Association between insulin resistance and haematological parameters in pregnant women: A cross-sectional study

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Abstract. Limited research has been conducted on the association between insulin resistance (IR) and haematological parameters, such as red cell distribution width, white blood cell count and mean platelet volume. To date, at least to the best of our knowledge, there are no published data available on IR and haematological parameters during pregnancy. In the present study, pregnant women were initially screened for gestational diabetes. Glucose tolerance tests and fasting plasma insulin (FPI) measurements were conducted between 24-28 weeks of gestational age. Homeostatic model assessment of insulin resistance (HOMA-IR), HOMA-β indices and quantitative insulin sensitivity check index (QUICKI) were determined and used to assess insulin sensitivity and β-cell function. A total of 105 non-diabetic pregnant women were included in the present analysis. The mean (± standard deviation) age, parity and gestational age were 28.3 (±5.6) years, 0.9 (±1.2) and 27.1 (±5.2) weeks, respectively. While there was a positive correlation between platelet count and HOMA-IR (r=0.251, P=0.009), there was no correlation between platelet count and the HOMA-β level in the pregnant women examined (n=105). No significant difference was observed in the haematological variables between women with IR (n=17) and women who did not display IR (n=88). On the whole, the present study demonstrates that platelet count is positively associated with IR. This indicates that haematological parameters may help identify pregnant women with IR. However, Further analyses are required in order to fully understand this association.

Introduction

Insulin resistance (IR) is a condition that is characterized by limited cellular uptake and usage of glucose. As a result of this condition, the pancreas releases extra insulin to compensate for hyperglycaemia (1). Metabolic analyses have detected various biomarkers that may be useful in early screening for gestational diabetes mellitus (GDM) (2). Maternal obesity is the main cause of IR during pregnancy (3,4). Hyperinsulinemia in women is associated with various disorders, such as metabolic syndrome, polycystic ovary syndrome, preeclampsia and GDM (5-8). The effect of insulin is not limited to the control of blood glucose levels, but is also related to metabolic pathways (9).

Previous studies have provided evidence for the effect of hyperinsulinemia on certain haematological parameters (10,11). Previous research has also investigated blood indices in patients displaying symptoms of IR during pregnancy, such as GDM and preeclampsia (12,13). The results of previous studies on blood parameters, such as red blood cell (RBC) count, haematocrit, white blood cell (WBC) count, platelets and IR vary (14-16); thus, additional research under different experimental conditions is warranted. Moreover, to the best of our knowledge, there is currently no published data available on haematological parameters and IR during pregnancy.

In the past, performing a complete blood count (CBC) was a manual and difficult procedure and yielded unreliable results. CBC is currently performed using automated analysers, which yield results rapidly and accurately, and can present more detailed indices, such as red cell distribution width (RDW), platelet distribution width (PDW), mean corpuscular volume (MCV), etc. (17). The results of a CBC can be used as reliable predictors of a number of diseases, such as malignancies, pulmonary disease and cardiovascular disease (18,19). The present study was conducted in order to investigate the correlation between haematological parameters and insulin sensitivity index in healthy pregnant women.

Patients and methods

Study population. A cross-sectional study was conducted at a tertiary maternity hospital in Khartoum, Sudan (Saad Abualila Hospital) between August to November, 2018. The study participants were Sudanese women with singleton pregnancy (24-28 weeks of gestation) who required screening for GDM.

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Women with any chronic diseases, such as diabetes, hypertension, thyroid disease, haemolytic disease, renal disease, liver disease and women on any long-term medications were excluded from the study. All women signed an informed consent form, after which their medical and obstetric history (age, parity, gestational age, education and occupation) were gathered through a questionnaire. Their weights and heights were used to compute body mass index (BMI), as kg/m^2. The present study was approved by the Research Ethics Committee of the Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum, Sudan (#2017, 08).

After fasting for 10 h, the study participants were administered a 75 g oral glucose load for an oral glucose tolerance test. GDM was diagnosed in the present study according to the guidelines of the International Association of Diabetes and Pregnancy Study Groups (IADPSG). According to the guidelines, GDM was diagnosed by a fasting blood glucose (FBG) level ≥92 mg/dl, /1-h blood glucose level ≥180 mg/dl, and /2-h blood glucose level ≥153 mg/dl (20). Subsequently, 5 ml of blood from all participants was withdrawn into a tube containing ethylene diamine tetra acetic acid (EDTA) and used for the analysis for haematological parameters, using an automated haematology analyser [Sysmex (Japan) KX-21] (17,21). A total of 2 ml of the blood sample was used for a hemogram analysis and the remainder was centrifuged at 3,000 x g for 10 min at room temperature and plasma was then stored at -20˚C until the insulin assay was performed. A glucose oxidase method (Shino-Test Corporation) and an immunoassay analyser (AIA 360, Tosoh Corporation) were used to measure the glucose and fasting insulin level, respectively. The homeostasis model assessment (HOMA) of insulin resistance index (HOMA-IR) was determined using the following formula: [fasting glucose level (mg/dl) x fasting insulin level (μU/ml)/405] (22). The quantitative insulin sensitivity check index (QUICKI) was determined using the following formula: 1/[log fasting insulin level (μU/ml) + log fasting glucose level (mg/dl)] (22,23). In addition, the HOMA of β-cell function (HOMA-β) (%) was calculated using the following formula: 360 x fasting insulin level (μU/ml)/[fasting glucose level (mg/dl)-63], and indicates insulin secretion (22). In accordance with previous research, the present study considered women to have IR if their HOMA-IR was >2.6 (24). A sample size of 105 pregnant women was used to determine the significant minimum difference in the correlations (r=0.27) between IR and haematological parameters. This sample size has 80% power and 5% precision at α=0.05.

Statistical analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 20.0 (SPSS Inc.). Proportions of the studied variables are expressed in percentages (%). The Shapiro-Wilk test was used to test for normality of the continuous variables. The mean (± standard deviations) were used to describe continuous variables if they were normally distributed, while the median (and interquartile range) was used to describe the continuous variables if they were abnormally distributed. Spearman's correlation analysis was performed between the following variables: Body mass index (BMI), haematological variables and insulin sensitivity indices. A Student's t-test and non-parametric test (Mann-Whitney U test) were used to compare the variables between the groups when the data were normally and not normally distributed, respectively. The Chi-squared test was used to compare categorical variables between women with IR and women without-IR. A two-sided P-value <0.05 was considered to indicate a statistically significant difference.

Results

A total of 126 pregnant women were screened for GDM. In total, 21 (16.6%) presented with GDM and the remainder were non-diabetic and were included in the present analysis. The general characteristics of the 105 participants and the comparison between 17 women with IR and 88 without IR are presented in Table I. The mean ± SD for age, parity and gestational age was 28.3±5.6 years, 0.9±1.2 and 27.1±5.2 weeks, respectively. No significant differences were observed in sociodemographic characteristics between women with IR and those without IR (Table I). A total of 18 (17.1%) and 12 (11.4%) of the women resided in rural regions and had a secondary school level of education or less, respectively.

While there was a positive correlation between platelet count and HOMA-IR (r=0.251, P=0.009), no correlation was observed between platelet count and the HOMA-β level in the pregnant women examined (n=105) (Table II). No significant difference was observed in the haematological variables of women with IR (n=17) and women displaying no IR (n=88) (Table III).

Discussion

To the best of our knowledge, the present study is the first to investigate haematological parameters in pregnant women displaying IR. The major finding of the present study was that platelet count significantly correlated with HOMA-IR. Additionally, no correlation was observed between the parameters of IR and RBC counts, WBC counts, haemoglobin and other blood indices. A previous study demonstrated that both the insulin level and HOMA-IR positively correlated with the platelet count in non-pregnant subjects (25). Moreover, the platelet-to-lymphocyte ratio has been observed to be a useful indicator for IR, apart from individuals who present with liver fibrosis (16). While maintaining homeostasis and facilitating thrombosis are the main function of platelets, studies have indicated that platelets can also modify immune systems, the inflammatory process and intracellular communication (26,27). Additionally, IR has been shown to be associated with the development of non-alcoholic fatty liver disease (NAFLD) in pregnant and non-pregnant women (28,29). The platelet count in non-pregnant women with NAFLD is an indicator for the severity of the disease (29). The platelet count in pregnancy may perhaps indicate the severity of IR and the increased risk of GDM, as it appears to do in non-pregnant individuals.

The present study found no correlation between leucocyte count and the parameters of IR. The finding is not in agreement with previous studies on non-pregnant subjects (14,30,31). In a previous study, compared with non-IR obese patients, obese patients with IR had higher neutrophil concentrations and a higher neutrophil/lymphocyte (N/L) ratio (14). Additionally,

Table I. General characteristics of pregnant and non-diabetic Sudanese women and comparisons of the sociodemographic characteristics between women with insulin resistance and women who displayed no insulin resistance.

Variable	Total no. of patients (n=105)	Women with insulin resistance (n=17)	Women without insulin resistance (n=88)	P-value
Age, years (mean ± SD)	28.3±5.6	28.3±5.1	27.9±5.8	0.798
Parity [median (25-75th interquartile range)]	0.9±1.2	0 (0-1.25)	0 (0-2)	0.654
Body mass index (kg/m^2) (mean ± SD)	27.1±5.2	27.8±5.9	26.9±4.9	0.529
Haemoglobin (g/dl) (mean ± SD)	10.8±0.9	10.7±0.9	10.8±0.9	0.759
Rural residence [n, (%)]	18 (17.1%)	4 (23.5%)	14 (15.9%)	0.248
Education level ≤ secondary level [n, (%)]	12 (11.4%)	0 (0%)	12 (13.6%)	0.141
Housewives [n, (%)]	77 (73.3%)	10 (58.8%)	67 (76.1%)	0.704
History of miscarriage [n, (%)]	26 (24.7%)	2 (11.7%)	24 (27.2%)	0.300

Data are expressed as the mean ± SD, or median (25-75th interquartile) or number (%) as applicable.

Table II. Spearman's correlations between insulin resistance variables and haematological parameters in pregnant women (n=105).

	HOMA-IR		QUICKI		HOMA-β	
Variable	R value	P-value	R value	P-value	R value	P-value
White blood cell (cells x10^9/l)	0.131	0.179	-0.131	0.179	0.152	0.133
Neutrophils (cells x10^9/l)	0.104	0.284	-0.104	0.284	0.133	0.189
Lymphocytes (cells x10^9/l)	0.069	0.478	-0.069	0.478	0.133	0.189
Red blood cell cells	-0.013	0.891	0.013	0.891	-0.011	0.915
Haemoglobin (gm/dl)	0.102	0.294	-0.102	0.294	0.133	0.189
Haematocrit (%)	0.150	0.124	-0.150	0.124	0.124	0.220
Red cell distribution width (%)	-0.029	0.767	0.029	0.767	-0.044	0.664
Platelet count (10^3/μl)	0.251	0.009[a]	-0.251	0.009[a]	0.075	0.462
Mean platelet volume (f)	-0.019	0.849	0.019	0.849	-0.035	0.731
Platelet distribution width (%)	0.095	0.332	-0.095	0.332	0.075	0.841

[a]P≤0.05, indicates a statistically significant difference. HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; HOMA-β, homeostatic model assessment of β-cell function.

Table III. Comparisons of median (interquartile) level of BMI and insulin sensitivity indices between women with insulin resistance and women who displayed no insulin resistance.

Variable	Women with insulin resistance (n=17)	Women without insulin resistance (n=88)	P-value
Body mass index (kg/m^2)	27.4 (23.3-31.2)	26.6 (24.3-29.6)	0.904
White blood cell (cells x10^9/l)	9.491 (7.9-9.9)	8.491 (7.2-9.1)	0.099
Neutrophils (cells x10^9/l)	5.952 (5.6-6.6)	5.952 (4.8-6.3)	0.375
Lymphocytes (cells x10^9/l)	1.909 (1.7-2.2)	1.909 (1.6-2.0)	0.444
Red blood cell cells	4.057 (3.9-4.1)	4.057 (3.8-4.2)	0902
Haemoglobin (gm/dl)	10.989 (10.4-11.2)	10.897 (10.6-11.3)	0.749
Haematocrit (%)	35.184 (33.8-36.6)	35.184 (33.8-36.5)	0.854
Red cell distribution width (%)	13.663 (13.3-13.7)	13.727 (12.9-13.7)	0.397
Platelet count (10^3/μl)	239.115 (230.0-282.0)	239.11 (209.2-250.0)	0.080
Mean platelet volume (f)	8.196 (8.0-8.6)	8.192 (7.7-8.5)	0.499
Platelet distribution width (%)	15.872 (15.6-15.9)	15.872 (15.7-8.5)	0.336

a positive correlation was reported between IR and leucocyte count (14). In another study, all WBCs were positively associated with HOMA-IR (30). The leukocyte count has also been shown to be positively associated with HOMA-β among non-diabetic individuals (31). Previous research has also provided evidence that hyperinsulinemia does not play a role in altering haematological parameters (32). Factors that may alter haematological parameters include the enhancement of erythropoiesis in bone marrow and increasing haemoglobin and RBC counts (10,11). WBCs are a trigger for the inflammatory process via epinephrine (the main sympathetic neurotransmitter) and are a useful predictor of cardiovascular disease (33,34). Inflammatory mediators, which are secreted from adipose tissue and placenta in the third trimester, can lead to inflammation during pregnancy (35,36). Moreover, inflammatory cytokines have been reported to have role in the pathogenesis of IR (37,38).

The present study found no correlation between RBCs and IR. Hyperinsulinemia enhances the synthesis of RBC through a number of mechanisms: First, growth factor-1, which mimics the insulin hormone, exerts a synergistic effect with erythropoietin and results in the stimulation of erythroid precursors (39,40); second, insulin is an anabolic hormone that generally stimulates protein synthesis. One of these proteins is hypoxia-inducible factor-1a (HIF-1α), which in turn stimulates the synthesis of vascular endothelial growth factor and erythropoietin (41,42). However, studies have found that a number of other factors may affect RBC count and haemoglobin levels, factors such as BMI, nutrition and infection (43,44). Thus, it may be hypothesized that IR may also display geographical variance among individuals in sub-Saharan Africa. However, future studies are required to investigate this matter.

In the present study, none of the investigated sociodemographic factors (age, BMI and parity) differed significantly between pregnant women with IR and pregnant women without IR. These findings are almost in line with those described in the stud by Karakaya *et al* (14), who reported no differences in the age of subjects with IR compared with those without IR. Yet, they reported a significant difference in BMI. This comparison should be taken with caution as Karakaya *et al* (14) performed their study in obese non-pregnant subjects, including those of the male gender.

The present study had several limitations that should be considered when interpreting the findings. First, inflammatory markers, which can identify the severity of the inflammatory state, such as C-reactive protein, cytokines and ferritin, were not measured. Second, the BMI measurement of the study participants was taken during pregnancy and data on pre-pregnancy BMI were not available for analysis. Pre-conception counselling services would be helpful in order to gather these data and develop more accurate interpretation of the results. Third, given the nature of the study design, which involved a cross-sectional study, it is difficult to understand the causes and outcomes of IR in pregnancy. Further studies employing different design methods are therefore warranted.

The present study suggests that CBC can be used to identify IR in pregnant women who otherwise appear healthy. This indicates that the measurement of haematological parameters has the potential to be a simple screening test for detecting IR and perhaps, GDM. Additional studies are required however, in order to confirm and elaborate on these findings.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NMM, RE and IA conceptualized and designed the study. RE, DAR and HZH conducted the study. RE, AI and NMM performed the statistical analyses. HZH, IA and DAR drafted the manuscript. IA and HZH confirm the authenticity of the all the raw data. All authors reviewed the draft and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of the Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum, Sudan (#2017, 08).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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