

The effect of iron supplementation on HBA1c levels in non-diabetic pregnant women.

Colak Eser^{1*}, Esinler Deniz², Yerebasmaz Neslihan², Tohma Aytac¹, Kandemir Omer², Yalvac Serdar³

¹Baskent University Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Turkey

²Etlık Zubeyde Hanim Maternity Hospital, Department of Obstetrics and Gynecology, Division of Maternal and Fetal Medicine, Ankara, Turkey

³Bozok University Faculty of Medicine, Department of Obstetrics and Gynecology, Yozgat, Turkey

Abstract

Background: It is estimated that 41, 8% of pregnant women worldwide are anemic. At least half of this burden is assumed to be due to iron deficiency. Although iron deficiency anemia is very common in pregnancy, there has been limited research investigating glycosylated hemoglobin (HBA1c) levels in non-diabetic anaemic pregnant women and the effect of iron supplementation on HbA1c levels. We aimed to investigate HBA1c level changes in anemic pregnant women after anemia is corrected and to evaluate the relation of HBA1c with haemoglobin, haematocrit, ferritin and red blood cell indices.

Materials and methods: Thirty seven pregnant women (16-30 weeks into their pregnancies) who had been diagnosed as having iron deficiency anemia (IDA) were enrolled in the study. IDA was corrected with iron supplementation. Haemoglobin, haematocrit, ferritin and red blood cell indices were analysed prior to and following (1 month) iron replacement therapy.

Results: HBA1c values significantly decreased after iron supplementation when compared to those in a pre-supplementation state (5.01 ± 0.39 vs. 4.69 ± 0.38).

Conclusion: The correction of iron deficiency anemia (IDA) in pregnant women via iron supplementation significantly decreased HBA1c values. Thus, the interpretation of HBA1c values should be carefully conducted in the presence of IDA in the case of pregnancy. If there is IDA in pregnancy, it should be corrected prior to making any decisions based on HBA1c values.

Keywords: HBA1c, Iron deficiency anemia, Pregnancy.

Accepted on December 05, 2017

Introduction

Glycosylated hemoglobin (HBA1c) has a glucose residue attached to the terminal NH₂ group (valine residue) of one or both HbA beta chains [1]. It is widely used by physicians to inquire past plasma glucose levels in last 2-3 months [1]. Several factors such as anemia, structural hemoglobinopathies and thalassemia syndromes may affect HBA1c results. Depending on the type of anemia, it may be associated with a rapid turnover of erythrocytes, resulting in lower HBA1c levels, or alternatively, slower turnover of erythrocytes, resulting in increased glycosylation of Hb and consecutively, higher HBA1c levels [2]. Accordingly, the presence of anemia may result in false interpretations of HBA1c results. In hemolytic anemia species and in patients with severe blood loss, there is a decrease in HbA1c levels and there is an increase in cases that lead to an increase in erythrocyte age such as iron deficiency anemia [2].

It is estimated that 41.8% of pregnant women worldwide are anemic [3]. At least half of this burden is assumed to be due to

iron deficiency [3]. Although iron deficiency anemia is very common in pregnancy, to our best knowledge, there has been limited research investigating HBA1c levels in non-diabetic anaemic pregnant women and the effect of iron supplementation on HBA1c levels [4-6]. In order to see the effect of anemia treatment on HBA1c levels, we analysed HBA1c levels in non-diabetic pregnant women before and after iron supplementation.

Materials and Methods

The study was designed as prospective and was conducted at the Perinatology Department of Etlık Zubeyde Hanim Womens Health and Teaching Hospital. The Institutional Review Board approved the study. Thirty-seven pregnant women (between 16-30 weeks gestation) diagnosed with iron deficiency anemia (IDA) from June 2013 to February 2014, were enrolled in the study. In our study, iron-deficiency anemia was diagnosed when the hemoglobin level was below 11 gr/dL in the first and third trimesters or below 10.5 gr/dL in the second trimester;

mean cell volume was lower than 75 fl and the serum ferritin level was lower than 30 ng/mL in the absence of the other causes of anemia. Pregnant patients with hemoglobin levels of 6-11 gr/dL were included in the study if the anemia was iron deficiency anemia and the patient was either intolerant or did not respond to oral iron therapy despite regular use. Patients having iron-deficiency anemia with hemoglobin levels below 6 gr/dL or symptomatic (severe fatigue, palpitations, tachycardia, shortness of breath) patients with hemoglobin levels greater than 6 gr/dL were candidates for RBC transfusion and those were excluded. After informed consent for intravenous iron therapy was taken, the patients were hospitalized. Patients with fasting plasma glucose levels >110 mg/dL and 50 gram glucose challenge test >140 mg/dL as well as patients with hemoglobinopathy, gestational diabetes mellitus (GDM) or Type I-II diabetes mellitus were excluded from the study were excluded from the study. The iron sucrose dosage was calculated according to the following formula:

Total iron deficit [mg]=body weight [kg] × [target Hb (usually taken as 11 gr/dL)-actual Hb] [g/dL] × 2.4+depot iron (usually taken as 500) [mg] [7].

The total amount of iron sucrose to be administered (in mL) was calculated by total iron deficit (mg) divided by 20 mg/mL. Iron sucrose was diluted only in sterile 0.9% sodium chloride solution as 100 mg iron (5 mL iron sucrose) in maximum 100 ml sterile 0.9% sodium chloride solution and for stability reasons, dilutions to lower iron sucrose concentrations was not allowed. As infusion, maximum tolerated single dose per day given, not more than once per week was: 500 mg iron (25 mL iron sucrose) in at least 3 h for patients above 70 kg and 7 mg iron/kg body weight in at least 3 h for patients of 70 kg and below. If the total dose to be administered was greater than the maximum tolerated single dose per day, the remaining dose was administered one week later. Hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), ferritin and HbA1c levels were measured before and at the end of the first month following iron supplementation. Direct enzymatic HbA1c assay (Abbott Laboratories, IL, USA) with intra- and inter percentage CV values of less than 3% was used to measure HbA1c values. Statistical analyses were performed using the SPSS version 21.0 (SPSS, Chicago, IL). Paired sample student t-test was used to compare HbA1c level changes. Pearson correlation coefficient was used to analyse the degree of linear dependence between two variables. Statistical tests were considered significant at the 95% level.

Results

Of 37 women enrolled into the study, 29.7% were primigravida and others were multigravida (second pregnancy in 32.4%, third pregnancy in 21.6%, 4th pregnancy in 10.8, 5th pregnancy in 2.7% and 7th pregnancy in 2.7%; Table 1). Mean fasting blood glucose (FBG) is 81.11 ± 11.14 , while mean glucose challenge test 50 g is 103.73 ± 17.05 . Median value of body mass index (BMI) is 35, and median value is 25 weeks by

gestational age (Table 1). As expected, following iron supplementation, Hb, Htc, MCV, MCH, MCHC and ferritin levels were significantly increased compared to pre-supplementation levels (Table 2). However, HbA1c levels were significantly lower following iron supplementation (5.01 ± 0.39 vs. 4.69 ± 0.38 , $p < 0.05$) (Table 2). We failed to find any significant correlation between the degree of HbA1c changes and the changes in parameters Hb, Htc, MCV, MCH, MCHC and ferritin.

Table 1. Basal characteristics of patients included in the study (n=37).

Variable	n=37
Gestational age (week)	25.0 ± 2.5
Body mass index (kg/m ²)	26.2 ± 3.9
Fasting plasma glucose (gr/dL)	81.1 ± 11.4
50 gr oral glucose tolerance test (mg/dL)	103.7 ± 17.0

Table 2. Comparison of glycosylated haemoglobin (HbA1c), hemoglobin, hematocrit, ferritin and red blood cell indices before iron supplementation and post-iron supplementation.

Variable	Pre-iron supplementatio n	Post-iron supplementation	P-value
HbA1c (%)	5.01 ± 0.39	4.69 ± 0.38	p<0.01
Hemoglobin (gr/dL)	9.8 ± 0.9	10.6 ± 1.0	p<0.01
Hematocrit (%)	25.2 ± 2.5	32.3 ± 3.1	p<0.01
Ferritin (ng/mL)	6.3 ± 2.1	37.6 ± 6.7	p<0.01
Mean corpuscular volume (fL)	71.2 ± 8.1	82.0 ± 7.8	p<0.01
Mean corpuscular hemoglobin (pg/cell)	22.7 ± 3.4	26.7 ± 2.9	p<0.01
Mean corpuscular haemoglobin concentration (g/dL)	31.7 ± 1.3	32.5 ± 1.1	p<0.05

HbA1c=glycosylated hemoglobin; ferritin was given as a mean ± standard error

Discussion

Iron therapy is the mainstay of iron-deficiency anemia treatment and intravenous iron is increasingly used when oral therapy is not effective or well tolerated. In this study, we found that intravenous iron therapy is effective in iron restoration and anemia treatment with few changes on laboratory values. Worth et al. investigated changes in HbA1c values in 21 pregnant women and showed that HbA1c reached at its nadir at 17 weeks, peaked at delivery, and dropped in the postpartum period [8]. Similarly, Phelps et al. analysed HbA1c concentrations throughout gestation in 377 non-diabetic pregnant women [9]. They noted significant biphasic changes in HbA1c concentrations, with an initial gradual decline to nadir level at 24 weeks, followed by a subsequent slow re-ascension to peak near term. Both authors concluded these changes in HbA1c as physiological changes related to

pregnancy and that care should be taken during the interpretation of HBA1c results in the presence of pregnancy. However, they did not suggest any possible mechanism for the cause(s) of these changes.

The effect of iron deficiency anemia (IDA) on HBA1c values was first investigated by Horton and Huisman [10], who noted the mean HbA1c concentration for four patients with IDA as 4.9%, compared to a mean HBA1c concentration of 5.3% among 14 healthy adults. In 1980, on the contrary, Brooks et al. [11] investigated HBA1c levels in 25 non-diabetic patients with IDA both prior to and following treatment with iv iron supplementation for six weeks and they reported that the mean HBA1c values were significantly decreased following iron supplementation (9.9 ± 0.3 vs. 7.9 ± 0.13 , respectively) and that IDA was associated with higher HBA1c values.

Tarim et al. [12] reported that patients (n=11) with Type I diabetes mellitus (DM) and IDA had higher levels of HBA1c than patients with DM but without IDA (n=26) (10.6 ± 2.6 vs. 7.7 ± 1.3 , respectively). In their study, iron supplementation significantly decreased mean HBA1c values in patients with DM (10.1 ± 2.7 vs. 8.2 ± 3.1). In accordance to the results of our study, Tarim et al. additionally noted that iron supplementation also decreased HBA1c levels in non-diabetic patients with IDA ($7.6 \pm 2.6\%$ vs. 6.2 ± 1.4). El-Agouza et al. [13] investigated the effect of iron deficiency anemia on the levels of HBA1c in 41 patients with IDA and noted that HBA1c fell significantly following iron supplementation from a mean of 6.15 ± 0.62 to 5.25 ± 0.45 . They also concluded that iron deficiency must be corrected before making any diagnostic or therapeutic decisions based on HBA1c levels. Coban et al. [14] investigated the effect of IDA on HBA1c values in 50 patients with IDA and 50 healthy control patients. HBA1c values in IDA patients were significantly higher compared to control patients prior to iron supplementation (7.4 ± 0.8 vs. 5.2 ± 0.2 , respectively). Also in accordance to our study, following iron supplementation, the HBA1c value in patients with IDA decreased significantly (7.4 ± 0.8 vs. 6.2 ± 0.6).

Koga et al. [15] demonstrated that red blood cell count was positively and hemoglobin, MCH and MCV were negatively associated with HBA1c levels in premenopausal women. Among the erythrocyte indices, the highest correlation coefficient for an association with HBA1c in pre-menopausal women was for MCH. A decrease of 1 pg in MCH corresponds to an increase of approximately 0.03% in HBA1c. Pre-menopausal women with low MCH (<27 pg) had significantly higher HBA1c levels. Koge et al. therefore concluded that the relatively iron deficient state of premenopausal women with lower MCH levels may be responsible for higher HBA1c levels. Recently, English et al. [4] reported a systematic review of 12 articles related to association of IDA on HBA1c levels and concluded that HBA1c was likely to be affected by iron deficiency and IDA, with a deceptive increase in HBA1c values. They also noted that this may lead to confusion when diagnosing diabetes using HBA1c.

In the literature, there is limited research investigating the relationship between IDA and HBA1c in pregnancy. Hashimoto et al. [5] conducted a study on 47 pregnant women in Japan in 2007 and found that HBA1c was negatively correlated with MCH, serum transferrin saturation and serum transferrin. They concluded that an increase in HBA1c levels during late pregnancy appears primarily attributable to an iron-deficient status at this period. Rafat et al. [6] recently assessed the influence of iron metabolism indices on HBA1c in non-diabetic pregnant women. They reported that HBA1c levels were higher in patients with IDA compared to controls. Moreover, HBA1c levels decreased from 5.2 ± 0.3 to 5.1 ± 0.3 following iron supplementation. They also observed a significant correlation between erythrocyte indices, iron metabolic indices and HBA1c levels.

In our study, we found that iron supplementation in patients with IDA significantly decreased HBA1c values. However, we failed to find a significant correlation between the degree of HBA1c change and the change in parameters Hb, Htc, MCV, MCH, MCHC and ferritin. The reason for this may be the small sample size. There are different hypotheses for explaining HBA1c increments in patients with IDA. Sluiter et al. [16] hypothesized that the formation of glycosylated hemoglobin was an irreversible process and therefore, the concentration of HBA1c in one erythrocyte would increase linearly according to the cell's age. However, in the case of an iron deficiency, red cell production rate would have dropped, leading not only to anemia but also to a higher than normal average age of circulating erythrocytes and therefore, increased HBA1c. Following IDA correction with iron supplementation, many younger erythrocytes will enter circulation, which in turn will result in a significant decrease in HBA1c levels. From our point of view, this hypothesis is the most instructive and logical option.

In the literature, there are a limited number of studies reporting that HBA1c values do not change in the presence of IDA. In a study conducted by Heyning et al. [17], authors reported no statistically significant differences in HBA1c values, which contradict our study and those in the literature. Likewise, Rai et al. [18] reported no differences between the HBA1c levels of 12 control subjects and 15 patients with IDA.

Conclusions

In our study the correction of iron deficiency anemia (IDA) in pregnant women by iron supplementation significantly decreased HBA1c values. Thus, IDA should be taken into account in the interpretation of HBA1c values in pregnancy.

References

1. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2011; 57: 1-47.
2. Ahmad J, Rafat D. Hba1c and iron deficiency: A review. *Diabetes Metabol Syndrome* 2013; 7: 118-122.

3. McLean E, Cogswell M, Egli I, Wojdyla D, Benoist B. Worldwide prevalence of anemia, iron, vitamin and mineral nutrition information system, 1993-2005. *Public Health Nutrition* 2009; 12: 444-454.
4. English E, Idris I, Smith G, Dhatariya K, Kilpatrick ES, John WG. The effect of anemia and abnormalities of erythrocyte indices on hba1c analysis: A systematic review. *Diabetologia* 2015; 58: 1409-1421.
5. Hashimoto K, Osugi T, Noguchi S, Morimoto Y, Wasada K, Imai S. A1c but not serum glycated albumin is elevated because of iron deficiency in late pregnancy in diabetic women. *Diabetes Care* 2010; 33: 509-511.
6. Rafat D, Rabbani TK, Ahmad J, Ansari MA. Influence of iron metabolism indices on hba1c in non-diabetic pregnant women with and without iron-deficiency anemia: Effect of iron supplementation. *Diabetes Metabolic Syndrome* 2012; 6: 102-105.
7. <http://www.medsafe.govt.nz/profs/Datasheet/f/FerrumHinj.pdf>
8. Worth R, Potter JM, Drury J, Fraser RB, Cullen DR. Glycosylated haemoglobin in normal pregnancy: A longitudinal study with two independent methods. *Diabetologia* 1985; 28: 76-79.
9. Phelps RL, Honig GR, Green D, Metzger BE, Frederiksen MC, Freinkel N. Biphasic changes in hemoglobin a1c concentrations during normal human pregnancy. *Am J Obstet Gynecol* 1983; 147: 651-653.
10. Horton BF, Huisman TH. Studies on the heterogeneity of haemoglobin. VII. Minor haemoglobin components in haematological diseases. *Br J Haematol* 1965; 11: 296-304.
11. Brooks AP, Metcalfe J, Day JL, Edwards MS. Iron deficiency and glycosylated haemoglobin a. *Lancet* 1980; 2: 141.
12. Tarim O, Kucukerdogan A, Gunay U, Eralp O, Ercan I. Effects of iron deficiency anemia on hemoglobin a1c in type 1 diabetes mellitus. *Pediatrics Int* 1999; 41: 357-362.
13. El-Agouza I, Abu Shahla A, Sirdah M. The effect of iron deficiency anemia on the levels of haemoglobin subtypes: Possible consequences for clinical diagnosis. *Clin Lab Haematol* 2002; 24: 285-289.
14. Coban E, Ozdogan M, Timuragaoglu A. Effect of iron deficiency anemia on the levels of hemoglobin a1c in nondiabetic patients. *Acta Haematologica* 2004; 112: 126-128.
15. Koga M, Morita S, Saito H, Mukai M, Kasayama S. Association of erythrocyte indices with glycated haemoglobin in pre-menopausal women. *Diabetic Med* 2007; 24: 843-847.
16. Sluiter WJ, van Essen LH, Reitsma WD, Doorenbos H. Glycosylated haemoglobin and iron deficiency. *Lancet* 1980; 2: 531-532.
17. Van Heyningen C, Dalton RG. Glycosylated haemoglobin in iron-deficiency anemia. *Lancet* 1985; 1: 874.
18. Rai KB, Pattabiraman TN. Glycosylated haemoglobin levels in iron deficiency anemia. *Indian J Med Res* 1986; 83: 234-236.

***Correspondence to**

Colak Eser
Baskent University Faculty of Medicine
Department of Obstetrics and Gynecology
Turkey