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Blood pressure and insulin resistance in non-diabetic and normotensive pregnant women

ENAAM TAJ ELSSIR ELHAJ[1], DURIA A. RAYIS[2], ISHAG ADAM[3], ASHWAG SALEH ALSHARIDAH[4] and HAMDAN Z. HAMDAN[5,6]

[1]Department of Medical Laboratories, College of Applied Medical Science, Shaqra University, Shaqra 15273, Saudi Arabia; [2]Faculty of Medicine, University of Khartoum, Khartoum 11111, Sudan; [3]Department of Obstetrics and Gynecology, College of Medicine, Qassim University, Unaizah 51911, Qassim, Saudi Arabia; [4]Department of Physiology, College of Medicine, Qassim University, Buraidah 52222, Qassim, Saudi Arabia; [5]Department of Pathology, College of Medicine, Qassim University, Unaizah 51911, Qassim, Saudi Arabia; [6]Faculty of Medicine, Al-Neelain University, Khartoum 11111, Sudan

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Abstract. Physiological and biochemical changes during normal pregnancy may precipitate a state of insulin resistance (IR) without disrupting the body's physiology. The present study aimed to investigate the association between the indices of insulin sensitivity and blood pressure among normotensive and euglycemic pregnant women. The present cross-sectional study was conducted between February and December, 2021. It comprised 133 normal pregnant women who were non-diabetic and had normal blood pressure. The oral glucose tolerance test and fasting insulin levels were assessed, and the indices of insulin sensitivity and β-cell function were computed between the 24th and 28th weeks of gestation. A multivariate linear regression analysis was conducted to investigate the factors affecting systolic and diastolic blood pressure levels, including the indices of insulin sensitivity, β-cell function and others. Univariate linear analysis revealed that fasting insulin levels (β=0.95, P=0.027), the quantitative insulin sensitivity check index (QUICKI; β=-24.39, P=0.012) and diastolic blood pressure (β=0.76, P<0.001) were associated with systolic blood pressure. Of note, parity (β=0.83, P=0.031), fasting insulin levels (β=0.63, P=0.010), homeostasis model assessment of IR (HOMA-IR; β=3.19, P=0.013) and QUICKI (β=-11.97, P=0.029) were the factors that were associated with diastolic blood pressure. In the multivariate linear regression analysis, neither fasting insulin, nor QUICKI were found to be associated with systolic blood pressure. Fasting insulin levels (β=0.48; P=0.040), HOMA-IR (β=2.51; P=0.043) were associated with diastolic blood pressure. On the whole, in the present study, fasting insulin levels and HOMA-IR were associated with diastolic blood pressure levels without the emergence of high blood pressure readings or gestational diabetes. Further studies with a longitudinal approach are warranted to further identify associations with IR.

Correspondence to: Professor Duria A. Rayis, Faculty of Medicine, University of Khartoum, AlQassr Main Street, Medical Campus, Building No. 3, Khartoum 11111, Sudan
E-mail: doctorduria8@gmail.com

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Introduction

During normal pregnancy, numerous physiological and biochemical changes occur to meet the escalating need for nutrients to cover the energy requirement for the growing fetus. One of these changes is an increase in the release of the insulin hormone, known as hyperinsulinemia. This hyperinsulinemia arises as the gestational age advances, reaching peak levels in the third trimester (1). Therefore, it is widely accepted that pregnancy per se is a state of insulin resistance (IR) (1). IR is a condition characterized by impaired glucose uptake and utilization by peripheral tissues despite the presence of hyperinsulinemia (1). The exact cause of IR in normal pregnancy is not yet fully understood; yet, a number of risk factors have been identified, such as maternal obesity, physical inactivity, placentation, genetics and epigenetic factors (1).

IR is considered a precipitating factor for obstetrics-related disorders, such as gestational diabetes and preeclampsia (2-4). Nevertheless, pregnant women with IR may remain normotensive and euglycemic throughout their pregnancy (5). The known effects of hyperinsulinemia extend to the sympathetic nervous system, increasing the sympathetic tone and inducing renal sodium retention. This retention shifts sodium movement inside the cells, particularly in the smooth muscle of the blood vessels (6,7). These changes may raise blood pressure and precipitate hypertension (8).

There is a paucity of publications investigating IR in normal pregnant women. However, it has been reported that IR precedes the clinical emergence of hypertension by a few years in non-pregnant women (9). An association has also been observed between insulin hormone indices and blood pressure in healthy adolescents prior to the onset of hypertension (10).

Little is known about IR indices and blood pressure in normal pregnancies. Therefore, the present study was conducted

in an aim to investigate the possible association between IR indices and blood pressure among healthy pregnant women screened negative for preeclampsia and gestational diabetes. The findings presented herein may guide clinicians in the early categorization of women who are at an increased risk of developing high blood pressure, preeclampsia and perhaps, gestational diabetes before becoming symptomatic.

Subjects and methods

The present cross-sectional study was conducted at the Antenatal Care Clinic of Saad Abuelela Maternity Hospital, Khartoum, Sudan, from February through December, 2021. Ethical clearance was obtained from the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Khartoum (Khartoum, Sudan). All subjects included in the present study were briefed about its objectives and all subjects gave their written consent to participate.

Inclusion criteria. All the participants selected for the present study were healthy, pregnant Sudanese women aged ≥18 years with singleton pregnancies. Screening for gestational diabetes mellitus and IR occurred between the 24 and 28th weeks of gestation. For each woman, a well-structured questionnaire was filled out to gather sociodemographic, clinical, and medical history data.

Exclusion criteria. Candidates were excluded from the study if they had a previous history of hypertension, diabetes mellitus, thyroid disease, liver disease, kidney disease or severe anemia (hemoglobin levels <7 g/dl) or if they were smokers or on regular medication(s) that may affect blood pressure or blood glucose levels.

A total of 133 pregnant women were enrolled in the present study, for each of whom blood pressure was measured twice following a resting period of ~10 min using an OMRON3 automated blood-measuring device (OMRON Healthcare). There was a 1-to-2-min time interval between the two readings, and the mean of the two readings was then calculated. The reading was rejected in the case that the difference between the two readings was >5 mmHg, and the measurement was repeated until the readings became stable. The OMRON M3 readings can be validated among pregnant women, including among women with preeclampsia. The mean ± SD of differences between the OMRON 3 and the standard mercury sphygmomanometer was -1.6±2.8 mmHg for systolic blood pressure and -0.1±2.3 mmHg for diastolic blood pressure. This was rated and rated A/A for systolic and diastolic blood pressure (11). The calculations for body mass index (BMI) were based on the measurements of the height (meters) and weight (kg) of each candidate. BMI was calculated using the following equation: BMI=weight in kg/height in m^2.

For each candidate, 2 ml venous blood sample was collected in a fluoride vacutainer in a fasting state (following overnight fasting for 10 h). A glucose tolerance test was then performed. Plasma glucose levels were measured by the enzymatic colorimetric method (BioSpectrometer, Eppendorf) using glucose oxidase reactions (Thermo Fisher Scientific, Inc.), following the manufacturer's instructions. Another sample of 2 ml blood was collected in ethylenediaminetetraacetic acid vacutainers to assess glycosylated hemoglobin (HbA1c). An i-chroma™ device (Biotech Med) was used to measure the HbA1c levels. The validation of the i-chroma™ device revealed a coefficient of variations of <2% in both the high and low HbA1c readings. The Spearman's correlation rank between the i-chroma device and the HPLC method is relatively low (Rho=0.368), and the mean bias is -0.50±1.62% (-5.5±17.7 mmol/mol) (12). Fasting levels of plasma insulin were measured using the immunoassay analyzer AIA 360 (Tosoh Bioscience). IR was calculated using the following homeostatic model assessment for IR (HOMA-IR) formula: Fasting insulin (U/l) x fasting glucose (mg/dl)/405 (13). The quantitative insulin sensitivity check index (QUICKI) was calculated using the following formula: 1/(log (fasting insulin μU/ml) + log (fasting glucose mg/dl) (14). Homeostatic model assessment for β-cell function (HOMA-β) was measured based on fasting plasma glucose (FPG) and fasting plasma insulin (FPI) concentrations using the following formula: HOMA-β=FPI concentration (μU/ml) x20/FPG (mmol/l)-3.5 (15).

Ethics approval and consent to participate. The present study received ethical clearance from the Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum (No. 032, 2020). Signed informed consent was collected from all participants prior to enrolment.

Sample size calculation. The sample size was calculated using the Sample Size Calculators based on the significant minimum difference in the Pearson's correlations (r=0.30) between the systolic, diastolic blood pressure and HOMA-IR. The needed sample was 133, with 80% power and 5% precision at α=0.05.

Statistical analysis. Data were entered into a computer using SPSS (version 20.0) software (IBM Corp.). The Shapiro-Wilk test was used to assess the continuous variables for normality. All continuous variables were abnormally distributed. Accordingly, the median [interquartile range (IQR)] was used to express the abnormally distributed variables. Univariate linear regression analysis was performed with systolic and diastolic blood pressure as dependent variables, and maternal age, parity, education level, residency, job status, indices of IR and fasting insulin levels as independent variables. Variables with a P-value ≤0.200 in the univariate analysis were shifted to built-up multivariable linear regression analysis to assess the confounder. The coefficient with a 95% confidence interval (CI) and the P-value were reported. A two-sided P-value <0.05 was considered to indicate a statistically significant difference.

Results

Sociodemographic and clinical data. A total of 133 pregnant women were enrolled in the present study. The median (IQR) of age and parity were 28.0 years (24.0-32.0 years) and 1 (0.0-2.0), respectively. The majority (90.2%) of these women had a secondary level of education or higher. Of note, three quarters (75.9%) of the study participants were housewives, and 72.2% resided in urban residences. The observed range and median (IQR) of the systolic blood pressure of the participants was 100-130 mmHg, 110 mmHg (110-110.7 mmHg). For diastolic blood pressure, the observed range and median

Table I. Sociodemographic, clinical and biochemical characteristics of the pregnant women (n=133) included in the present study.

Variables	Value
Education level, n (%)	
≥Secondary	120 (90.2)
<Secondary	13 (9.8)
Residence, n (%)	
Urban	96 (72.2)
Rural	37 (27.2)
Employment, n (%)	
Housewife	101 (75.9)
Employed	32 (24.1)
Age (years), median (IQR)	28.0 (24.0-32.0)
Parity (number), median (IQR)	1.0 (0.0-2.0)
Systolic blood pressure (mmHg), median (IQR)	110 (110-110.7)
Diastolic blood pressure (mmHg), median (IQR)	70 (70.0-72.4)
Mean blood pressure (mmHg), median (IQR)	83 (83.0-85.1)
Fasting blood glucose (mg/dl), median (IQR)	70 (63.0-78.0)
Fasting insulin (μIU/ml), median (IQR)	2.2 (1.1-4.6)
Homeostatic model assessment for insulin resistance, median (IQR)	0.356 (0.18-0.76)
Quantitative insulin sensitivity check index , median (IQR)	0.463 (0.40-0.53)
Homeostatic model assessment for β-cell function, median (IQR)	58.0 (9.4-144.0)
Body mass index (kg/m^2), median (IQR)	26.9 (23.9-30.2)

IQR, interquartile range.

(IQR) was 60-80 mmHg, 70 mmHg (70.0-72.4 mmHg); for median blood pressure, the observed range and median (IQR) was 73.3-100 mmHg, 83 mmHg (83.0-85.1 mmHg) among the study participants. Fasting glucose levels ranged between 48-82 mg/dl with a median (IQR) of 70 mg/dl (63.0-78.0 mg/dl). Fasting insulin levels ranged between 0.5-12.5 mg/dl with a median (IQR) of 2.2 mg/dl (1.1-4.6 mg/dl). The median (range) was 0.356 (0.18-0.76) for HOMA-IR, 58.0 (9.4-144.0) for HOMA-β, and 0.463 (0.40-0.53) for QUICKI (Table I).

Univariate linear regression analysis. Univariate linear regression analysis revealed that fasting insulin levels (β=0.95; 95% CI, 0.10 to 1.80; P=0.027), QUICKI (β=-24.39; 95% CI, -43.1 to -5.59; P=0.012) and diastolic blood pressure (β=0.76; 95% CI, 0.44 to 1.08; P=<0.001) were associated with systolic blood pressure (Table II). Of note, parity (β=0.83; 95% CI, 0.07 to 1.58; P=0.031), fasting insulin levels (β=0.63; 95% CI, 0.15 to 1.10; P=0.010), HOMA-IR (β= 3.19; 95% CI, 0.67 to 5.71; P=0.013) and QUICKI (β=-11.97; 95% CI, -22.72 to -1.22; P=0.029) were the factors that were associated with diastolic blood pressure (Table III).

Multivariate linear regression analysis. Among the variables investigated in the multivariate linear regression analysis, only diastolic blood pressure (β=0.64, 95% CI, 0.30 to 0.98; P<0.001) was found to be significantly associated with the levels of systolic blood pressure (Table II). Multivariate linear regression analysis for diastolic blood pressure revealed that fasting insulin levels (β=0.48; 95% CI, 0.02 to 0.94; P=0.040), HOMA-IR (β=2.51; 95% CI, 0.08 to 0.4.95; P=0.043) were associated with the levels of diastolic blood pressure (Table III).

Discussion

The main finding of the present study was that the multivariate regression model revealed that fasting insulin levels, HOMA-IR and systolic blood pressure were significantly associated with the levels of diastolic blood pressure among normotensive and euglycemic pregnant women. The ability of HOMA-IR to predict the levels of diastolic blood pressure in the present study was similar to the results reported in the study by Furugen *et al* (16), who tried to predict the development of hypertension in a cohort of normotensive adult Japanese subjects. They found that HOMA-IR and the Matsuda-DeFronzo insulin sensitivity index (ISI-M) were associated with blood pressure. However, the ISI-M was found to be more sensitive than HOMA-IR in the prediction of hypertension, which indicates an extra-hepatic source of IR (16). However, the present study did not calculate the ISI-M of the participants; otherwise, the findings could differ. Perhaps the presence of the placenta in pregnant women represents an additional source of IR (17). This is supported by the findings reported in the study by Jacober *et al* (18), who investigated insulin indices with blood pressure among nulliparous preeclamptic women at 3 to 6 months postpartum and found no association. This may point to the transient effect

Table II. Univariate and multivariate linear regression analysis of factors associated with systolic blood pressure in pregnant women (n=133) Khartoum, Sudan, 2021.

	Univariate linear analysis			Multivariate linear analysis		
Variables	Coefficient	95% Confidence interval	P-value	Coefficient	95% Confidence interval	P-value
Age, years	0.20	(-0.09 to 0.50)	0.170	0.18	(-0.16 to 0.53)	0.308
Parity	1.13	(-0.21 to 2.047)	0.098	0.67	(-0.90 to 2.25)	0.397
Education level	-3.61	(-8.61 to 1.37)	0.154	-4.48	(-9.42 to 0.45)	0.075
Residency	-0.12	(-4.64 to 4.39)	0.956			
Employment	0.62	(-3.24 to 4.48)	0.751			
Body mass index	0.29	(-0.01 to 0.60)	0.062	0.16	(-0.15 to 0.48)	0.312
Fasting blood glucose	-0.06	(-0.22 to 0.08)	0.398			
Fasting insulin levels[a]	0.95	(0.10 to 1.80)	0.027[b]	0.54	(-0.28 to 1.38)	0.195
Homeostatic model assessment for insulin resistance[a]	4.47	(-0.01 to 8.96)	0.050[b]	2.26	(0.32 to 0.99)	0.314
Quantitative insulin sensitivity check index[a]	-24.39	(-43.1 to -5.59)	0.012[b]	-16.11	(-35.55 to 3.32)	0.103
Homeostatic model assessment for β-cell function[a]	0.10	(-0.01 to 0.06)	0.798			
Diastolic blood pressure	0.76	(0.44 to 1.08)	<0.001[b]	0.64	(0.30 to 0.98)	<0.001[b]

[a]These factors were added one by one in the multivariable model. The multivariate model was adjusted for age, parity, education level, body mass index, fasting insulin, homeostatic model assessment for insulin resistance, quantitative insulin sensitivity check index and diastolic blood pressure. [b]Indicates statistical significance (P<0.05).

Table III. Univariate and multivariate linear regression analysis of factors associated with diastolic blood pressure in pregnant women (n=133), Khartoum, Sudan, 2021.

	Univariate linear analysis			Multivariable linear analysis		
Variables	Coefficient	95% Confidence interval	P-value	Coefficient	95% Confidence interval	P-value
Age, years	0.16	(-0.01 to 0.35)	0.051	0.10	(-0.08 to 0.29)	0.247
Parity	0.83	(0.07 to 1.58)	0.031[b]	0.62	(-0.24 to 1.50)	0.158
Education level	0.13	(-2.72 to 2.99)	0.925			
Residency	0.26	(-2.29 to 2.86)	0.837			
Employment	-1.19	(-3.37 to 0.98)	0.279			
Body mass index	0.157	(-0.01 to 0.33)	0.078	0.05	(-0.12 to 0.23)	0.562
Fasting blood glucose	-0.02	(-0.11 to 0.06)	0.627			
Fasting insulin levels[a]	0.63	(0.15 to 1.10)	0.010[b]	0.48	(0.02 to 0.94)	0.040[b]
Homeostatic model assessment for insulin resistance[a]	3.19	(0.67 to 5.71)	0.013[b]	2.51	(0.08 to 4.95)	0.043[b]
Quantitative insulin sensitivity check index[a]	-11.97	(-22.72 to -1.22)	0.029[b]	-8.89	(-19.92 to 2.14)	0.113
Homeostatic model assessment for β-cell function[a]	0.00	(-0.003 to 0.003)	0.861			

[a]These factors were added one by one in the multivariate model. The multivariate model adjusted for age, parity, body mass index, fasting insulin, homeostatic model assessment for insulin resistance, quantitative insulin sensitivity check index. [b]Indicates statistical significance (P<0.05).

of IR associated with the presence of the placenta during pregnancy. It is worth mentioning that it is considered that the placenta synthesizes adipokines, such as leptin and others, and mediates IR by affecting insulin hormone signaling and initiating cascades of events in endothelial cells, leading to preeclampsia (19).

In the present study, HOMA-IR and fasting insulin levels were found to be associated with blood pressure. This is consistent with a previous study by Kazumi *et al* (20), which compared insulin-resistant indices in young normotensive subjects and subjects who were not hypertensive, but had high blood pressure readings. Hyperinsulinemia associated with IR (1) may indicate that the secretory function of β-cells remains responsive as long as the blood pressure readings remain within the normal range, as in the present study sample. However, this sustained hyperinsulinemia state may precipitate elevated blood pressure. A number of hypotheses have been postulated to explain the mechanism of hyperinsulinemia in the pathogenicity of hypertension. It has been mentioned that hyperinsulinemia leads to the dysfunction of immune cells, particularly T-cells and macrophages, a cardinal pathological mechanism in preeclampsia (21). Through this mechanism, the activity of Th1/Th2 cells is increased in the maternal circulation and the fetus-placenta interface (21). In addition to modulating the immune system, hyperinsulinemia triggers the sympathetic tone of the nervous system, increases renal sodium retention and imbalances the cation distribution across the membrane (6,7). Collectively, these mechanisms at least partially contribute to the pathogenicity of hypertension. However, it is uncertain why the patients in the present study did not develop hypertension or preeclampsia. Perhaps they did not reach the threshold at which the endothelial changes become irreversible. Long-standing and pre-gestational IR is considered a risk factor for preeclampsia (22). However, the exact turning point from normotension to hypertension is uncertain. This issue remains unresolved, whether during pregnancy or not.

In conclusion, measuring IR indices is not a routine antenatal care test. However, the current findings shed light on the association between HOMA-IR, fasting insulin levels and blood pressure readings. Although the blood pressure readings of the participants in the present study were still within the normal range, strict follow-up, close monitoring and timely intervention may alleviate major maternal-fetal cardiovascular complications. The present study was a single center initial study, and had certain limitations that need be addressed for a clear interpretation of our findings. Firstly, the design was a cross-sectional design; therefore, causality cannot be inferred; in addition, due to design, the authors could not determine whether the onset of IR in the study sample was before pregnancy or during pregnancy. Additionally, gestational complications, such as preeclampsia and gestational diabetes, were not addressed. Secondly, some confounding factors, such as a family history of diabetes/hypertension were not enquired. Therefore, further multi-center studies with a longitudinal design are required to measure more IR indices, such as ISI-M to establish/exclude extra-hepatic IR and detect pregnancy related complications, such as preeclampsia and gestational diabetes.

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Availability of data and materials

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

Authors' contributions

ETEE and DAR were involved in the conceptualization of the study. IA, HZH and ASA were involved in the study methodology and design. ASA, DAR and IA were involved in data curation. ETEE, HZH and IA were involved in the formal analysis. ASA and HZH were involved in the investigative and procedural aspects of the study. DAR, IA and ETEE confirm the authenticity of all the raw data. ASA, DAR, HZH, ETEE and IA were involved in the drafting and reviewing of the primary version of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Board of the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Khartoum and accordingly Ethical Approval was issued under number (#2020, 08). Informed written consent was obtained after explaining the research objectives. All experiments, sample collection and handling of patient data were conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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