No effect of fetal sex on maternal insulin resistance: A cross-sectional study

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Abstract. The association between fetal sex and maternal insulin resistance and β-cell functions during pregnancy has not yet been fully elucidated. The present study thus aimed to investigate this association among non-diabetic pregnant women. For this purpose, a cross-sectional study was conducted between February to October, 2022. Pregnant women between the 24 and 28th week of gestation were enrolled in the present study; glucose tolerance tests were performed and indices of insulin resistance and β-cell function were examined. The results revealed that out of the 113 pregnant women included in the study, 55 gave birth to boys and 58 delivered girls. The mean (standard deviation) for age and body mass index in all the participants were 27.6 (5.6) years, and 27.1 (5.6) kg/m^2, respectively. There was no significant difference between the mean (standard deviation) for age [28.1 (5.4) vs. 27.1 (5.7) years; P=0.318] and body mass index [26.8 (4.9) vs. 27.3 (6.2) kg/m^2; P=0.638] of mothers who gave birth to boys and those who delivered girls, respectively. The median (interquartile range) of fasting insulin levels [7.31 (3.49-14.6 vs. 7.31 (3.73-14.6) μU/ml; P=0.858] and indices of homeostatic model assessment for insulin resistance [19.78 (11.73-38.7) vs. 21.7 (10.0-42.1), P=0.692] and homeostatic model assessment for β-cell function [2.1 (1.09-4.03) vs. 2.1 (1.06-4.39), P=0.993] were comparable between the mothers bearing boys and those bearing girls. No significant difference was observed in the mean (standard deviation) of fasting glucose levels between the two groups [71.0 (13.1) vs. 68.2 (9.9) mg/dl; P=0.207]. On the whole, the present study found that fetal sex was not associated with maternal insulin resistance. However, further studies are required to confirm these findings.

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Introduction

In normal pregnancy, a number of physiological changes allow the maternal body to accommodate the growing fetus. These changes include insulin resistance (IR), which is characterized by hyperglycemia accompanied by hyperinsulinemia (1). In some cases, this IR escalates and may precipitate gestational diabetes (2). However, there is limited information available on the definite cause of maternal IR. However, multiple factors have been found to promote IR during pregnancy, such as maternal obesity, ethnicity and genetic factors (3-5). There is a growing body of compelling evidence indicating the involvement of fetal sex in contribution to maternal IR (6-8). It has been reported that females pregnant with a male fetus have more deteriorated function of the pancreas (8) and are at an increased risk of developing gestational diabetes (9). Conversely, bearing a female fetus has been shown to be accompanied by a lower risk of maternal IR (7).

Previous studies have emphasized that the maternal-fetal association is considered reciprocal (7,10), where the maternal biological system can affect the biology of the fetus and vice versa. This concept may partially explain the effect of fetal sex on maternal health. For instance, diabetic mothers have been shown to exhibit fetal macrosomia and neonatal hypoglycemia (11). On the other hand, previous studies have confirmed the association between the sex of the baby and the incidence of obstetrical complications, such as preterm labor, preeclampsia and cesarean section delivery (12-14). The placenta is a product of fetal genes, thus controlled by the genome of the fetus, including the sex chromosome of the fetus (15). It has been documented that the placenta secretes hormones and hormone-like substances associated with the development of diseases related to IR, such as preeclampsia and gestational diabetes (16,17). Previous research has documented physiological differences in placentas based on fetal sex. These differences emerge early in pregnancy, following implantation, and involve interactions between sex chromosomes and autosomes that contribute to determining fetal sex (18). A previous meta-analysis identified 142 differentially expressed genes between male and female placentas, with these genes being enriched in pathways related to hormone signaling, cell growth and differentiation (19). Since hormonal

dysregulation plays a key role in the pathogenesis of maternal conditions, such as preeclampsia and gestational diabetes mellitus (GDM), these findings suggest that fetal sex may influence maternal IR (20). However, the exact mechanisms through which the sex of the fetus can affect the maternal IR status are not yet fully understood.

The present study investigated the potential association between fetal sex and the maternal IR status during the second trimester of pregnancy in Sudanese pregnant women who were non-diabetic/hypertensive. To the best of our knowledge, the present study is the first to examine such an association in the Sudanese population. Different factors can influence the development of IR, such as ethnicity and genetic makeup. To the best of our knowledge, no previous study has investigated the effect of fetal sex on IR markers in a Sudanese population of North African ethnicity. Clinically, an association of fetal sex with maternal IR may help the clinician and caregiver to identify pregnant women who are at an increased risk of developing gestational diabetes and preeclampsia. The determination of this association may lead to early detection, closer follow-up, prevention and intervention strategies. Thus, it is hoped that the findings presented herein may provide some insight into this matter.

Subjects and methods

Study design and study setting. A cross-sectional study was conducted between February to October, 2022 at the antenatal unit of Saad Abuelela Maternity Hospital, a tertiary-level university hospital affiliated with the University of Khartoum, located in the southern part of Khartoum, Sudan. The study protocol and procedures were approved by the Research Board at the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Khartoum, Khartoum, Sudan and the ethical clearance was issued under number (#2020, 08). Pregnant women who visited antenatal care clinics at a gestational age of 24-28 weeks were approached to participate in the study. The study objectives were briefly explained to the participants, and consent was obtained through signing. Only apparently healthy (without any medical history of disease) singleton pregnant Sudanese women were included and women with a history of thyroid disorder, diabetes, hypertension, or any chronic disease were excluded from the study. Women who refused to provide consent to participate were also excluded from the study. The obstetric history and sociodemographic characteristics of the pregnant women were recorded using questionnaires. The gestational age was calculated with reference to the final menstruation and confirmed by an ultrasonography. Body mass index (BMI) was calculated using the standard method based on height and weight. The participating pregnant women were followed-up until delivery. Following delivery, the participants were divided into two groups based on the sex of the newborn. Newborns with ambiguous genitalia were excluded.

Methods of sampling and laboratory testing. Venous blood samples were collected from each participant, and 5.0 ml blood were kept in a heparin-containing vacutainer. Plasma was harvested following centrifugation (3,000 x g for 15 min at room temperature) and the insulin levels were then measured. An immunoassay analyzer AIA 360 (Tosoh Bioscience, Inc.) was used to quantify fasting insulin levels as per manufacturer's instructions. An oral glucose tolerance test was performed after collecting three samples of blood, each one kept in a 3.0 ml vacutainer containing fluoride. After the fasting sample was collected, a 75-g glucose meal was given to the participant, and blood glucose levels were measured 1 and 2 h after the meal using the glucose oxidase method. In the case that the blood glucose reading exceeded the following values at the specified time points: Fasting levels, ≥92 mg/dl; at 1 h, ≥180 mg/dl; and at 2 h, ≥153 mg/dl, GDM was then diagnosed, and the patients were excluded from the study (21). The levels of glycated hemoglobin (HbA_{1C}) were measured using an automatic analyzer (HLC-723G7, Tosoh Corporation).

Assessment of insulin resistance by homeostatic model assessment for insulin resistance (HOMA-IR) and homeostatic model assessment for β-cell function (HOMA-β). HOMA-IR is a mathematical model for assessing peripheral IR. Matthews *et al* (22) proposed this model, which is used to measure fasting insulin and fasting glucose concentrations as follows: Fasting blood glucose (mg/dl) x fasting insulin (μU/ml)/405.

The physiological value of the index was 1.0. Higher values are indicative of IR. Low HOMA-IR indicate good insulin sensitivity. A small amount of insulin is sufficient to maintain glucose homeostasis, while a higher HOMA-IR denotes greater IR. A healthy IR range is between 0.5-1.4; <1.0 indicates optimal insulin sensitivity; >1.9 indicates early IR; and >2.9 indicates marked IR (23).

HOMA-β is calculated mathematically based on the input from the fasting insulin level and fasting blood glucose level as follows: (20 x Ins0)/(Glu0-3.5) (22).

Sample size calculation. A sample size of 113 women was calculated based on the summation of at least 55 females who would have male and female babies (24). This would allow for a significant difference of 0.5 in the parameters HOMA-IR and HOMA-β. This sample had 80% power and a difference of 5% at α=0.05.

Statistical analysis. All statistical analyses were performed using the Statistical Package for the Social Science software for Windows (SPSS version 22.0; IBM Corp.). Continuous data (including fasting blood glucose, insulin hormone, HOMA-IR, HOMA-β, age, parity, gravidity and HbA_{1C}) were examined for normality using the Shapiro-Wilk test. Continuous data are expressed either as the median (interquartile range), in the case that they were not normally distributed, or as the mean (SD), in the case that they were normally distributed. The Chi-squared test was used to compare categorical variables between women bearing boys and women bearing girls. The Mann-Whitney U test was used to compare the skewed continuous data, and the unpaired Student's t-test was used to compare the normal distributed continuous data between the two groups. A P-value <0.05 was considered to indicate a statistically significant difference.

Table I. Socio-demographic and clinical characteristics of the participating pregnant women.

Variables	All participants (n=113)	Women who delivered a boy baby (n=55)	Women who delivered a girl baby (n=58)	P-value
Age in years, mean (SD)	27.6 (5.6)	28.1 (5.4)	27.1 (5.7)	0.318
BMI in kg/m^2, mean (SD)	27.1 (5.6)	26.8 (4.9)	27.3 (6.2)	0.638
Gestational age in weeks, mean (SD)	38.9 (1.5)	38.6 (1.6)	39.2 (1.4)	0.867
Birth weight in kg, mean (SD)	3.1 (0.5)	3.19 (0.52)	3.06 (0.48)	0.167
Systolic blood pressure in mmHg, mean (SD)	110.4 (7.2)	110.0 (8.1)	110.9 (6.2)	0.516
Diastolic blood pressure in mmHg, mean (SD)	72.2 (5.4)	71.7 (6.0)	72.7 (4.8)	0.354
Parity, median (25-75th percentile)	0 (0-1.5)	1 (0-2)	0 (0-1.25)	0.175
Gravidity, n (%)				0.156
Primigravid	55 (48.6)	23 (41.8)	32 (55.2)	
Multigravida	58 (51.3)	32 (58.2)	26 (44.8)	
Level of education, n (%)				0.170
Secondary	13 (11.5)	4 (7.3)	9 (15.5)	
University	100 (88.5)	51 (92.7)	49 (84.5)	
Occupation, n (%)				0.798
Housewife	83 (73.5)	41 (74.5)	42 (72.4)	
Employee	30 (26.5)	14 (25.5)	16 (27.6)	
Mode of delivery, n (%)				0.360
Cesarean section	40 (35.4)	17 (30.9)	23 (39.7)	
Vaginal delivery	73 (64.6)	38 (69.1)	35 (60.3)	

Continuous data are expressed as the mean (SD) or median (interquartile range; 25-75th percentile) as applicable. Categorical data are expressed as number and percentage. BMI, body mass index.

Results

A total of 113 pregnant women enrolled in the present study, with 55 giving birth to boys and the remaining 58 delivering girls. There was no significant difference between the mean (SD) of BMI [26.8 (4.9) vs. 27.3 (6.2) kg/m^2; P=0.638] or age [28.1 (5.4) vs. 27.1 (5.7) years; P=0.318] between the mothers delivering boys and those delivering girls, respectively. Both groups had comparable obstetrical and sociodemographic characteristics (Table I).

The mean (SD) of fasting blood glucose levels [71.0 (13.1) vs. 68.2 (9.9) mg/dl; P=0.207] and HbA_{1C} levels [4.3 (1.22) vs. 4.1 (1.03)%; P=0.641] was slightly higher in women with boys compared to those with girls. However, this difference was not statistically significant. The result of the oral glucose tolerance test following the ingestion of 75 g glucose was similar between the two groups (Table II). Likewise, the median (IQR) of the fasting insulin level [7.31 (3.49-14.6) vs. 7.31 (3.73-14.6) μU/ml, P=0.858], HOMA-IR [19.78 (11.73-38.7) vs. 21.7 (10.0-42.1), P=0.692] and HOMA-β [2.1 (1.09-4.03) vs. 2.1 (1.06-4.39), P=0.993] were comparable between the two groups (Table II).

Discussion

The main finding of the present study was that there were no differences in the indices of IR (HOMA-IR) and indices of β-cell function (HOMA-β) between pregnant women bearing boys and those bearing girls during the early weeks of the second trimester. These findings are consistent with those of the studies by Rafferty *et al* (25), Retnakaran *et al* (8) and Geng *et al* (6) findings, who found no significant difference in HOMA-IR between women pregnant with boys and those pregnant with girls. Rafferty *et al* (25) recruited Irish pregnant women in their study, and these women were selected based on a BMI between >25 kg/m^2 and <39.9 kg/m^2. Since their study was originally a clinical trial, they followed-up the patients. They collected blood samples three times, the first at the 16th week of gestation, the second sample between the 28 and 34th week, and the final sample was collected at delivery, which was a fetal-cord blood sample. Of note, fetal sex did not affected IR either in the maternal or fetal samples (25). The BMI of the patients in the present study was within the range reported in the study by Rafferty *et al* (25); therefore, these findings can be comparable. Although in their study, Retnakaran *et al* (8) reported the same finding, this should be taken with caution, since Retnakaran *et al* (8) recruited a highly heterogeneous population that encompassed subjects of Asian, White, South-Asian and African ethnicity. On the other hand, a body of published researchers considers fetal sex as a novel independent risk factor for maternal IR. For instance, Yamashita *et al* (26) reported significantly higher levels of HOMA-IR in pregnant women with female fetuses compared to women carrying male fetuses. Moreover, they found that

Table II. Oral Glucose tolerance test and insulin resistance panel.

Variables	Women who delivered a boy baby (n=55)	Women who delivered a girl baby (n=58)	P-value
Fasting blood glucose, mg/dl	71.01 (13.1)	68.2 (9.9)	0.207[a]
1-h blood glucose, mg/dl	130.1 (28.6)	129.6 (22.2)	0.931[a]
2-h blood glucose, mg/dl	115.3 (28.3)	117.5 (27.1)	0.671[a]
HbA_{1C}, %	4.3 (1.22)	4.1 (1.03)	0.641[b]
Fasting insulin level, μU/ml	7.31 (3.49-14.6)	7.31 (3.73-14.6)	0.858[b]
HOMA-β	2.1 (1.09-4.03)	2.1 (1.06-4.39)	0.993[b]
HOMA-IR	19.78 (11.73-38.7)	21.7 (10.0-42.1)	0.692[b]

Data were analyzed using the [a]Student's t-test or [b]Mann-Whitney test.

bearing a female fetus was an independent risk factor for maternal IR; this remained valid even following adjustment for maternal age, pre-gestation BMI and gestational age (26). It is worth mentioning that Yamashita *et al* (26) conducted their study in a Japanese population, which is considered a homogenous community descended from a single ethnicity. By contrast, Walsh *et al* (7) found the reverse and reported higher HOMA-I values in women bearing boys in comparison to women pregnant with girls. The exact mechanisms by which the fetal sex affects the maternal IR status remain to be elucidated. However, observational studies have documented that the placenta of women bearing female fetuses secretes estrogen and lactogen to a greater extent than that of women bearing male fetuses (27,28). These hormones are widely accepted to exacerbate IR (29,30). Moreover, it has been reported that placental adipokines, such as leptin are released in higher amounts in women with female fetuses than male fetuses. A positive correlation between maternal leptin and HOMA-IR has been reported among normoglycemic pregnant women regardless of fetal sex (31). It is worth mentioning that fetal leptin levels may reflect the fetal adipose tissue density, which is influenced by sex hormones, such as estradiol and testosterone (32). Perhaps fetal sex chromosomes may indirectly control the gene expression of the placental adipokines and peptides, such as leptin, which may contribute in part to the development of maternal IR. Additionally, Francis *et al* (33), investigated the impact of maternal healthy diet quality during pregnancy on the metabolic profile of the offspring based on offspring sex. They reported that a high maternal healthy eating index was associated with lower HOMA-IR and adiponectin levels in neonatal blood, but only in boys. Low maternal adiponectin levels are linked to maternal IR and tend to be particularly low in the third trimester of pregnancy, when IR peaks (34). Yet, this aspect was not investigated in the present study.

In addition to fetal sex, maternal characteristics, such as pre-gestational BMI and weight gain during pregnancy have previously been examined as potential determinants of maternal IR, with the findings revealing no significant effect (6). Maternal lifestyle factors, including physical activity and smoking, have also been investigated and have been found to have no significant effect (7,8). The present study did not investigate theses variables; this is perhaps a limitation of the present study, as this may have provided better insight and understanding.

The present study evaluated the function of β-cells of the pancreas by calculating the HOMA-β index, which is used to assess the initial β-cell response to blood glucose. It was found that the β-cell function of the pancreas is comparable between pregnant women bearing boys and those bearing girls. This finding are in agreement with those in the study by Yamashita *et al* (26). However, Geng *et al* (6) reported a significantly lower HOMA-β value in pregnant women bearing boys compared to those bearing girls Yet, Geng *et al* (6) also reported a lower insulinogenic index (IGI), which is also used to assess β-cell function, in women with boys compared to women carrying girls. However, this difference was not statistically significant. It has been reported that β-cell function is affected by ethnic variation (35), genetic makeup and certain variants related to inhibitory miRNAs (36). Moreover, certain hormones, such as prolactin and growth hormone have also been documented to affect β-cell functions (37,38). However, there are multiple indices used to assess β-cell functions, such as HOMA-β, insulinogenic index/HOMA-IR, IGI and insulin secretion sensitivity index 2 (39). All these indices depend on the measurement of the insulin level, which has been proven to be affected by the type of anticoagulant tubes used to collect the blood samples (40). These factors and the differences in sample size and ethnicity can explain the discrepancies in the literature regarding the evaluation of β-cell function.

Measuring insulin resistant indices is not a routine test in antenatal care visits; however, fetal sex determination is routinely conducted during the early second trimester. An established association between fetal sex and maternal IR could help clinicians identify pregnant women who are at ab increased risk of developing IR-related diseases, such as preeclampsia and GDM. Such a prioritization can allow for earlier management and intervention strategies aimed at reducing adverse outcomes for both the fetus and the mother.

To the best of our knowledge, the present study was the first to investigate the possible association between fetal sex and maternal IR in Sudan. However, several limitations should be mentioned. Although the sample size was powered, it remains relatively small. Secondly, the insulin levels and plasma glucose in maternal blood were measured only, without evaluating fetal circulation levels. Investigating the insulin

resistant indices in fetal circulation could yield further information. Thirdly, a single-point blood sample was used in the second trimester, limiting conclusions about early pregnancy or the late trimester effect. Fourthly, the present study did not measure the pre-gestational BMI, weight gained during pregnancy period and lifestyle factors, which may have provided further insight in this regard.

In conclusion, the present study investigated the impact of fetal sex on IR among normoglycemic pregnant women of North African ethnicity. The present study did not find any differences in IR indices or pancreatic β-cell function between pregnant women bearing boys and those bearing girls. Therefore, further studies with a longitudinal design and larger sample size, using gold standard tests, expanding the scope to include placental proteiomics analysis and considering fetal insulin indices are required.

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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

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

Ethics approval and consent to participate

The study protocol and procedures were approved by the Research Board at the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Khartoum, Khartoum, Sudan and the ethical clearance was issued under number (#2020, 08). The study objectives were briefly explained to the participants, and consent was obtained through signing.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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