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Original Research

Impact of Iron Deficiency Anemia on Hemoglobin A1c Levels in Diabetic and Non-Diabetic Pregnant Women

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Abstract

Background: Gestational diabetes mellitus (GDM) is a well-known risk factor for pregnancy complications. While hemoglobin A1c (HbA1c) is widely used as a glycemic control indicator, it is known to exhibit falsely low or high levels during gestation. The purpose of the present study is to analyze the fluctuations in HbA1c levels throughout pregnancy in diabetic (DM) and non-DM women with or without iron deficiency anemia (A). **Methods**: Medical records of pregnant women who were followed up in our obstetrics clinic between 2018 and 2022 were reviewed. Demographics, gestational history, and biochemistry values including fasting glucose, HbA1c, erythrocyte and iron metabolism indexes were recorded. Statistical analysis was carried out by Mann-Whitney U and Bonferroni corrected one-way analysis of variance (ANOVA) tests. **Results**: 670 pregnant women (32 $\pm$ 14.2 years) were included with matched subgroups. In the non-DM and non-A group, HbA1c exhibited a significant decrease towards mid-pregnancy (5.29 *vs.* 5.08%, $p < 0.01$), followed by a steep increase towards the second half of pregnancy, reaching its initial value (5.08 *vs.* 5.27%, $p < 0.01$). In the non-DM and A pregnant women, HbA1c decreased from 5.25 to 5.19% ($p > 0.05$) in first half, followed by a significant increase to 5.37% ($p < 0.05$) in the second half of pregnancy when serum ferritin values dropped to 5.03 $\pm$ 3 µg/mL ($p < 0.01$). As for DM and non-A group, a biphasic change in HbA1c level was also recorded, however not significant (6.05 *vs.* 5.81%, $p > 0.05$). However, in the DM and A group, HbA1c levels were higher (7.09 *vs.* 6.01%, $p < 0.01$), along with iron deficiency indicated by ferritin levels (4.7 $\pm$ 2.2 µg/mL, $p < 0.01$). **Conclusions**: HbA1c exhibits biphasic changes throughout pregnancy, characterized by decreases towards mid-pregnancy and subsequentincreases in the third trimester. Therefore, questioning HbA1c levels is warranted, considering the changes in maternal physiology in early gestation and the increasing need for iron in later period. Furthermore, iron deficiency anaemia seems to have significant impact on the reliability of HbA1c in both the non-DM and DM pregnant women.

Keywords: diabetes mellitus; pregnancy; hemoglobin A1c; iron deficiency anemia; gestational diabetes

1. Introduction

The prevalence of diabetes mellitus (DM) among women of child-bearing age has been steadily increasing worldwide [1]. International Diabetes Federation estimated a global prevalence of 16% for hyperglycemia in pregnancy, adding gestational diabetes mellitus (GDM) to type I and II DM [2]. Several recent studies have shown that tight control of blood glucose during this period is necessary to reduce the risk of maternal complications, such as preeclampsia, and adverse perinatal outcomes, such as intrauterine death, congenital abnormalities, macrosomia, and neonatal morbidities [3,4]. Hemoglobin A1c (HbA1c), formed by glycation of the terminal chain of hemoglobin which reflects, patients' glycemic status over previous 3 to 4 months. It is currently the most widely used standard marker, serving as a diagnostic criterion for DM and as a screening test for clinical management [5].

However, many recent studies have shown that HbA1c is influenced by several physical factors, such as hemoglobinopathies, hemolytic anemia (A), bleeding, renal azotemia, vitamin B12 deficiency, pregnancy, and iron deficiency A, and it may not reflect glycemic control accurately [6,7]. Furthermore, several studies report a link between reduced iron stores and increased glycation of HbA1c, resulting in false high values in non-diabetic (non-DM) individuals [4,8,9]. Moreover, several recent reports have demonstrated that HbA1c shows a biphasic change, with the trough level occurring at week 24 of pregnancy [8–10]. Most of these studies suggest a significant increase in HbA1c in late pregnancy as iron deficiency proceeds [10,11].

In the present study, we aimed to measure the changes in HbA1c level throughout pregnancy in DM and non-DM women. We also evaluated the influence of iron deficiency A on HbA1c values during pregnancy.

2. Methods

Patients provided written informed consent to allow the use of data from their medical records in research. The study was approved by our institutions's Ethics' Committee (Health Sciences University, Istanbul Education and Research Hospital, date: 25.03.2022, number: 102). Reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki, as revised in 2000 [12]. Medical records of pregnant women

who were followed up in our obstetrics clinic, between January 2018 and December 2022, were reviewed. Demographic data, gestational history, and biochemistry values were recorded cross-sectionally using Excel software (Microsoft Office, Windows 11, Chicago, IL, USA). Only singleton pregnancies were included. Patients with chronic inflammatory diseases, high C-reactive protein (CRP) levels, those under 18 years of age, or those with folate or vitamin B12 deficiency were excluded from the study. Women with all types of hemoglobinopathies (fetal haemoglobin (HbF), hemoglobin A2 (HbA2), hemoglobin E (HbE), sickle hemoglobin (HbS), etc.) were also excluded.

Indicators of glycemic control (fasting serum glucose and HbA1c) and iron-related parameters (hemoglobin, hematocrit, serum ferritin, and mean corpuscular volume (MCV)) were analyzed by high-performance liquid chromatography, calorimetric and chemiluminescent immunoassay methods using auto-analyzers (Siemens Healthineers Diagnostics Co., Erlangen, Germany). Patients with hemoglobin level below 11 g/dL and serum ferritin value below 15 µg/mL were defined as to have iron deficiency A, while those with previous history of DM, abnormal oral glucose tolerence test (OGTT) at 24 weeks of pregnancy or with high fasting glucose level above 100 mg/dL or HbA1c above 6% were diagnosed as DM (gestational, type I or II) [11].

Statistical package for social sciences (SPSS 2018 IBM version 11.5, Chicago, IL, USA) was used for the statistical analysis. Descriptive values were expressed as number (n), percentage (%), median or mean with standard deviation (±SD). Chi-square test was used for nominal and categorical values, and Kolmogorov-Smirno and Shapiro-Wilk tests were used to compare the nonparametric variables. Group comparisons were done with Mann-Whitney U and Kruskall Wallis tests to ascertain the group that cause the difference. Bonferroni corrected one-way analysis of variance (ANOVA) post-hoc test was used for subgroup comparisons. $p < 0.05$ was considered statistically significant.

3. Results

A total of 670 pregnant women (mean age ± SD, 32 ± 14.2 years) were included, and all subgroups were matched for age, gender, and previous obstetric and reproductive history (gravidity, parity, abortus and living children) (each, $p > 0.05$; Table 1). Almost half of the patients were non-DM and non-A (48.8%), and this group was used as control group (Table 2). 10% of the patients were both DM and A (N = 67). Distribution of pregnant women into subgroups (DM, non-DM, A, non-A) and into periods as first, second or third trimester, and first or second half of pregnancy is shown in Table 2. Blood parameters used for the diagnosis of iron deficiency A (hemoglobin, hematocrit, MCV and ferritin levels; mean ± SD) and DM (fasting glucose and HbA1c; mean ± SD) are shown in Table 3.

In normal pregnant women (non-DM and non-A; control group), HbA1c levels were seen to decrease considerably from the beginning to the middle of pregnancy (mean 5.29 *vs*. 5.08%; $p < 0.01$) (Fig. 1). However, a steep increase was recorded in the second half of pregnancy, reaching its initial value has observed in early pregnancy (from 5.08 to 5.27%; $p < 0.01$).

As for non-DM and A pregnant women, there was a statistically insignificant decrease in HbA1c level from 5.25 to 5.19% ($p > 0.05$) in the first half of pregnancy. In second half, this value reached to 5.37% ($p < 0.05$) (Fig. 2). In these A pregnant women, despite the HbA1c level at the end of pregnancy being higher than the value recorded at the beginning of pregnancy, the difference was still statistically insignificant ($p > 0.05$).

In DM and non-A pregnants, the mean HbA1c level at the beginning of pregnancy was 6.05% (just above the upper range). According to above described, this value dropped to 5.79% in the second trimester, and then increased to 5.81% in third trimester of pregnancy (for each group, $p > 0.05$) (Fig. 3). On the other hand, in DM and A group, the initial HbA1c levels were remarkable, being significantly above the normal upper range (7.09% at the beginning of pregnancy) (Fig. 4). As seen in previous groups, HbA1c level decreased to 5.94% very significantly in mid-pregnancy ($p < 0.01$), and then increased up to its upper range insignificantly at the end of pregnancy (6.01%; $p > 0.05$), comparing to the second trimester HbA1c levels.

Graphics showing fluctuations in HbA1c levesl during pregnancy in all subgroups (DM, non-DM, A, non-A) are shown together to make comparisons easier (Fig. 5). Correlations between iron related parameters and HbA1c in both non-DM and DM women can also be seen in Figs. 6,7.

4. Discussion

Currently, HbA1c is widely used for the target value of glycemic control or the diagnosis of DM, but it has some limitations, and there are a number of factors that can falsely raise or lower its level independent of glycemia [6,7,13]. First, Phelps *et al*. [8] analyzed HbA1c concentrations in 377 non-DM pregnant women and found significant biphasic changes, with initial decline to a nadir level at the 24th week of gestation. This was followed by a subsequent rise to peak near term. Then, in a report of the Japanese Society of Diabetes and Pregnancy, similar tendencies were shown [14]. The authors reported that HbA1c tends to decrease during the first and second trimesters, followed by an increase during the last trimester of gestation, in an analysis of 136 normal pregnant women. Hashimoto *et al*. [11] also demonstrated HbA1c levels were elevated significantly in relation to glycemia in late pregnancy. They hypothesized that increased iron deficiency in the second half of gestation was involved in this significant rise. Similarly, Coban *et al*. [15] reported falsely high levels of HbA1c in patients

Table 1. Demographics and characteristics of patients.

Variable	DM	Non-DM	A	Non-A	Trimesters			Pregnancy		p
					First	Second	Third	First	Second	
Age (y ± SD)	33 ± 14	30 ± 14.7	31.5 ± 13.1	31 ± 14	32 ± 12.4	32 ± 13	31 ± 15	33 ± 13	31 ± 15	>0.05
Gravida (n ± SD)	3 ± 2.6	2 ± 1.9	3 ± 2.8	2 ± 1.8	2 ± 1	2 ± 1.9	3 ± 1	2 ± 1.1	3 ± 1.4	>0.05
Parity (n ± SD)	2 ± 1.9	1 ± 0.9	2 ± 1.9	1 ± 0.9	1 ± 0.4	1 ± 0.4	1 ± 0.1	1 ± 0.9	1 ± 0.9	>0.05
Abortus (n ± SD)	0.4 ± 0.1	0	0.2 ± 0.1	0	0.5 ± 0.1	0	0	0.5 ± 0.1	0	>0.05
Living children (n ± SD)	2 ± 0.6	1.9 ± 0.7	2 ± 0.2	1.8 ± 0.8	1 ± 0.9	1 ± 0.6	1	2 ± 1	2 ± 1	>0.05

DM, diabetes mellitus (diabetic patient); Non-DM, non-diabetic; A, anemia (anemic patient); Non-A, non-anemic; SD, standard deviation; Trimesters: first (0–13 weeks), second (14–28 weeks), third (29–42 weeks); Pregnancy: first half (0–20 weeks), second half (>20 weeks to delivery); $p > 0.05$: statistically insignificant.

Table 2. Distribution of pregnant women in each trimester and halves of pregnancy in all groups.

Groups	Number (N)	Trimester			Pregnancy	
		First	Second	Third	First	Second
Non-DM and non-A	327 (48.8%)	75 (22.9%)	84 (25.6%)	168 (51.3%)	112 (34.2%)	215 (65.7%)
Non-DM and A	103 (15.3%)	4 (3.8%)	19 (18.4%)	80 (77.6%)	11 (10.6%)	92 (89.3%)
DM and non-A	173 (25.8%)	21 (12.1%)	51 (29.4%)	101 (58.3%)	35 (20.2%)	138 (79.7%)
DM and A	67 (10%)	5 (7.4%)	17 (25.3%)	45 (67.1%)	9 (13.4%)	58 (86.5%)
Total	670 (100%)	105 (15.6%)	171 (25.5%)	394 (58.8%)	167 (24.9%)	503 (75%)

DM, diabetes mellitus (diabetic patient); Non-DM, non-diabetic; A, anemia (anemic patient); Non-A, non-anemic; Trimesters: first (0–13 weeks), second (14–28 weeks), third (29–42 weeks); Pregnancy: first half (0–20 weeks), second half (>20 weeks to delivery).

Table 3. Blood parameters for iron deficiency, A, and DM in our pregnant patients.

Parameters	Non-DM and non-A (N = 327)	Non-DM and A (N = 103)	DM and non-A (N = 173)	DM and A (N = 67)
Hemoglobin (g/dL)	13.1 + 1.9	9.6 + 1.4**	12.9 + 1	9.1 + 1.9**
Hematocrit (%)	38.4 + 2.7	34.7 + 3.7**	37 + 2.2	32.1 + 4**
MCV (fL)	84.1 + 4.1	74 + 2.1*	82.9 + 2.1	73 + 3.1*
Ferritin (µg/mL)	18.4 + 3.6	5.03 + 3**	17 + 2.4	4.7 + 2.2**
Fasting glucose (mg/dL)	85 + 7	88 + 4.6	128 + 12**	135 + 21**
HbA1c (%)	5.1 + 0.8	5.2 + 0.9	6 + 0.4*	6.4 + 0.7**

DM, diabetes mellitus (diabetic patient); Non-DM, non-diabetic; A, anemia (anemic patient); MCV, mean corpuscular volume; HbA1c, hemoglobin A1c; all values are expressed as mean ± SD (standard deviation), *$p < 0.05$ (statistically significant), **$p < 0.01$ (statistically very significant).

with iron deficiency A. However, subsequent studies have documented slight increases of HbA1c in patients with iron deficiency A [16,17].

In our study, regardless of the existance of glucose intolerence or DM, we observed that the level of HbA1c decreased in the first half of pregnancy, as shown in previous studies. However, in non-DM and non-A cases, this decrease was more remarkable ($p < 0.01$), in comparison with non-DM and A cases ($p > 0.05$). This phenomenon supports the hypothesis that iron deficiency A increases HbA1c level. In this group (non-DM and A), HbA1c increases significantly ($p < 0.05$) in the second half of pregnancy and exceeds the original level.

On the other hand, in the DM cases without iron deficiency A (DM and non-A), this biphasic change was still present, but was statistically not significant. However, in DM and A cases (DM and A), we observed that A exacerbated the effects of DM at the beginning of pregnancy with HbA1c level of 7.09%, and then, it caused a sharp decline towards mid-pregnancy. Increase in the levesl of HbA1c in late pregnancy was statistically insignificant. However, it was still quite obvious in comparison to the DM and non-A group.

The mechanism of this biphasic change in HbA1c is not yet fully understood. In the first half of pregnancy, the significant fall in HbA1c can be explained by physiological changes occuring to nurture the developing fetus [18,19]. Expansion in plasma volume is greater than the increase in red cell mass, and this hemodilution results in a fall in hemoglobin concentration without any change in MCV [20]. Moreover, increased erythropoiesis and decreased erythrocyte turnover rate in early pregnancy may also play a role to this mechanism [21]. HbA1c is known to increase in the second half of pregnancy since demand for iron increases with fetal development, and when iron intake cannot meet this requirement, iron deficiency A is

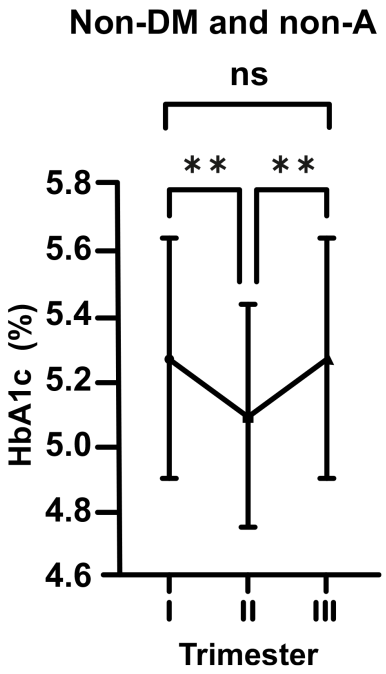

Fig. 1. Changes in HbA1c levels in non-diabetic (non-DM) and non-anemic (non-A) women throughout gestation. Trimesters: I, first (0–13 weeks); II, second (14–28 weeks); and III, third (29–42 weeks). $^{**}p < 0.01$ (statistically very significant); ns, non-significant ($p > 0.05$).

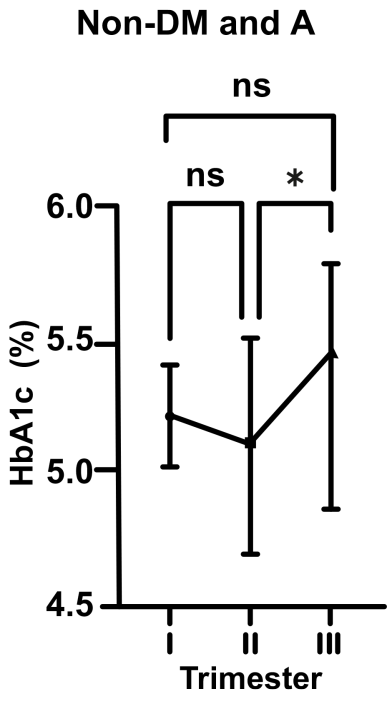

Fig. 2. Changes in HbA1c levels in non-diabetic (non-DM) and anemic (A) women throughout gestation. Trimesters: I, first (0–13 weeks); II, second (14–28 weeks); and III, third (29–42 weeks). $^{*}p < 0.05$ (statistically significant); ns, non-significant ($p > 0.05$).

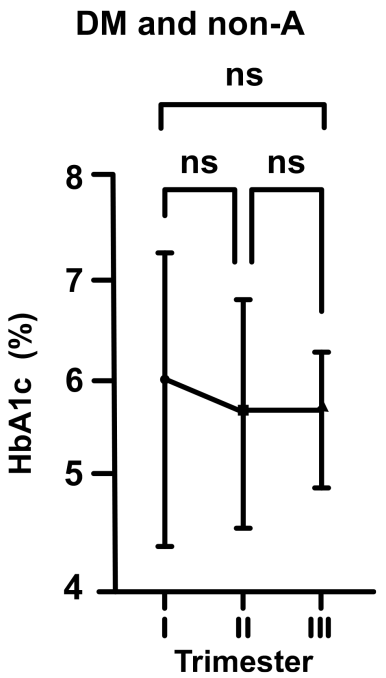

Fig. 3. Changes in HbA1c levels in diabetic (DM) and non-anemic (non-A) women throughout gestation. Trimesters: I, first (0–13 weeks); II, second (14–28 weeks); and III, third (29–42 weeks). ns, non-significant ($p > 0.05$).

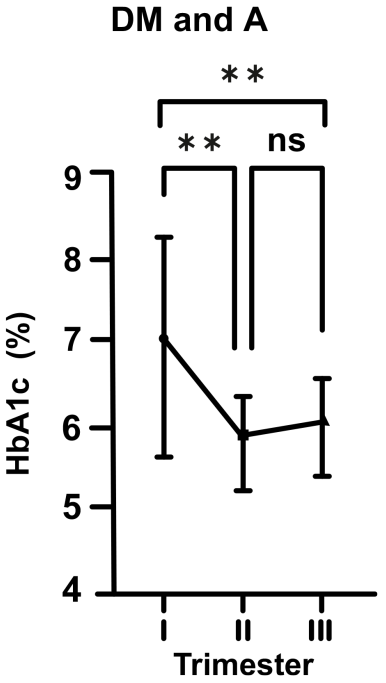

Fig. 4. Changes in HbA1c levels in diabetic (DM) and anemic (A) women throughout gestation. Trimesters: I, first (0–13 weeks); II, second (14–28 weeks); and III, third (29–42 weeks). $^{**}p < 0.01$ (statistically very significant); ns, non-significant ($p > 0.05$).

inevitable [22]. In iron deficiency, red cell production de-

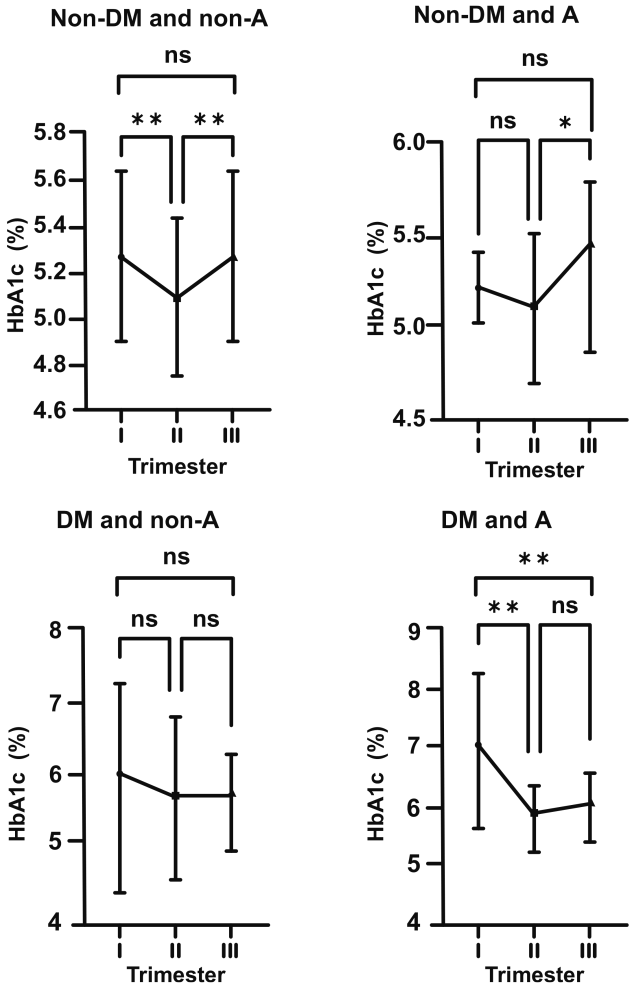

Fig. 5. Biphasic changes in HbA1c levels during pregnancy in all subgroups (DM, non-DM, A, non-A) and steep increase in HbA1c in the second half of gestation, being remarkable in the anemic (A) subgroups. Non-DM groups (top row), DM groups (bottom row), non-A groups (left side), A groups (right side). . Trimesters: I, first (0–13 weeks); II, second (14–28 weeks); and III, third (29–42 weeks). *$p < 0.05$ (statistically significant); **$p < 0.01$ (statistically very significant); ns, non-significant ($p > 0.05$).

creases and consequently, an increased life span of circulating erythrocytes ultimately leads to elevated HbA1c levels [23]. Therefore, under these conditions, estimation of glycemic control based solely on HbA1c levels may lead to a risk of misjudging. However, several researchers have reported the effects of iron therapy on glycated hemoglobin and found a significant reduction in HbA1c levels after iron therapy in both non-DM and DM populations [16,24]. On the other hand, there are other studies reporting that iron supplementation during pregnancy does not affect HbA1c levels and has no significant clinical impact in the final interpretation of blood indices [25].

There are several more studies which report a relationship between iron deficiency A and HbA1c on basis

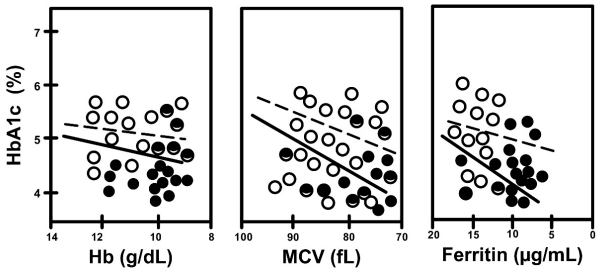

Fig. 6. Correlation between HbA1c and iron related parameters in non-A (open circles, dotted line) and A (closed circles, straight line), in women without gestational DM (non-DM subgroups). Non-A *vs.* A, R = 0.186 *vs.* R = 0.576, and $p < 0.05$ for A in each graphic. Hb, hemoglobin; MCV, mean corpuscular volume.

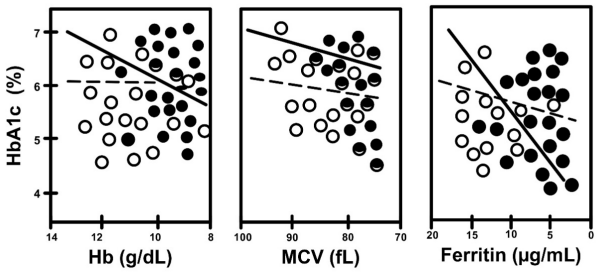

Fig. 7. Correlation between HbA1c and iron related parameters in non-A (open circles, dotted line) and A (closed circles, straight line) in women with gestational DM (DM subgroups). Non-A *vs.* A, R = 0.210 *vs.* R = 0.599, and $p < 0.05$ for A in each graphic.

of structural modifications of hemoglobin in erythrocytes [16,26]. Brooks *et al.* [27] has shown that a relative absence of iron results in the alteration of quaternary structure of hemoglobin leading to excessive glycation of the N-terminal of the beta chain. In another study, it was reported that glycation of hemoglobin molecule is an irreversible process, and aging of the cell causes a linear increase in HbA1c [28]. Our results are concordant with these literature findings investigating the significance of iron deficiency in both DM and non-DM pregnant women. Lastly, several recent studies have recommended glycated albumin (GA) as a more reliable biomarker in monitoring gestational DM and its probable consequences [29,30].

The main limitation of the present study is its retrospective design and its observational nature, leaving the possibility of residual confounding. Follow-up examinations after delivery are also missing. However, being one of the largest studies to investigate HbA1c throughout pregnancy in 670 women with or without A and DM is its main strength.

5. Conclusions

In conclusion, HbA1c level exhibits biphasic changes throughout pregnancy, with decreases towards mid-pregnancy, followed by increases in the third trimester. Iron deficiency A makes reliable interpretation of HbA1c difficult in both DM and non-DM pregnant women.

Availability of Data and Materials

All raw data (on Excel format with all patients' names shaded) and statistical work about this study are available upon request as supplementary files (please contact the corresponding author).

Author Contributions

AF: conception, data curation, formal analysis, investigation, methodology, writing original draft, re-writing after review and final editing. DCK: data curation, methodology, completion of writing original draft, interpretation of data and review. NU: conception, formal analysis, review and last editing after major revision. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final version of manuscript.

Ethics Approval and Consent to Participate

Approval for the present study was obtained from the institutional review board of Health Sciences University Istanbul Education and Research Hospital (date: 25.03.2022, number: 102). All patients provided informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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