Original Article

High Insulin Resistance in Saudi Women with Unexplained Recurrent Pregnancy Loss: A Case–control Study

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Abstract

Background: Unexplained recurrent pregnancy loss (RPL) accounts for >50% of the patients with RPL. Insulin resistance (IR) is a potential cause of unexplained RPL.

Objectives: To evaluate the relationship between insulin resistance (IR) and unexplained RPL among Saudi women.

Methods: This is a single-center, case–control study conducted at a tertiary hospital in the Eastern Province of Saudi Arabia. The study group comprised Saudi women with unexplained RPL, while the control group had Saudi women with at least one live birth and no RPL. Blood samples were taken to determine the fasting glucose (FG) and fasting insulin (FI) levels. Women with diabetes mellitus and polycystic ovarian syndrome were excluded. A homeostatic model assessment of insulin resistance index (HOMA-IR) value ≥3 was considered as IR.

Results: The study and control groups comprised 43 and 56 women, respectively. Between the groups, there was a significant difference in the mean age (case: 37.9 ± 5.4 years; control: 32.2 ± 5.9 years; $P < 0.0001$) and the mean BMI (case: 31.5 ± 6.0; control: 26.1 ± 2.8; $P < 0.0001$). FG level was slightly higher in the control group (90.9 mg/dL vs 88.7 mg/dL; $P = 0.068$). FI level was significantly higher in the study group (16.33 μU/mL vs. 6.17 μU/mL; $P < 0.0001$). HOMA-IR of ≥3 was significantly more common in the study group ($n = 22$; 51.2%) than the control group (4; 7.1%) ($P < 0.0001$). After adjusting for age and BMI, IR ≥3 was found to be independently associated with unexplained RPL (aOR: 13.2; 95% CI: 3.77–46.36).

Conclusions: This study showed that Saudi women with unexplained RPL had significantly higher levels of fasting insulin and insulin resistance than those without a history of RPL. Therefore, it is recommended to assess IR in women with RPL.

Keywords: Fasting glucose, fasting insulin, homeostatic model assessment of insulin resistance, insulin resistance, polycystic ovarian syndrome, recurrent pregnancy loss, unexplained

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INTRODUCTION

The definition of recurrent pregnancy loss (RPL) remains debatable: the Royal College of Obstetricians and Gynaecologists (RCOG) defines RPL as three or more consecutive pregnancy losses in the first trimester,[1] whereas The American Society for Reproductive Medicine (ASRM) Practice Committee defines RPL as two or more pregnancy losses confirmed by ultrasound or histology, not necessarily consecutive.[2] After a significant debate, the European Society of Human Reproduction

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and Embryology (ESHRE) stated that "RPL could be considered after the loss of two or more pregnancies and stresses the importance of the need for further scientific research, including epidemiological studies on the effect of various RPL definitions on diagnosis, prognosis and treatment."[3]

The prevalence of RPL has been reported to range from 1%–5% among women in the reproductive age.[4] About >50% of those with RPL are diagnosed as unexplained RPL after thorough investigations.[2] Among Saudi women, the prevalence of unexplained RPL has been reported to be 39%.[5] Expectedly, unexplained RPL leads to further stress and anxiety, which may further contribute to pregnancy loss in the future. The associated risk factors of RPL are uterine anomalies, parental abnormal karyotype, endocrine, immunological, thrombophilia, and environmental factors. In terms of endocrine factors, thyroid dysfunction, hyperprolactinemia, and polycystic ovarian syndrome (PCOS) have been associated with higher rates of miscarriage. PCOS has been estimated to affect around 5%–12% of the general population, when the Rotterdam criteria are applied.[6]

Most women with PCOS are also hyper-insulinemic and insulin resistant, independent of obesity, compared with women without PCOS, with a prevalence ranging between 40% and 70%.[7] Several studies have demonstrated that insulin resistance (IR) is a potential cause of pregnancy loss.[8] Furthermore, a meta-analysis of 13 studies (five randomized) concluded that insulin-sensitizing agents such as metformin significantly reduced the possibility of miscarriage for women with PCOS.[9]

A recent systematic review reported that RPL is associated with a higher degree of IR and highlighted the importance of screening and treatment of IR. Nevertheless, none of the included studies were from Saudi Arabia.[10] The aim of the current study was to evaluate the relation between IR and unexplained RPL in Saudi women.

METHODS

This manuscript was prepared following the STROBE guidelines. The study was conducted after obtaining ethical approval from the Institutional Review Board.

Study design, setting, and participants

This is a single-center, observational prospective case–control study conducted at the Department of Obstetrics and Gynecology, King Fahd Hospital of the University (KFHU), Al Khobar, Saudi Arabia, between January 01, 2015, and December 31, 2019. KFHU is one of the largest public tertiary hospitals in the Eastern Province of Saudi Arabia and serves a representative population within this region.

During the study period, a total of 75 non-pregnant Saudi women aged 18–48 years with two or more consecutive pregnancy losses before the 20th week of gestation were referred to a RPL clinic and underwent a full assessment including: hysterosalpingography, karyotype of both partners, serum TSH, prolactin, antibodies for antiphospholipid syndrome, as well as protein S, C, and antithrombin III deficiency. Normal results were found in 50 of the 75 women (66%), and thus they were diagnosed as having an unexplained RPL. Participants in the control group were recruited from consecutive patients in the routine antenatal care clinics, who were aged 18–48 years, had at least one live birth and had ≤1 pregnancy loss before the 20th week of gestation. The exact age and BMI matching was not done to report differences in these variables in the source population.

In both groups, patients with diabetes mellitus or PCOS were excluded. PCOS was diagnosed according to the revised Rotterdam criteria, i.e., the presence of two or more of the following: (1) oligo and/or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, (3) polycystic ovaries on ultrasound (presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume >10 mL, with the exclusion of other etiologies such as congenital adrenal hyperplasia, androgen-secreting tumors, or Cushing's syndrome).[6]

All patients were informed that participation was voluntary and were assured of data confidentiality and anonymity. All participants provided written informed consent before inclusion in the study.

Measurements and outcomes

Under aseptic conditions, venous blood was obtained after a period of 12-h fasting in both groups to test for fasting glucose (FG) and fasting insulin (FI). The blood was analyzed using the glucose oxide method and electrochemiluminescence method for insulin levels. Homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated using the formula: fasting blood sugar (mg/dL) × fasting blood insulin (μU/mL)/405.[11] HOMA-IR score ≥3 was considered as high insulin resistance (IR).

The primary outcome measure was comparing the FG and FI levels, and the secondary outcome measure was comparing the HOMA-IR in both groups.

Statistical analysis

The statistical analysis was performed using SPSS version 23. Age, BMI, FG, and FI levels in both groups were compared using the independent sample *t*-test; Chi-square test was used to determine the significance between groups. A logistic regression analysis was performed for age, BMI, and IR index. $P \leq 0.05$ was considered statistically significant.

RESULTS

In the study group, a total of 43 women met the inclusion criteria and consented for participation. In the control group, 56 women were included. Between the two groups, there was a significant difference in the mean age (case: 37.9 ± 5.4 years; control: 32.2 ± 5.9 years; $P < 0.0001$) and the mean BMI (case: 31.5 ± 6.0; control: 26.1 ± 2.8; $P < 0.0001$).

The mean FG level was non-significantly lower in the study group compared with the control group (88.7 ± 4.2 mg/dL vs. 90.9 ± 2.8 mg/dL, $P = 0.068$). The mean FI level was higher in the study group compared with the control group (16.33 ± 3.7 μU/mL vs. 6.2 ± 0.6 μU/mL; $P < 0.0001$). The mean HOMA-IR in the study group was significantly higher than that in the control group (3.2 ± 0.89 vs. 1.58 ± 0.59; $P < 0.0001$) [Table 1]. A HOMA-IR ≥3 was found in 22 (51.2%) women in the study group and in 4 (7.1%) women in the control group, which was statistically significant ($P < 0.0001$) [Table 2].

To adjust for confounders, a logistic regression analysis was performed and showed a significantly higher IR in the study group compared with the control group, and that IR ≥3 was independently associated with unexplained RPL ($P < 0.0001$; aOR: 13.2; 95% CI: 3.77–46.36) [Table 3].

Table 1: Comparison of variables between the two groups

Parameter	Mean±SD		*P*
	Study group (*n*=43)	Control group (*n*=56)	
Age (years)	37.9±5.4	32.2±5.9	<0.0001*
Weight (kg)	69.2±9.6	65.3±10.6	0.062
Height (cm)	157.4±2.0	157.4±3.5	1
BMI (kg/m^2)	31.5±6.0	26.1±2.8	<0.0001*
Fasting glucose (mg/dL)	88.7±4.2	90.0±2.8	0.068
Fasting insulin (μU/mL)	16.3±3.7	6.2±0.6	<0.0001*
HOMA-IR	3.2±0.89	1.58±0.59	<0.0001*

*Statistically significant difference ($P<0.05$). BMI – Body mass index; HOMA-IR – Homeostatic model assessment of insulin resistance index; SD – Standard deviation

Table 2: Comparison of insulin resistance according to the homeostatic model assessment of insulin resistance index

HOMA-IR	Study group, *n* (%)	Control group, *n* (%)	*P*
<3	21 (48.8)	52 (92.9)	<0.0001*
≥3	22 (51.2)	4 (7.1)	

*Statistically significant difference ($P<0.05$). 95%. HOMA-IR – Homeostatic model assessment of insulin resistance index

Table 3: Logistic regression analysis between groups comparing age, body mass index, insulin resistance ≥3

Variable	OR	*P*	95% CI	
			Lower	Upper
IR ≥3	13.229	0.0001*	3.775	46.362
Age	1.123	0.003*	1.042	1.210
BMI	1.010	0.842	0.917	1.112

*Statistically significant difference ($P<0.05$). CI – Confidence interval; OR – Odds ratio; BMI – Body mass index; IR – Insulin resistance

DISCUSSION

This study found that women with unexplained RPL had significantly higher IR compared with those in the control group, and that IR was an independent predictor of unexplained RPL. This is in concordance with a recent meta-analysis where it was found that HOMA-IR was significantly higher among patients with a history of RPL.[12]

IR, defined as a decreased sensitivity or responsiveness to the metabolic action of insulin, is clinically assessed through tests such as FG/FI ratio and HOMA-IR.[7] However, there is no consensus on the cut-off value to define IR using HOMA-IR; some studies use a cut-off value of >2.5, while others of >2.69.[7,13] Another study defined IR if HOMA-IR was ≥3.15.[14]

The mechanism by which IR may lead to miscarriage is thought to be related to plasminogen activator (PA) inhibitor activity. PA inhibitor leads to a hypercoagulable state (impaired fibrinolysis) and increased inflammatory cytokine levels at the maternal-fetal interface, resulting in placental insufficiency and risk of miscarriage.[15] It has been reported in the Nimes Obstetricians and Haematologists (NOHA) study that PA inhibitor was found to be high in women with unexplained RPL.[16] Furthermore, PA inhibitor increases with increased insulin levels, and is found to decrease when insulin-sensitizing agents are used to reduce IR.[15]

The other hypothesis of the association of IR and RPL is that IR leads to an uncontrolled diabetes-like state in the fetal environment, where high levels of insulin increase the transport of glucose by the cytotrophoblasts in the first trimester by upregulation of the glucose transporter system.[17] Moreover, IR plays a critical role in the ovarian androgen excess, which may promote miscarriage. In addition, hyperinsulinemia decreases the expression of glycodelin and insulin-like growth factor-binding protein

1 (IGFBP1) at the implantation site.[18] Both glycodelin and IGFBP1 are essential in the early phases of pregnancy. Glycodelin inhibits the endometrial response toward the embryo, while IGFBP1 facilitates the adhesion process of the blastocyst at the feto-maternal interface.[19] Furthermore, hyperinsulinemia and IR have been associated with high levels of homocysteine, which may impair pregnancy by interfering with endometrial blood flow and the integrity of the vessels. Hyperhomocysteinemia also increases oxidative stress in the vascular endothelium and activates platelets, leading to a higher chance of early pregnancy loss.[20-22]

Studies have reported that insulin-sensitizing agents such as metformin lower the rate of miscarriage in women with PCOS.[23] Metformin has been found to reduce the level of PA inhibitor by decreasing the insulin level and alleviating IR.[24] This eventually improves uterine vascularity. In a very recent meta-analysis, Yuan *et al.* reported a reduction in endometrial artery resistance (RI) in patients with PCOS receiving metformin compared with those who did not, eventually improving the clinical pregnancy rate and reducing the miscarriage rate.[25]

In the present study, the control group was selected consecutively to the study group from the antenatal clinic. Age and BMI were not matched at enrollment to report the differences in the population. The patients in the study group were significantly older and had a higher BMI than those in the control group, which was not the case in other studies.[26,27] While these baseline differences between the two groups could itself be a contributing factor to higher insulin level and IR, the logistic regression analysis, which included both these factors as confounders, found IR to be an independent predictor of unexplained RPL. Notably, the mean FG was marginally higher in the control group than the study group. These findings are in contrast to those of other studies where the mean FG in the study group was higher.[26,27] In the current study, the mean FI was significantly higher in the study group than the control group, which is similar to the findings of previous studies.[26-29]

The mean HOMA-IR in the study was significantly higher in the study group compared with the control group (3.2 ± 0.89 vs. 1.58 ± 0.5; $P < 0.0001$). These findings are very similar to the findings by Wani *et al.* (3.4 ± 1.51 vs. 1.5 ± 1.27).[26] Ispasoiu *et al.* reported that the mean HOMA- IR was 2.98 in the study group and 1.69 in the control group.[8] When using HOMA-IR of ≥3 as an indication of IR, we found 51% and 7% of women in the study and control groups, respectively, had IR [Table 2]. When HOMA-IR ≥2 was used as a cut-off for IR, 83.7% and 17.9% of the women in the study and control groups, respectively, had IR ($P < 0.0001$). Similar results were found by Ispasoiu *et al.* and Michael Diejomaoh *et al.*[8,30]

Strengths and limitations

To the best of the authors' knowledge, this is the first study that assessed the association between unexplained RPL and IR in Saudi women. In addition, all women were assessed and investigated in the same hospital and managed by the same physician, thereby limiting heterogeneity in the source population and in interpreting laboratory results or in diagnosing the etiology of RPL.

The study has a few limitations, including a small sample size, which could also have contributed to the difference in age and BMI across the two groups, and that it was conducted at a single tertiary hospital, which may limit its generalizability. Therefore, large-scale, multi-center studies are needed to support the findings of this study.

CONCLUSION

The current study showed that Saudi women with unexplained RPL had significantly higher levels of fasting insulin and insulin resistance than those without a history of RPL. While a larger multi-center study is required to confirm this association, the findings of the current study can help in the counseling and treatment of women in whom an underlying cause of their pregnancy loss has not been reached. Further studies addressing the effect of insulin sensitizers on the pregnancy outcome in unexplained RPL patients in Saudi Arabia should also be conducted.

Ethical considerations

The study was approved by the Institutional Review Board of Imam Abdulrahman Bin Faisal University (Ref. no.: IRB-2014-01-160; date: January 26, 2014). All study participants provided written consent before inclusion in the study. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: A.A.A.; Methodology: A.A.A. and A.S.A.; Data analysis: A.A.A. and A.S.A.; Writing–original

draft preparation: A.S.A.; Writing – review and editing: A.A.A.

Both the authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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