Original Article

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Obstetrics and Gynaecology Section

Serum Ferritin, Iron Deficiency Anaemia and Haemoglobin A1c in Non-diabetic Pregnant Women

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ABSTRACT

Introduction: The association between Iron Deficiency Anaemia (IDA) and Haemoglobin A1c (HbA1c) levels is not yet fully investigated. It is suggested that iron-deficiency anaemia may increase concentrations of HbA1c during pregnancy.

Aim: To assess the association between serum ferritin (S-ferritin), IDA and HbA1c among non-diabetic pregnant women.

Materials and Methods: A cross-sectional study was carried out at Saad Abuelela hospital (Khartoum) during the period from February 2017 to August 2017. Data were gathered using a questionnaire. A 75-gram oral glucose tolerance test was performed. HbA1c and S-ferritin were measured. t-test, Mann–Whitney U test and linear regression were performed.

Results: One hundred and fifty-four non-diabetic pregnant women were enrolled. The mean (SD) of age, parity and gestational age were 27.8 (4.7) years, 0.9 (1.0) and 26.8 (1.0) weeks, respectively. The median (interquartile) of HbA1c and S-ferritin were 4.4 (3.8-5.0)% and 20.7 (10.1-35.7) μg/L respectively. Of the 154 women, 103 (66.9%) had anaemia, 56 (36.4%) had iron deficiency (ID) and 38 (24.7%) had IDA. There was no significant difference in the level of HbA1c {4.4 (3.6-5.2)% vs. 4.4 (3.9-4.9)%, p=0.726} between women with IDA and women with no IDA. Likewise, there was no significant difference in the median (interquartile) of HbA1c level in anaemic women {4.5 (4.0-5.0)% vs. 4.4 (3.8-5.1)%, p=0.496}, ID {4.4(3.9–5.0)% 4.4 (3.8-4.9)%, p=0.562} compared with non-anaemic women. There was no association between haemoglobin, S-ferritin, IDA and log of HbA1c in linear regression.

Conclusion: This study found no association between IDA and HbA1c in non-diabetic Sudanese pregnant women.

Keywords: Diabetes, Pregnancy, Sudan

INTRODUCTION

Achievement of strict glycemic control during pregnancy is critical for both the fetus and the mother. Recently, haemoglobin A1c HbA1c has been frequently used as a screening and diagnostic tool for diabetes in pregnancy instead of blood glucose [1]. The use of blood glucose measurement in the diagnosis of diabetes mellitus, though considered the "gold standard", is subject to several reservations. Moreover, the use of HbA1c measurement is appealing as it reflects the glycaemic control over a long period in comparison to the single point of time reflected by the blood glucose measurement. The use of HbA1c measurement becomes more engaging during pregnancy, and it is used in conjunction with home blood glucose measurement, to reflect the true average blood glucose level more precisely and help with metabolic regulation [2-5]. Therefore, HbA1c measurement seems suitable for use during pregnancy; however, it has some reservations: a number of factors can falsely influence HbA1c levels independent of glycaemia. It is important to know that a number of factors affect the HbA1c level and these include the mean blood glucose, the age distribution of the red blood cells and the in-vivo glycation constant [6,7]. The correlation between levels of HbA1c and glycaemia has been extensively studied with establishment of solid evidence of a direct relationship between HbA1c and mean glycaemia [7,8]. However, literature on the association between IDA and HbA1c levels are lacking. It is suggested by some researchers that IDA may increase concentrations of HbA1c [9,10].

There is no clear hypothesis regarding how IDA and serum ferritin might be associated with HbA1c. This is of special importance in a country like Sudan where iron deficiency during pregnancy is a real health problem [11,12]. Providing evidence on such an issue can have its positive impact on health planning in a country needy for any effort that helps to utilise the resources in the proper way. To the best of authors' knowledge, there is no published data from Sudan regarding this issue. Thus, the current study was designed to study the relationship between HbA1c and iron deficiency in non-diabetic pregnant Sudanese women.

MATERIALS AND METHODS

A cross-sectional study was carried out at Saad Abuelela hospital (Khartoum) during the period from February 2017 to August 2017. Ethical approval for the current study was obtained from the Research Board at the Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum, Sudan (#2016, 14). written informed consent was obtained from all participants. All pregnant women who attended antenatal clinic and the screening for gestational diabetes were recruited for the study.

The inclusion criteria were pregnant women with singleton viable baby. Women with hypertension, diabetes, chronic alcohol ingestion, renal diseases and history of haemolytic anaemia were excluded. Medical and obstetrics history (age, parity, gestational age) was recorded for each participant using questionnaire which was filed by trained medical officer. Weight and height were measured using the standard methods and Body Mass Index (BMI) was computed as kg/m^2.

A 75-gram oral glucose tolerance test was performed at 24-28 weeks of gestation. The diagnosis of gestational diabetes mellitus followed the recommendations of International Association of Diabetes and Pregnancy Study Groups (IADPSG), "Fasting Blood Glucose (FBG) ≥92 mg/dL or 1-hour blood glucose was ≥180 mg/dL and/or 2-hour blood glucose ≥153 mg/dL, after 75-g oral glucose load [13]. The glucose level was measured by glucose oxidase method (Shino-Test Corp. Tokyo, Japan). Two millilitres of blood were taken in an ethylenediamine tetra acetic acid and immediately analysed for a complete haemogram, including haemoglobin using an automated haematology analyser [14]. Roche modular system by turbidimetric immune inhibition was used for determination of HbA1c levels. Blood were delivered into a dry clean plain container, centrifuged after clotting and kept at -20°C until analysis for the serum ferritin level which was measured by immunofluorescent assay using Immulite kits (Siemens, Los Angeles, CA, USA).

Anaemia was defined as hemoglobin <11 g/dL, ID was defined as serum ferritin <15 µg/L and IDA was defined as haemoglobin less than 11 g/dL and serum ferritin level <15 µg/L [15].

A total sample size of 154 participants was calculated to investigate the factors influencing HbA1c level. A formula was used to calculate the difference in the mean of the proposed variables (HbA1c) between women with IDA and women without IDA. This sample would provide 80% power to detect a 5% difference at α=0.05, with an assumption that complete data might not be available for 13% of participant.

STATISTICAL ANALYSIS

Data were entered in computer using SPSS (version 20.0) for Windows for data analyses. After assessment for normality of distribution, normally distributed variables were expressed as means (standard deviations), while abnormally distributed variables were expressed as median (interquartile). t-test and non-parametric test (Mann-Whitney U) were used to compare the normally distributed and abnormally distributed data, respectively between the two groups. Linear regression was used where the log of HbA1c was the dependent factor and the obstetrics, medical data, haemoglobin, ferritin, IDA were independent variables. Haemoglobin, ferritin, IDA were entered in the model one by one. p-value of <0.05 was considered statistically significant.

RESULTS

One hundred and eighty pregnant women were recruited to the study. Twenty-six women (14.4%) had gestational diabetes mellitus and were excluded from the analyses. The data of 154 women without gestational diabetes mellitus were presented in this analysis.

The mean (SD) of the age, parity and gestational age were 27.8 (4.7) years, 0.9 (1.0) and 26.8 (1.0) weeks, respectively. Of 154 women, 20 (13.0%) stayed in rural area and 27 (17.5%) had history of miscarriage. The median (interquartile) of HbA1c and serum ferritin were 4.4 (3.8-5.0) % and 20.7 (10.1-35.7) µg/L, respectively, [Table/Fig-1]. Of the 154 women, 103 (66.9%) had anaemia, 56 (36.4%) had iron deficiency (ID) and 38 (24.7%) had IDA.

Variable	Mean (SD)
Age, years	27.8(4.7)
Parity	0.9 (1.0)
Gestational age, weeks	26.8 (1.0)
Body mass index kg/m^2	27.4 (5.3)
Haemoglobin, gm/dL	10.9(0.7)
Variable	**Median (interquartile)**
Fasting blood glucose, mg/dL	68.0 (60.7-75.0)
One hours blood glucose, mg/dL	129.0 (111.0-140.0)
Two hour blood glucose, mg/dL	110.0 (95.0-125.0)
HbA1c, %	4.4 (3.8-5.0)
S-ferritin, µg/L	20.7 (10.1-35.7)

[Table/Fig-1]: The characteristics of the enrolled pregnant non-diabetic women (n=154).

While median (interquartile) level of one hour blood glucose was significantly lower, there was no significant difference at the two hours' time point of the FBG test or the HbA1c measurements {4.4 (3.6-5.2)% vs. 4.4 (3.9-4.9)%, p=0.726} when they were compared between women with IDA and women without IDA, these are shown in [Table/Fig-2]. Likewise there was no significant difference in the median (interquartile) of HbA1c level in women with anaemia {4.5(4.0-5.0) % vs. 4.4(3.8-5.1), p=0.496}, ID {4.4 (3.9-5.0) % 4.4 (3.8-4.9) %, p=0.562} compared with the controls.

Variable	Women with IDA (38)	Women without IDA (116)	p-value
Age, years	27.1 (4.8)	28.0 (4.7)	0.366
Parity	0.9 (1.2)	0.9 (1.0)	0.953
Gestational age, weeks	26.9 (1.2)	26.8 (0.9)	0.560
Body mass index kg/m^2	27.8 (5.6)	27.3 (5.3)	0.634
Fasting blood glucose, mg/dL	65.1 (60.0-69.1)	69.1 (61.2-75.7)	0.113
One hour blood glucose, mg/dL	121.0 (106.5-130.8)	130.7 (112.0-141.7)	0.042
Two hour blood glucose, mg/dL	102.0 (88.0-120.0)	112.5 (97.2-125.0)	0.079
HbA1c, %	4.4 (3.6-5.2)	4.4 (3.9-4.9)	0.726

[Table/Fig-2]: Comparing variables between pregnant women with IDA and pregnant women without IDA (N=154).

There was no significant association between haemoglobin, serum ferritin (coefficient=0.001, p=0.179), IDA (coefficient=-0.011, p=0.595) and log of HbA1c levels in linear regression. Age was significantly associated with log of HbA1c levels ((coefficient=0.005, p=0.019), [Table/Fig-3].

Variables	Coefficient	Standard error	p-value
Age, years	0.005	0.002	0.019
Parity	-0.015	0.010	0.133
Gestational age, weeks	-0.015	0.009	0.088
Body mass index kg/m^2	0.001	0.002	0.729
Haemoglobin, g/dL	0.004	0.012	0.732
S ferritin, µg/L	0.001	0.001	0.179
Iron deficiency anaemia	-0.011	0.021	0.595

[Table/Fig-3]: Linear regression of the factors associated with Log of HbA1c.

DISCUSSION

The main finding of the current study was the absence of any association between HbA1c and IDA. It seems that there is no previous study on this topic during pregnancy.

In line with the present findings, a Dutch study conducted among a paediatric population with Type 1 diabetes mellitus, found no relation between HbA1c and IDA, probably because of the mild anaemia their cohort had [16]. Likewise Adeoye S et al., described an absence of any effect on HbA1c levels after correction of anaemia in their study that compared between 461 anaemic and non-anaemic subjects. They attributed this to a minimal increase in haemoglobin and a too short persistence of correction to impact change [17]. Previous studies have reported significant association between HbA1c and iron deficiency anaemia, [16,18-20]. On the other hand, an association between IDA and HbA1c has been described by Hong JW et al., in their cross sectional study among a large Korean cohort of around eleven thousand subjects, which was actually part of a representative national Korean survey. However, anaemia shifted HbA1c level only among normal subjects and pre-diabetics but not diabetic subjects [20]. Moreover, English E et al., described in a systematic review of twelve articles, the likelihood of HbA1c to be affected by IDA, where it is expected to spuriously increase [21]. This finding could probably be explained by the relatively mild iron deficiency status among our study subjects as reflected by their mean serum ferritin of almost 20 ng/mL.

In their review (12 articles) English E et al., reported that ID (with or without anaemia) led to an increase in HbA1c levels compared with controls, with no effects on glucose indices [21]. Likewise Rafat D et al., observed significantly higher level of HbA1c in non-diabetic pregnant women with IDA compared with the controls. Interestingly the level of HbA1c decreased after iron supplement [22].

LIMITATION

Perhaps the effect of IDA on HbA1c is greater in women with gestational diabetes. Furthermore, we did not include some of the inflammatory markers such as C-reactive protein in order to gauge the serum ferritin level against them.

CONCLUSION

This study found no association between IDA and HbA1c in non-diabetic Sudanese pregnant women.

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