Recurrent Pregnancy Loss: A Cross-Sectional Study Exploring Risk Factors in Babylon, Iraq

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Abstract

Background: Recurrent pregnancy loss (RPL), affecting 2%–4% of couples, is a common challenge in obstetrics. **Objectives:** This study investigated risk factors for RPL in Iraqi women, acknowledging the variations in how different organizations define RPL. **Materials and Methods:** The researchers conducted a case–control study involving 80 women: 40 with confirmed RPL and 40 healthy controls. The cases were recruited from those who attended the outpatient clinics and the emergency department of Babylon Maternity and Pediatric Teaching Hospital. The study compared characteristics between the groups, including anthropometric data (body measurements), medical and obstetric history, blood tests (fasting glucose and insulin and insulin resistance), and ultrasound examinations. **Results:** While there was no significant age difference between the RPL and control groups, parity differed greatly. Nearly all controls had prior live births, whereas most RPL cases did not. Interestingly, the study found that women with RPL had a higher body mass index compared to the control group, suggesting a link between obesity and RPL. This association was further strengthened by the finding of higher fasting insulin levels and a greater prevalence of moderate-to-severe insulin resistance in the RPL group. However, there was no statistically significant connection between blood sugar levels and RPL. **Conclusion:** The study's findings support the association between nulliparity, obesity, and insulin resistance with RPL in Iraqi women. The underlying reasons for how insulin resistance might be linked to RPL need further investigation. The researchers emphasize the importance of larger studies to confirm these observations and explore potential preventive strategies. While the study provides valuable insights, the relatively small sample size limits the generalizability of the results, and the case–control design cannot definitively establish cause-and-effect relationships between the identified factors and RPL.

Keywords: HOMA-IR, insulin resistance, parity, recurrent pregnancy loss

Introduction

Recurrent pregnancy loss (RPL), which affects both spontaneously conceived pregnancies and those acquired following assisted reproductive technology therapy, affects 2%–4% of reproductive-age couples[1] and presents a dilemma for specialists.[2] RPL is still defined differently by various associations. The American Society for Reproductive Medicine describes RPL as ≥2 PL confirmed by sonography or histologic assessment, not necessarily repeated, while the Royal College of Gynecologists and Obstetricians describes RPL as ≥3 RPL in the first trimester.[1] Following a substantial discussion, the European Society of Human Reproduction and Embryology declared that "additional scientific research, such as epidemiological surveys on the effect of different RPL definitions on diagnosis, scenario, and treatment, is necessary and underscores the importance of RPL might be considered after the loss of two or more gestations."[3,4]

There is a substantial correlation between unexplained RPL and insulin resistance[5] according to several

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studies. In comparison to women without pregnancy loss, those with idiopathic RPL had significantly higher fasting insulin levels (15.24 vs. 12.83, $P < 0.001$) and the homeostasis model assessment of insulin resistance (HOMA-IR) scores (2.98 vs. 2.69, $P < 0.05$), according to a case–control study.[6] In comparison to controls, RPL patients had substantially greater fasting serum glucose, fasting insulin values, HOMA-IR, and reduced glucose-to-insulin ratios, as stated by a comprehensive meta-analysis and review included 19 studies comprising 4453 women, in addition to aberrant fasting insulin levels, HOMA-IR, and the glucose-to-insulin ratio.[7] All indicated greater incidences of IR in RPL patients. In research including Saudi women, the RPL group's mean HOMA-IR was 4.3, while the control group's was 2.5 ($P < 0.0001$). Only 25% of controls satisfied the IR threshold (HOMA-IR ≥ 3), but 86% of the RPL grouping was achieved.[1]

The findings of several pieces of evidence suggest that monitoring fasting sugar levels, particularly in the milieu of insulin resistance, is crucial in the assessment and management of unexplained RPL.[8]

Hence, multiple high-quality studies have consistently demonstrated that IR is significantly more common in females with unexplained RPL compared to those with normal pregnancy histories. Screening for and treating IR may be an important part of the workup and management of RPL.[5] Additional research is needed to clarify the causal mechanisms, optimize screening and treatment, and elucidate the contribution of IR in the context of other risk factors for RPL.

Addressing these gaps could lead to improved reproductive outcomes for females with IR. The current study investigated insulin resistance as one possible risk factor for idiopathic RPL in a group of Iraqi females living in Babylon.

This study provides valuable insights into potential risk factors associated with RPL in a population of women in Babylon, Iraq. By identifying factors like parity and body mass index (BMI) as areas of concern, this research lays the groundwork for future studies to explore the underlying mechanisms and develop targeted preventive strategies to improve pregnancy outcomes for women at risk of RPL.

Materials and Methods

Design and study setting

This research was intended as a prospective case–control analysis and was conducted at the Sector of Gynecology and Obstetrics, Babil Maternity and Pediatric Teaching Hospital. The study extended from November 2013 to November 2014, following an agreement by the Iraqi Council of Medical Specializations.

Inclusion criteria

The study included two distinct groups. The first comprised patients who had ≥2 successive gestational losses during the first few months of pregnancy (less than 24 weeks). All gestational losses in this group were confirmed through sonography or post-uterine curettage histologic inspection. The second group comprised females with no history of RPL and no less than one live birth.

Exclusion criteria

Participants were omitted if they had a diagnosis of congenital adrenal hyperplasia, androgen-secreting cancers, Cushing syndrome, diabetes mellitus, or if they were currently pregnant. Additionally, females with polycystic ovarian syndrome (PCOS) were excluded based on the revised Rotterdam criteria.

Patients' collection

Initially, 100 women were considered for the study. However, 20 females with RPL were excluded, as confirmed by the presence of positive antiphospholipid antibodies, PCOS, or anatomical abnormalities. This left 80 women, divided into two equal groups: 40 women in the cases, aged 19–39 years, and 40 women in the control subjects, aged 18–41 years. Every individual involved was referred to the Babylon Maternity and Pediatric Teaching Hospital's outpatient clinics and emergency department.

Data collection

A comprehensive methodology was employed for both groups, beginning with the collection of a detailed history and a full physical examination. Written prearranged consent was obtained from all applicants after a detailed description of the objectives of the involved research and laboratory tests. The detailed history collected included information on age, gravidity, parity, past clinical, family, and obstetric history (including gestational age, type of miscarriage, and methods of pregnancy termination), menstrual history, and any history of congenital abnormalities.

Anthropometric measurements like height, weight, and the calculated BMI were also recorded. Blood investigations performed included the blood group and Rh factor, complete blood picture, thyroid function tests (thyroid stimulation hormone and free thyroxine if clinically indicated), screening for genetic thrombophilic mutations via proteins C and S, serum prolactin levels, and screening for antiphospholipid syndrome using anticardiolipin antibodies (IgM and IgG). These investigations were performed to fulfill the selection criteria.

For both the case and control groups, fasting serum insulin and glucose measures were taken to estimate the HOMA-IR with the subsequent formula:

$$\text{HOMA-IR} = \frac{\text{FG}(\text{mg/dL}) \times \text{FI}(\text{mIU/mL})}{405}.$$

HOMA-IR values were categorized as follows: normal: <3, moderate: 3–5, and severe: >5.

To measure fasting glucose and insulin, 5 mL of venous blood was drawn from both groups after an 8-h fast. One milliliter was used for serum fasting glucose measurement by using a spectrophotometer, with normal levels defined as 74–100 mg/dL (4.1–5.6 mmol/L) and high values as >100 mg/dL (>5.6 mmol/L). On two separate occasions, a fasting blood glucose above 126 mg/dL (7 mmol/L) might indicate diabetes.

Two milliliters of serum was used for fasting insulin measurement via immunoassay using the TOSHO, AIA 360 device, with normal fasting insulin levels defined as 2–25 mIU/mL.

Ultrasound examinations, either transvaginal or transabdominal, were performed for all participants in the case group. These examinations, conducted using a Philips HD 11 XE apparatus with a 5–9 MHz endovaginal probe and a 3–5 MHz abdominal probe, aimed to exclude pregnancy and detect congenital uterine abnormalities using three-dimensional ultrasound.

Statistical analysis

Statistical Package for the Social Sciences version 20 was implemented for the statistical analysis (SPSS, IBM Company, Chicago, IL 60606, USA). The means ± SD were presented to represent continuous data, whereas frequencies and percentages were presented to describe categorical study variables. Pearson's Correlation Coefficient was utilized when evaluating correlations between continuous parameters, while for the categorical parameters, Pearson's (χ^2) chi-square test was utilized. Statistical significance was expressed as a *P* value of <0.05.

Results

In Figure 1, the overall mean age of cases and control was (28.54 ± 6.65) years, and 50.0% of cases were aged between 20 and 30 years, while 40% of the control group were aged between 20 and 30 years. There is no statistical alteration in age ranges between cases and controls), *P* > 0.05.

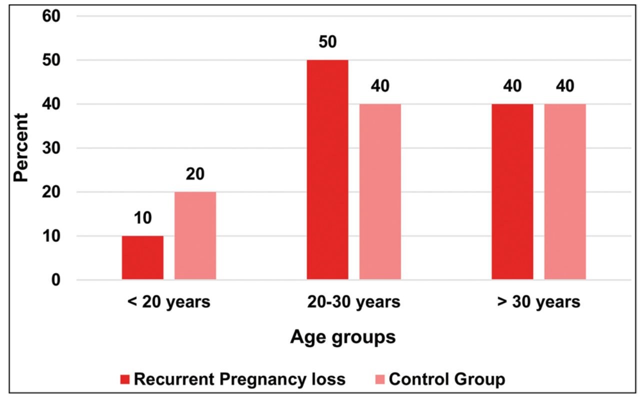

Figure 1: Distribution of females with recurrent pregnancy loss and healthy group by age

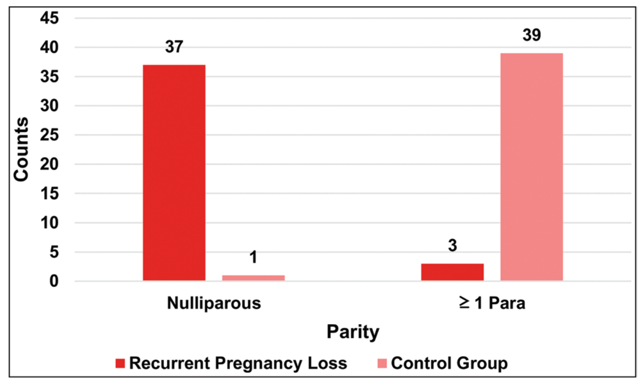

Figure 2: Distribution of females with recurrent pregnancy loss and control group by parity

As shown in Figure 2, 92.5% of cases of RPL were nulliparous; meanwhile, all control groups were parous women. There is a statistical difference in parity between case and control groups (<0.001).

The data presented in Table 1 provide insights into the characteristics and management of RPL in the patient population, indicating common patterns and methods of handling such cases. The majority of patients with RPL have experienced two or three abortions, with over half (52.5%) having had two abortions and 37.5% having had three abortions. A smaller percentage (10.0%) have had four or more abortions. The most common type of abortion among these patients is incomplete abortion (50.0%), followed by complete abortion (32.5%) and missed abortion (17.5%). Most abortions occur in the 1st trimester (80.0%), with a smaller percentage occurring in the second trimester (20.0%). The methods of pregnancy termination are almost evenly distributed, with a slight preference for medical termination (51.8%) over surgical termination (48.2%).

Table 2 revealed a significant variation between patients with RPL and the control group regarding parity and BMI; patients with RPL are 14 times more expected to be nullipara; meanwhile, patients with RPL are eight times more likely to be obese, *P* ≤ 0.05.

Table 2 compares the demographic features of patients with RPL and the control subjects. The age distribution between the two groups was not significantly different (*P* = 0.411), indicating that age was not a distinctive factor in this study. There were highly substantial differences in parity between the study groups (*P* < 0.001). Patients with RPL are much more expected to be nulliparous than the control people. There is a significant variation in BMI between the groups ($P = 0.007$). Patients with RPL are more possible to have a higher BMI, particularly in the >30 kg/m² category, which shows a strong association (OR = 8.94). These findings suggest that parity and BMI are important demographic factors associated with RPL in this study, whereas age does not appear to be a distinguishing factor [Table 3].

Table 4 presents the correlation of fasting insulin with fasting glucose among patients with RPL and a control group. Both groups show weak correlations between fasting insulin and fasting glucose, as indicated by the low R-square values. The RPL group has a positive correlation, while the control group has a negative correlation, but neither is statistically significant. The *P* value for the two groups are greater than 0.05, suggesting that the detected correlations could be due to chance and are not statistically significant. The data indicate no strong correlation between circulatory fasting insulin and glucose in either the RPL or control participants.

Table 5 presents the correlation of HOMA-IR with BMI among RPL patients and the control group. In the RPL group, there are moderate and significant correlations of HOMA-IR with the BMI. This indicates that higher insulin resistance is linked with higher BMI among cases with RPL. In the control group, the correlation between HOMA-IR and BMI is weak and not statistically significant, suggesting a less clear relationship in this population.

Table 1: Distribution of patients with recurrent pregnancy loss by number, type, time, and methods of termination of pregnancy

Variable	Frequency (%)
No. of abortion	
Two abortions	21 (52.5)
Three abortions	15 (37.5)
≥4 abortions	4 (10.0)
Type of abortion	
Complete	13 (32.5)
Incomplete	20 (50.0)
Missed	7 (17.5)
Time of abortion	
First trimester	24 (80.0)
Second trimester	16 (20.0)
Termination of pregnancy	
Medical termination	14 (51.8)
Surgical termination	13 (48.2)

Discussion

This study in Babylon, Iraq, explored risk factors for RPL. The main outcomes were that females with RPL had high measures of fasting blood insulin and a prevalence of moderate-to-severe IR compared to the healthy control. The findings also highlight the importance of parity and BMI as factors influencing pregnancy outcomes. Additionally, the study exposed a higher prevalence of obesity among females with RPL.

While multiple studies have found a robust association between insulin resistance and RPL, the underlying mechanisms by which IR may contribute to pregnancy loss are not fully elucidated. Specifically, more research is needed to clarify several interrelated factors: first, the precise pathways by which IR impairs implantation, placentation, and fetal development, leading to miscarriage.[9] Furthermore, IR is closely related to

Table 2: Comparison of females with recurrent pregnancy loss (RPL) and the control by demographic characteristics

Variable	Study groups		χ^2	*P* value	OR (95% CI)
	Patients with RPL (%)	Control group (%)			
Age					
Mean ± SD	27.72 ± 6.00	29.35 ± 7.22			
Range	19–39	18–41			
<20 years**	4 (10.0)	8 (20.0)			
20–30 years	20 (50.0)	16 (40.0)	1.778	0.411	0.40 (8.10–1.57)
>30 years	16 (40.0)	16 (40.0)	0.961	0.327	0.50 (0.12–1.99)
Parity					
Nulliparous	37 (92.5)	0 (0.0)	**35.208**	**<0.001***	**14.33 (4.81–42.69)**
≥1 para	3 (7.5)	40 (100.0)			
BMI, kg/m²					
Mean ± SD	28.45 ± 2.96	26.33 ± 1.97			
18.5–24.9**	4 (10.0)	11 (27.5)			
25–29.9	23 (57.5)	25 (62.5)	2.030	0.154	2.53 (0.71–9.07)
>30	13 (32.5)	4 (10.0)	**7.183**	**0.007***	8.94 (1.80–44.34)

BMI: body mass index, SD: standard deviation.

*P value ≤ 0.05 is significant.

**Reference group use for comparison of other groups

Table 3: Comparison of recurrent pregnancy loss (RPL) and control by fasting insulin, fasting glucose, and homeostasis model assessment of insulin resistance (HOMA-IR)

Variable	Study groups		$\chi 2$	*P* value	OR (95% CI)
	Patients with RPL (%)	Control group (%)			
Fasting blood insulin					
Mean ± SD	20.92 ± 8.21	6.37 ± 0.86			
2–25 mIU/L	11 (27.5)%	40 (100.0)%	**4.636**	**<0.001***	**4.64 (2.75–7.82)**
> 25 mIU/L	29 (72.5)%	0 (0.0)%			
HOMA-IR					
Mean ± SD	5.28 ± 2.37	1.96 ± 0.50			
Normal <3**	6 (15.0)%	37 (92.5)%			
Moderate 3–5	15 (37.5)%	3 (7.5)%	0.203	0.899	0.72 (0.13–1.11)
Severe >5	19 (47.5)%	0(0.0)%	**19.800**	**<0.001***	**30.83 (6.81–139.60)**
Fasting glucose					
Mean ± SD	102.34 ± 12.66	88.49 ± 13.91	2.051	0.152	0.50 (0.19–1.30)
74–100 mg/dL	24 (60.0)%	30 (75.0)%			
>100 mg/dL	16 (40.0)%	10 (25.0)%			

*P value ≤0.05 is significant.

**Reference group use for comparison of other groups

Table 4: Correlation of fasting insulin with fasting glucose among females with recurrent pregnancy loss (RPL) and the control groups

Groups	R^2	*T*	*F*	Sig.
RPL	0.042	1.721	2.960	0.090
Control	0.072	−1.382	3.357	0.074

Table 5: Correlation of insulin resistance (HOMA-IR) with body mass index among females with recurrent pregnancy loss and the controls

Groups	R-square	*t*	*f*	Sig.
Patients	0.236	2.007	4.026	0.049
Control	0.054	1.964	3.858	0.054

gestational diabetes, spontaneous miscarriage, and several other adverse gestations, and when not corrected in time, may increase the potential of expected metabolic disorders and obesity in the offspring in the long term;[10] second, the relative contributions of impaired endometrial receptivity, elevated homocysteine levels, increased oxidative stress, and other potential mechanisms in IR-related RPL;[7] third, whether the association between IR and RPL is independent of other factors like obesity, PCOS, and thyroid dysfunction or if there are interactions between these conditions also requires more investigation.[9,11] Finally, whether there are differences in the IR-RPL relationship based on ethnicity, age, chromosomal, or other demographic factors that could inform targeted screening and prevention efforts.[5,9] ABO blood groups may also contribute to some predisposition for RPL.[12-15]

In summary, while the link between insulin resistance and unexplained RPL is well-established, additional research is needed to clarify the underlying mechanisms, optimize screening and treatment, and clarify the role of IR in the context of other risk factors for RPL. Addressing these gaps could lead to improved reproductive outcomes for females with IR.

The results of the present study, which exposed an intriguing interaction among BMI, RPL, and IR, are supported by several pieces of data. BMI also appeared as a potential risk factor. Obesity (BMI > 30 kg/m^2) was substantially higher prevalent among RPL cases in comparison to the control subjects. These findings were also supported by recent research, signifying a complex interaction between metabolic and hormonal factors. These could include altered endocrinal levels of hormones like adiponectin, leptin, and insulin.[16]

Similarly, the RPL group exhibited BMI means greater than those of the control subjects in a preceding trial, though the alteration was not statistically significant.[17] Another recent study reported that the average BMI level in the RPL participants was 31.5 ± 6.0 kg/m^2, while in the control group, it was 26.1 ± 2.8 kg/m^2, with a significant statistical difference.[1]

Prior research, however, revealed that although the groups' BMIs were equal, the RPL group exhibited a greater prevalence of IR than the control group.[17] Another current study reported that after adjusting for age and BMI, IR ≥ 3 was shown to be independently linked with unexplained RPL.[1]

On the other hand, multiple studies have consistently shown that females with RPL have significantly higher fasting serum insulin levels and rates of insulin resistance than controls.[17-19] A systematic review and meta-analysis concluded that RPL patients had significantly higher fasting serum insulin, fasting glucose, HOMA-IR, and lower glucose-to-insulin ratios compared to controls.[7] The mechanisms by which IR may contribute to RPL include impaired endometrial receptivity, elevated homocysteine levels impairing blood flow, and increased oxidative stress.[20] Our outcomes are consistent with evidence linking IR and obesity to RPL risk. This might indicate compensated insulin resistance, where the body maintains blood sugar levels despite reduced insulin sensitivity. It was found that metformin treatment, which improves insulin sensitivity, has been shown to diminish the risk of miscarriage in females with RPL.[1,17] Insulin resistance is a significant risk factor for RPL, and addressing IR through lifestyle changes and insulin-sensitizing medications like metformin may improve reproductive outcomes. The current study exposed a higher prevalence of obesity among females with RPL. Obesity is thought to be linked to RPL through various mechanisms,[21] including hormonal imbalances and altered endometrial receptivity to implantation.[19,22,23] Understanding the specific pathways by which obesity influences pregnancy outcomes can inform the development of weight management strategies for women at risk of RPL.

Statistical analysis revealed no significant alteration in age between the case and control females. However, a striking disparity emerged in parity. Nearly all the control participants had delivered no less than one live birth, while the vast majority of women with RPL were nulliparous (had never given birth). This finding aligns with those of previous studies highlighting the strong association between a history of successful pregnancy and a lower risk of RPL.[24-26]

Females with RPL are 14 times more possibly to be nullipara in the current study, highlighting the importance of parity as a factor influencing pregnancy outcomes. This finding aligns with those of past research, suggesting a protective effect of prior successful pregnancies. The parity is an important issue in understanding the context of RPL as it can help identify the number of successful pregnancies and the number of abortions or stillbirths. A similar recent study found that women with RPL had a significant decreased parity compared to controls ($P < 0.001$).[27] These findings have supported those of a preceded study comparing women with RPL to those without RPL on various factors, including parity. Females with RPL were found to have fewer births compared to the healthy controls, which is in part associated with ovarian reserve.[15]

However, Chinè *et al*.[27] found that females with RPL had fewer births compared to controls and that the pregnancy losses increased with the frequency of previous pregnancy losses, but there was a nonsignificant difference in parity between low-order and high-order RPL groups. This suggests that underlying physiological mechanisms associated with a successful pregnancy may also contribute to a lower risk of miscarriage in subsequent pregnancies.[23] Additional research is needed to explore these mechanisms and recognize potential interventions for women with a history of RPL.

This study has a few limitations that have to be considered. The study sample size was rather small, possibly restricting the generalizability of the conclusions. Moreover, the study design might not allow for exploring causal relationships between identified risk factors and RPL. Future studies with larger, more varied populations and longitudinal strategies are required to confirm these findings and establish causality.

Conclusion

In Iraqi women, this study identified key risk factors for RPL. Never having given birth (nulliparity) and obesity were considerably more prevalent among females with RPL, suggesting a protective effect of prior successful pregnancies and a potential link between excess weight and miscarriage risk.

Females with RPL showed 30-fold higher frequency of moderate-to-severe insulin resistance based on HOMA-IR analysis. This, along with a four-fold increase in the odds of having elevated fasting insulin measures compared to control subjects. This suggests a potential role for insulin resistance in RPL, even if the initial glycemic analysis and insulin levels did not show a definitive association, and further data revealed a crucial finding. These conclusions highlight the need for further exploration of insulin sensitivity and its potential contribution to RPL and can pave the way for future studies to develop targeted preventive strategies for women at risk of RPL.

Ethical policy and Institutional Review Board statement

Not applicable.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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