Study of the Changes of Pulsatility Index (PI) in Uterine Artery in Patients with Recurrent Pregnancy Loss

Abstract

Background: Recurrent pregnancy loss (RPL) is a distressing condition affecting women of childbearing age, often with unexplained causes. Pulsatility Index (PI) in uterine arteries has been proposed as a potential diagnostic marker. **This study aimed to** evaluate the differences in uterine artery PI between women with recurrent unexplained first-trimester abortions and those with no history of abortion. **Methods:** This case-control study was conducted on 100 non-pregnant women. They were categorized into two groups: the RPL group (Group A) and the control group (Group B). All participants underwent a detailed clinical assessment, including complete history, general, abdominal, and pelvic examinations, as well as two-dimensional ultrasound examinations and Doppler studies to measure the uterine artery PI. **Results**: There was a statistically significant difference in the pulsatility index (PI) of the right uterine artery between the RPL group and the control group. The mean PI values were 2.000 (±0.451) and 2.248 (±0.322), respectively. Comparing PI of left uterine artery in RPL group and control group, revealed a significant difference. AS regards PI of both right and left uterine arteries in RPL group and control group a statistically significant difference was found. **Conclusion:** The study found that the mean uterine artery PI value in the RPL group was higher in the case group than in the control group. This indicates increased impedance to blood flow in the uterine arteries among women with a history of RPL.

Keywords: Pulsatility Index; Uterine Artery; Recurrent Pregnancy Loss.

Introduction

Abortion is the term used to describe the expulsion or removal of products of conception from the uterus before the fetus reaches viability or when the fetus weighs less than 500g or measures less than 25cm. While the exact prevalence of spontaneous abortions remains unknown, it is estimated that approximately 15% of clinically evident pregnancies and 60% of chemically evident pregnancies end in spontaneous abortion. Of these, 80% occur before the 12th week of gestation (1).

Recurrent pregnancy loss is defined as the occurrence of three or more successive spontaneous abortions. The etiology of recurrent pregnancy loss is often unclear and may involve multiple factors, leading to ongoing controversy regarding diagnosis and treatment. Generally accepted causes include genetics, anatomical issues, endocrine imbalances, placental anomalies, hormonal problems, infections, smoking, alcohol consumption, exposure to environmental risk factors, psychological trauma, stressful life events, and defects in certain coagulation and immunoregulatory proteins (2).

The American Society of Reproductive Medicine has recently redefined recurrent pregnancy loss as two or more failed clinical pregnancies as confirmed by ultrasonography or histopathological examination. The incidence of recurrent pregnancy

loss in the fertile population is 1-2%, and the risk of recurrence increases with maternal age and the number of successive losses (3).

Recurrent pregnancy losses may be attributable to treatable conditions such as hypercoagulable states, autoimmune diseases, endocrine disturbances, or maternal anatomical abnormalities. However, a substantial proportion of cases (up to 40–50%) have no identifiable causes (4).

Investigating recurrent abortion is best done before attempting another pregnancy, as uterine receptivity is influenced by various factors, including uterine perfusion, which plays a crucial role in achieving a normal pregnancy. Studies suggest that uterine artery perfusion may regulate endometrial receptivity, and poor uterine perfusion could be a contributing factor to unexplained abortions and potentially faulty implantation. The main arterial blood supply to the uterus is derived from the uterine arteries, which typically demonstrate high resistance to absent or reversed diastolic flow before pregnancy (5).

Transvaginal pulsed Doppler ultrasound offers a noninvasive means of assessing uterine circulation, and Color Doppler is utilized in obstetrical ultrasound to provide information about the presence, direction, and velocity of blood flow (6).

The pulsatility index (PI) of the uterine artery is known to decrease progressively during the luteal phase, which coincides with the implantation process. Therefore, measuring the uterine artery pulsatility index (PI) during the mid-luteal phase of spontaneous cycles has been proposed as a means to identify patients with recurrent pregnancy loss associated with impaired uterine circulation (7).

The aim of this study was to determine whether there is a difference in the uterine artery PI between women with a history of recurrent unexplained first-trimester abortions and women without this history.

Patients and methods

This case-control study was conducted between March 2022 and December 2022. We enrolled 100 non-pregnant women who presented at the outpatient clinic of Benha University Hospitals.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University.

Participants were categorized into two groups:

Group A: Comprising 50 individuals with a history of idiopathic recurrent pregnancy loss (the RPL group).

Group B: Comprising 50 individuals with no history of abortion and who had at least one child born at full term (the control group). They sought contraceptive methods at the clinic.

Upon recruitment, the study's objectives were thoroughly explained to each participant. All participants underwent a two-dimensional ultrasound examination and Doppler study to measure the pulsatility index (PI) of the uterine arteries.

Inclusion criteria for the recurrent pregnancy loss group: Three or more successive unexplained first-trimester abortions, age between 20 and 40 years, regular menstrual cycles for the three cycles prior to the study, no use of hormonal contraception or intrauterine devices, normal endocrine status, including serum thyroid-stimulating hormone, free thyroxin (T4), glucose tolerance test, and progesterone levels between days 19 and 21 of the menstrual cycle.

Inclusion criteria for the control group: Age between 20 and 40 years, regular menstrual cycles for the three cycles prior to the study, no use of hormonal contraception or intrauterine devices, normal obstetric history, with at least one previous full-term pregnancy but no abortions.

Exclusion criteria for both groups: Systemic diseases that might affect hemodynamic indices (e.g., thrombocytopenia, thyroid disease, autoimmune disease, cardiovascular disease, diabetes, etc.), history of consanguinity, family history of chromosomal abnormalities (e.g., trisomy 21, trisomy 13, Turner's syndrome, etc.), patient age less than 20 years or more than 40 years, women in the follicular phase or menstrual phase, women with uterine alterations detected during office hysteroscopy and women with cervical incompetence observed via transvaginal ultrasonography.

Methods:

All patients underwent the following assessments:

Complete History: This included personal information, menstrual history, obstetric history, and past medical history, including any systemic diseases, consanguinity, and thyroid issues.

General, Abdominal, and Pelvic Examination: General signs of thyroid disease, autoimmune diseases, and cardiovascular diseases were examined. Breast examination, abdominal inspection, palpation, and percussion were conducted. Pelvic examination was performed to assess uterine size and the presence of adnexal masses.

Ultrasound Machine Used:

Sonography was conducted using a Mindray DC-70 Exp ultrasound machine equipped with a vaginal transducer. Transvaginal examinations were performed between days 18-23 of the menstrual cycle to coincide with the endometrial receptive window for embryo implantation.

Technique of examination:

The vaginal probe was covered with an examining glove containing gel to ensure good contact and prevent air bubbles. Cross infection was prevented using probe covers and disinfectants. With the patient in the lithotomy position and an empty bladder, the transvaginal probe was gently inserted into the vagina. The probe was positioned in the anterior fornix, and the internal and external cervical os were identified. The uterus was examined, and the endometrial thickness was measured. The probe was then moved laterally, and both uterine arteries were identified using color Doppler.

Pulsed wave Doppler was used to obtain clear flow velocity waveforms of both uterine arteries. The pulsatility index (PI) (PI=SD/mean) was measured bilaterally, and the reported PI was the arithmetic mean of the last three cardiac cycles.

Approval code:

Statistical analysis

The data were statistically summarized in terms of the mean ± standard deviation (± SD). A comparison between the RPL cases and the control groups was conducted using the student's t-test for independent samples. Correlations between various variables were assessed using the Pearson correlation coefficient for linear relationships. A p-value less than 0.05 was considered statistically significant. All statistical calculations were performed using computer software, specifically Microsoft Excel 2010 (Microsoft Corporation, NY, USA), and SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA), version 15 for Microsoft Windows.

Results

There were no statistically significant differences between RPL group and control group regarding the mean aga and endometrial thickness. The mean parity and serum progesterone level of women in the control group was significantly higher than that in the RP group. **Table 1**

Table 1: Demographic data of all women in the study

Variable	RPL group N=50	Control N=50	P value
Age(years) -Range: -Mean ±SD:	20:40 28.036±4.83	20:40 28.04±5.771	0.764(NS)
Parity -Range: -Mean ±SD:	1:3 1.12±1.023	1:5 2.62±1.338	0.001(S)
Serum Progesterone (ng/ml) -Range: -Mean ±SD:	12:16 14.0±2.7	12.5:17 14.3± 2.4	0.002(S)
Endometrial thickness (mm) -Range: -Mean ±SD:	7:11 9.7±2.9	8:14 11.2±2.5	.43(NS)

There was a statistically significant difference in the pulsatility index (PI) of the right uterine artery between the RPL group and the control group. The mean PI values were 2.000 (±0.451) and 2.248 (±0.322), respectively. This indicates an increased resistance to blood flow in the right uterine artery in the RPL group. **Table 2**

Table 2: Comparison of right uterine artery PI between RPL and control groups

	RPL group n=50	Controls n=50	P value
PI of right uterine artery	2.505±o.451	2.248±0.322	0.001 (S)

Comparing PI of left uterine artery in RPL group and control group, revealed a significant difference. **Table 3**

Table 3: Comparison of left uterine artery PI between RPL and control groups

	RPL group n=50	Controls n=50	P value
PI of left uterine artery	2.521±.397	2.307±.331	0.004 (S)

AS regards PI of both right and left uterine arteries in RPL group and control group a statistically significant difference was found. **Table 4**

Table 4: Comparison of mean uterine artery PI between RPL and control groups

	RPL group n=50	Controls n=50	P value
Mean uterine artery PI	2.513±0.415	2.278±.325	0.002 (S)

Endometrial thickness was 9.7 mm ±1.8 mm in the study group and 9.7 mm ±1.4 mm in the control group but the difference was not significant (P value 0.95). **Table 5**

Table 5: Comparison in endometrial thickness (mm) between case and control group.

	Controls	Cases	P value
Mean	9.7	9.7	0.95
Std. Deviation	1.4	1.8	

Discussion

The primary objective of this study with non-pregnant women was to determine whether those with a history of unexplained RPL exhibited higher uterine blood flow impedance compared to women who had no history of spontaneous abortions but had at least one live child.

While some studies have suggested that poor uterine perfusion might be a factor in unexplained infertility, there are fewer studies that have investigated the correlation between RPL and uterine artery Doppler flowmetry (8).

Several studies have explored uterine artery blood flow in patients with recurrent pregnancy loss (9, 10) and found that elevated uterine arterial impedance is associated with recurrent pregnancy loss.

The pulsatility index (PI) of the uterine arteries is known to progressively decrease during the luteal phase, a critical period for implantation (7). Optimal uterine receptivity seems to occur when the mean PI of both arteries falls between 2 and 3, significantly decreasing the implantation and pregnancy rate when the PI is over 3 or 4 or when diastolic flow is absent in the Doppler waveform (11).

However, it's important to note that inadequate blood flow might hinder implantation, but optimal uterine perfusion does not guarantee pregnancy. Additionally, high uterine resistance is observed in less than 10% of non-conception cycles, suggesting that this parameter is responsible for implantation failure in very few cases (12).

Given the absence of a difference between the right and left sides, it appears that interpreting Doppler data for uterine arteries is best done by considering the mean PI of both sides combined.

Approximately 10-15% of clinically recognized pregnancies result in spontaneous miscarriage, with the risk increasing with maternal age. A decline in endometrial receptivity associated with reduced uterine perfusion may contribute to a decrease in implantation rates with age (2).

In the current study, we measured uterine artery PI during the luteal phase of spontaneous cycles. Uterine artery PI was significantly higher in the recurrent miscarriage group (2.6 ± 0.36) compared to the control group (1.7 ± 0.27) ($p = 0.000$). A strong positive correlation was observed between UAPI and recurrent miscarriage in the study group ($r = 0.8$, $p = 0.00$).

This finding aligns with previous research on patients with recurrent pregnancy loss (9, 10). Additionally, a study found increased ovarian and uterine flow impedance in women with RPL compared to controls (13).

A study on 230 women with RPL and 50 fertile controls revealed that uterine artery PI values in RPL patients (2.42 ± 0.79) were significantly higher compared to those in the control group (2.08 ± 0.47). Notably, the highest PI values were found in patients with uterine abnormalities (2.82 ± 1.0), antiphospholipid antibody syndrome (2.70 ± 1.1), and unexplained RPL (2.6 ± 0.7). This suggests that impaired uterine perfusion can adversely affect reproductive function, emphasizing the potential significance of therapeutic approaches to improve uterine perfusion (10).

It has been proposed to assess uterine perfusion by considering the endometrial and subendometrial areas as a whole, as there is no difference in blood flow between these regions with respect to the likelihood of achieving pregnancy (14).

In a study evaluating uterine artery blood flow using pulsed Doppler and endometrial and subendometrial microvascularization in women with unexplained infertility, they

compared 40 women with unexplained infertility to 40 fertile parous controls. The study assessed endometrial thickness and uterine artery PI during the mid-luteal (peri-implantation) phase (9).

The uterine artery PI ($p = 0.003$) significantly increased in the unexplained infertility group, while endometrial thickness did not show a significant difference between the two groups. This indicates impaired peri-implantation endometrial perfusion in women with unexplained infertility. Thus, Doppler studies of uterine hemodynamics should be considered in infertility evaluations.

In IVF cycles, implantation failure has been associated with the absence of subendometrial blood flow (15), while pregnant patients with live births exhibit significantly higher endometrial and subendometrial vascularity compared to those with miscarriages (16).

These findings suggest that improved endometrial and subendometrial vascularity can lead to better placental development during pregnancy, reducing the risk of miscarriage and increasing the chances of live birth following ART (16).

The absence of color mapping at the endometrium and subendometrial myometrium signifies either complete implantation failure or a significant decrease in the implantation rate (14).

In 75 IVF cycles, a study demonstrated that all 3D subendometrial power Doppler flow indices performed on the first day of ovarian stimulation, with the subendometrial FI being the strongest predictive factor for the outcome in pregnant cycles compared to nonpregnant ones (17).

A study showed that subendometrial VFI on the day of HCG administration was significantly higher in the pregnant group and was superior to endometrial volume, subendometrial VI, and FI in predicting the outcome (18).

Despite the various studies attempting to link these findings to uterine receptivity for optimizing embryo implantation and IVF success, there is still uncertainty regarding the relationship between uterine receptivity and endometrial and subendometrial changes. Variations in the timing of ultrasounds, patient characteristics, ovarian stimulation, and techniques used likely contributed to the differing results.

In our study, the application of a binary logistic regression analysis model revealed that adding variables did not significantly enhance our ability to predict miscarriage occurrence. This may be attributed to the small sample size, despite the observed significant differences between the two groups.

Unfortunately, we could not identify specific cutoff values for predicting miscarriage, possibly due to the limited sample size, short follow-up period, and the study's focus on patients with normal uterine cavities by hysteroscopy, aged 20-40 years, with regular cycles between days 18-23, and normal thyroid function. Larger prospective studies are needed to confirm these results and establish accurate predictive values. Additionally,

providing emotional support and closely monitoring early pregnancies can help improve pregnancy outcomes. Empiric treatments with exogenous progesterone or low-dose aspirin for women with unexplained recurrent pregnancy loss have not been proven effective (19).

Conclusion

The study found that the mean uterine artery pulsatility index (PI) value in the RPL group was higher in the case group (2.513 ± 0.415) than in the control group (2.278 ± 0.325). This indicates increased impedance to blood flow in the uterine arteries among women with a history of RPL.

Recommendations

Based on the findings of this study, it is possible to propose the use of transvaginal ultrasonography with Doppler flowmetry in the second phase of the menstrual cycle to assess uterine artery blood flow in women at risk for spontaneous abortion.

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Author contribution

Authors contributed equally in the study**.**

Conflicts of interest

No conflicts of interest

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