

Evaluation of the relationship between insulin resistance and recurrent pregnancy loss

Ocena związku pomiędzy insulinoodpornością a nawracającymi utratami ciąży

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Abstract

Objective: To investigate insulin resistance in patients with recurrent pregnancy loss (RPL).

Design: Single center, case-control, prospective study.

Methods: The study was performed at the Obstetrics and Gynecology Clinic at the Dicle University Medical Faculty, from May to October 2009. 64 study subjects who had RPL were compared to 64 controls. Both groups were compared with fasting glucose, fasting insulin, fasting glucose/fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) index values to assess insulin resistance.

Results: No significant differences in age and BMI index were found between the study and control subjects ($p > 0.005$). The mean number of abortions was 3.04 in the study and 0.2 in the control group ($p < 0.001$). The mean fasting glucose value was 100.84 in the study group, and 89.67 in the control group ($p < 0.001$). Also, the mean fasting insulin value was 15.51 in the study group and 7.17 in the control group ($p = 0.001$). The mean glucose/insulin ratio was 12.24 in the study group and 28.27 in the control group ($p = 0.017$), and the mean HOMA-IR value was 4.16 in the study group and 1.62 in the control group ($p = 0.002$).

Conclusion: Compared with the control group, patients with RPL were more likely to have insulin resistance.

Key words: **recurrent / miscarriage / etiology / insulin resistance /**

Streszczenie

Cel: Ocena insulinoodporności u pacjentek z nawracającymi utratami ciąży.

Materiał i metody: Prospektywne, jednośrodkowe badanie z grupą kontrolną, które przeprowadzono w Klinice Położniczo-Ginekologicznej Wydziału Medycznego Uniwersytetu Dicle, od maja do października 2009. Porównano 64 pacjentki z nawracającymi utratami ciąży z grupą kontrolną (64 kobiety). W obu grupach oznaczono glukozę na czczo, insulinę na czczo, glukoza na czczo/insulina na czczo oraz wskaźnik HOMA-IR celem oceny insulinoodporności.

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Wyniki: Nie znaleziono istotnych różnic w wieku i indeksie BMI pomiędzy grupą badaną a grupą kontrolną ($p>0,005$). Średnia liczba poronień w grupie badanej wynosiła 3,04 a w grupie kontrolnej 0,2 ($p<0,001$). Średnie stężenie glukozy na czczo wynosiło 100,84 w grupie badanej i 89,67 w grupie kontrolnej ($p<0,001$). Średnie stężenie insuliny na czczo wynosiło 15,51 w grupie badanej i 7,17 w kontrolnej ($p=0,001$). Średni wskaźnik glukoza/insulina wynosił 12,24 w grupie badanej i 28,27 w kontrolnej ($p=0,017$) a wartość wskaźnika HOMA-IR 4,16 w grupie badanej i 1,62 w kontrolnej ($p=0,002$).

Wnioski: Pacjentki z nawracającymi utratami ciąży mają większe prawdopodobieństwo wystąpienia insulinooporności.

Słowa kluczowe: **poronienie / etiologia / insulinooporność /**

Introduction

The risk of spontaneous abortion in pregnant women has been reported to be 15% and is often due to chromosomal abnormalities. Recurrent pregnancy loss (RPL) is a determination made when a woman had three and more consecutive miscarriages. The incidence of RPL by chance alone would be approximately 0.35%. However, epidemiological studies have revealed that 1–2% of women experience RPL. A number of conditions including parental chromosomal abnormalities, antiphospholipid antibody syndrome, uterine abnormalities, cervical incompetence, thrombophilic defects, and a variety of endocrine factors have been found to be associated with RPL [1]. Unfortunately, in approximately 40–50% of RPL patients, no causes for their losses can be identified [2].

However, polycystic ovary syndrome (PCOS) has been found to be associated with RPL. Forty percent of PCOS patients have insulin resistance (IR) [3]. This raises the question of whether there exists an association between IR and RPL. Thus, in the current study, we aimed at investigating the prevalence of IR in patients with RPL.

Materials and Methods

The study was performed between May 2009 and October 2009 in the Obstetrics and Gynecology Clinic at the Dicle University Medical Faculty.

During the study period, 113 consecutive patients presenting with RPL were screened to establish the etiology of the RPL. Sixty-four patients who had unexplained etiology and at least two consecutive miscarriages were enrolled in the study group. Study subjects were matched for age and body mass index (BMI) with 64 women who were included in the control group. For the etiological sub-study, subjects were screened for chromosome anomalies (with parental karyotype studies), uterine anomalies, antiphospholipid syndrome, and endocrinological disorders (including hypothyroidism, diabetes mellitus, and hyperprolactinemia). Subjects in both groups were neither diabetic nor pregnant. All controls were parous, fertile, and did not have a history of RPL.

Pregnancy was defined as a positive serum b-HCG or ultrasound documentation of a current pregnancy. Pregnancy loss was defined as any natural abortion occurring before 20 weeks gestation or with fetal weight of less than 500g [2].

IR was diagnosed when fasting insulin levels were $\geq 20\mu\text{U}/\text{mL}$ or the fasting glucose/ fasting insulin ratio was <4.5 . We also calculated the homeostasis model assessment of insulin resistance (HOMA-IR) index in both groups [4-6].

Blood was drawn from the study and the control subjects to determine fasting blood glucose and fasting insulin levels. The subjects fasted for a 12-hour overnight period prior to the blood draw, which occurred between 8.00 and 10.00 a.m. on the day of the test.

Statistical Analysis

Both groups were compared according to age, gravidity, parity, number of abortions, number of living children, and BMI index. Fasting glucose, fasting insulin, fasting glucose/fasting insulin ratio, and HOMA-IR values were compared using the Student's *t*-test for the parametric data and Mann-Whitney *U*-test for the non-parametric data in both groups. A *p*-value <0.05 was considered statistically significant. For the statistical analysis, SPSS (Statistical Package for the Social Sciences) version 10.0 was used.

Results

The age and BMI of the RPL and the control groups were similar. The number of abortions in the study group was significantly higher, but parity was significantly lower in the study group when compared with controls (both $p < 0.001$). (Table I).

In the study group, the mean values for fasting glucose, fasting insulin, and HOMA-IR were higher, and the G/I ratios were lower compared with those for the control group, and for each of the parameters, statistical significance was found. (Table II).

In our study, a HOMA-IR index of >4.5 identified IR in 14 of 64 patients (21.9%) and 5 of 64 controls (7.8%). Fasting insulin levels $\geq 20\mu\text{U}/\text{mL}$ identified IR in 13 women with RPL (20.3%) and 5 controls (7.8%). A fasting glucose/fasting insulin ratio of <4.5 identified IR in 8 women with RPL (12.5%) and 2 of the fertile controls (3.1%). (Table II).

Consequently, more patients had IR in the RPL group when compared with the controls. Moreover, the IR values detected using the three methods were found to be significantly higher in patients with RPL. (Table II).

Discussion

Traditionally, a patient with three and more consecutive pregnancy losses would have been diagnosed with RPL, but current approach recommends evaluating a patient after two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination [7]. Following more recent recommendations, in this study we recruited patients after two or more consecutive abortions.

Table I. Demographics of RPL patients and parous controls.

Characteristics	Study group (n=64)	Control group (n=64)	P values
Age (years) (Mean ± SD)	29.5 ± 6.0	30.7 ± 6.0	0.28
Gravidity (Mean ± SD)	4.7 ± 2.2	3.6 ± 2.6	0.97
Parity (Mean ± SD)	1.3 ± 1.6	2.4 ± 1.6	<0.001*
Miscarriages (Mean ± SD)	3.0 ± 1	0.2 ± 0.4	<0.001*
Number of living children	1.2 ± 1.4	3.1 ± 2.0	<0.001*
BMI (kg/m ²) (Mean ± SD)	25.7 ± 4.3	24.9 ± 4.2	0.28

Note: BMI = body mass index; SD = standard deviation.
* statistically significant

Table II. Biochemical data of women with RPL and parous controls.

Biochemical data	Study group (n=64)	Control group (n=64)	P values
Fasting glucose (mg/dL)	100.8 ± 12.8	89.7 ± 15.1	<0.001*
Fasting insulin (μU/mL)	15.5 ± 19.7	7.2±5.9	0.001*
Glucose: insulin ratio	12.2 ± 13.5	28.3±15.4	0.017*
HOMA-IR score	4.2 ± 6.3	1.6±1.6	0.002*
Insulin (μU/mL)(≥20uU)	13 (%20.3)	5 (%7.8)	0.042*
Glucose: insulin ratio (<4.5)	8 (%12.5)	2 (%3.1)	0.048*
HOMA-IR (>4.5)	14 (%21.9)	5 (%7.8)	0.028*

Note: HOMA-IR = homeostasis model assessment of insulin resistance index.
* statistically significant

Several studies have found a high incidence of RPL in women with PCOS [8-10].

Several researchers have also demonstrated a significant reduction in abortion rates with metformin therapy as an insulin-sensitizing agent in pregnant women with PCOS [11-13]. IR has been reported in about 40% of patients with PCOS [3, 14]. IR may be associated with an increased risk of spontaneous abortion in women who are overweight/obese or have PCOS.

The glucose clamp technique is considered the gold standard for patients with the IR diagnosis, but it is laborious and expensive. Fasting insulin levels ≥20μU/mL, fasting glucose/fasting insulin ratios <4.5, or a HOMA-IR index >4.5 are other methods used to define IR.

In our study, we used all three of these methods to diagnose patients with IR, similar to the methods used in the earlier studies [4-6].

Tian et al. carried out a study of pregnancies after infertility treatment among patients with and without IR. In patients with IR, pregnancy loss was statistically more frequent [15]. In the present study, we found that more patients had IR in the RPL group when compared with controls. Also, the IR values detected using the three methods were significantly higher in patients with RPL.

The prevalence of IR was investigated among women with RPL in a study by Craig et al. They compared 74 patients with RPL to 74 normal, parous female controls and studied IR in all subjects. Findings in that study indicated that 38 patients had an identified cause of RPL, whereas 36 patients had an unknown RPL etiology. They found significantly more women with RPL had IR compared with controls [16]. In another study, Diejomaoh et al. compared IR in 35 women with RPL of unknown etiology with 30 controls matched for age and BMI.

They reported that IR was more prevalent in the study group than in the control group, but the difference between the two groups failed to reach statistical significance [17]. The study sample size in Diejomaoh et al. study was smaller than that used in the work by Craig et al. and in our study sample. We investigated the prevalence of IR in 64 patients who had an unexplained RPL etiology. We found that IR was significantly more prevalent in RPL subjects than in controls. Our findings are similar to the results of Craig et al. Overall, the results of our study contribute to previous works indicating that IR is higher in women with RPL. Moreover, our patient group consisted only of patients who had an unexplained RPL etiology, in contrast to earlier studies.

IR has been associated with a number of metabolic abnormalities including excess androgens, glucose intolerance, and increased circulating levels of plasminogen activator inhibitor-1 (PAI-1) [18]. The effect of IR as an independent contributor to RPL is not completely clear. However, a few potential mechanisms of IR may contribute to abortion. First, IR may cause excessive transport of glucose to the fetal environment, leading to an increased loss in the first trimester. Second, hyperinsulinemia can elevate PAI-1 concentrations, which can lead to thrombotic induction and placental insufficiency [16]. Third, increased insulin concentrations are responsible for decreased concentrations of serum glycodelin and insulin growth factor binding protein 1 (IGFBP-1), which have been observed in the first trimester of PCOS patients pregnancy. Decreased concentrations of these proteins suggest deficient endometrial development during the peri-implantation period [11, 19].

In conclusion, the present study showed significantly higher IR in patients with RPL compared with the control group. These results are important for practitioners in determining the diagnosis and choice of treatment for RPL patients because IR may require treatment that includes life style changes, exercise, and metformin drug therapy. We recommend a clinical determination of IR in patients with RPL.

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Symposium Polskiego Towarzystwa Menopauzy i Andropauzy

Najnowsze trendy w diagnostyce i terapii u kobiet w okresie menopauzy

Kazimierz Dolny n/Wisłą

18 czerwca 2011 r.
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