supplement used from the first trimester in pregnant women in the risk group for GDM did not have a significant negative effect on glucose metabolism and did not cause an increase in the risk of GDM. We think that there is a need for prospective studies with large participation on the subject.

Disclosure

Authors have no potential conflicts of interest to disclose.

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