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

Original Article

Sara Taha Moustafa Hamed, Ayman Ahmed Abdel-Hamid Shedid, Ghada Mohammed El-Said Abdel-Halim* and Ahmed Qasim Mohamed Zainel-Din

Department of Obstetrics & Gynecology, Faculty of Medicine, Benha University, Egypt.

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.

Objectives: To assess disparities in uterine artery PI between women experiencing recurrent unexplained first-trimester miscarriages and those with no prior history of miscarriage.

Study Design: A case-control study.

Materials and Methods: A cohort of 100 non-pregnant women was the focus of this research. They were categorized into two distinct groups: the RPL group, denoted as Group A, and the control group, identified as Group B. All participants underwent comprehensive clinical evaluations, including an exhaustive medical history, general health, abdominal and pelvic examinations, in addition to two-dimensional ultrasound assessments and Doppler studies aimed at quantifying the PI of the uterine arteries.

Results: A statistically significant variance was observed in 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. A notable distinction in the PI of the left uterine artery between the RPL group and the control group was also detected (*P-value < 0.05*). Furthermore, PI values of both the right and left uterine arteries exhibited a statistically significant difference between the RPL and control groups (*P-value < 0.05*).

Conclusion: The mean uterine artery PI value was greater in RPL group in contrast to control group. This suggests an elevated resistance to blood flow within uterine arteries among women who have experienced RPL.

Key Words: Pulsatility index, uterine artery, recurrent pregnancy loss.

Received: 28 October 2023, **Accepted:** 20 November 2023

Corresponding Author: Ghada Mohammed El-Said Abdel-Halim, MSc, Departmernt of Obstetrics & Gynecology, Faculty of Medicine, Assiut University, Egypt., **Tel.:** +201099669101, **E-mail:** gm4307647@gmail.com

ISSN: 2090-7265, February 2024, Vol.14, No. 1

INTRODUCTION

Abortion refers to the expulsion or removal of pregnancy products from the uterus before the fetus reaches viability or when the fetus weighs less than 500g or measures less than 25cm. While the precise prevalence of spontaneous abortions remains uncertain, it is estimated that about 15% of clinically evident pregnancies and 60% of chemically evident pregnancies result in spontaneous abortion. Among these cases, approximately 80% occur before the 12th week of gestation[1].

When three or more spontaneous abortions occur back-to-back, it is considered a recurrent pregnancy loss. The reasons behind repeated miscarriages often remain unclear and can involve various factors, sparking ongoing debates about diagnosis and treatment. Established factors include genetics, anatomical issues, hormonal imbalances, placental irregularities, issues with the endocrine system, infections, smoking, drinking, being exposed to dangers in the environment, psychological trauma, stressful life events, and impairments in particular coagulation and immunoregulatory proteins[2].

Recurrent pregnancy loss has recently been defined by the American Society of Reproductive Medicine as two or more clinically unsuccessful pregnancies confirmed by ultrasonography or histological analysis. The risk of recurrence increases with maternal age and the number of successive losses in the fertile population, where the incidence of recurrent pregnancy loss is between one and two percent[3].

Treatable problems including autoimmune diseases, endocrine disruptions, maternal anatomical defects, or hypercoagulable states may contribute to recurrent pregnancy losses. However, a significant percentage of cases (up to 40–50%) lack identifiable causes[4].

 DOI:10.21608/EBWHJ.2023.245173.1269

It is advisable to investigate recurrent abortion prior to attempting another pregnancy, as uterine receptivity is influenced by various factors, including uterine perfusion, which plays a pivotal role in having a healthy pregnancy. According to studies, endometrial receptivity may be influenced by uterine artery perfusion, and insufficient uterine perfusion may be a factor in unexplained abortions and problematic implantation. The primary arterial blood supply to the uterus is provided by uterine arteries, which typically exhibit high resistance to diastolic flow before pregnancy[5].

Transvaginal pulsed Doppler ultrasound offers a noninvasive approach to assessing uterine circulation, and Obstetrical ultrasound uses color Doppler to provide details regarding the existence, direction, and speed of blood flow[6].

It is known that during luteal phase, which coincides with the implantation process, the uterine artery's PI gradually decreases. Therefore, it has been suggested that uterine artery PI assessment during the mid-luteal phase of spontaneous cycles be used to identify individuals with recurrent pregnancy loss connected with poor uterine circulation[7].

The objective of this investigation was to ascertain whether disparities exist in PI of the uterine artery between women who have experienced recurrent unexplained first-trimester miscarriages and those who have not encountered such events.

PATIENTS AND METHODS

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

Informed written consent was diligently acquired from all patients, each of whom was provided with a thorough justification of study's purpose and assigned a confidential code number. After receiving approval from Benha University Faculty of Medicine's Research Ethics Committee, the study was done. (Approval code: MS.32.1.2022).

Participants were divided into two distinct groups:

Group A: Comprising 50 individuals with a documented history of unexplained recurrent pregnancy loss (referred to as RPL group).

Group B: Comprising 50 individuals with no prior history of abortion, each has produced offspring at least one child at full term and currently seeking contraceptive methods at the clinic.

Upon enrollment, the study's objectives were meticulously elucidated to every participant. All participants completed a Doppler investigation and two-dimensional ultrasound scan to determine PI of the uterine arteries.

For the group with repeated pregnancy losses, the following criteria were required:

Three or more consecutive first-trimester abortions that are unexplained; three consecutive periods of normal menstruation; age between 20 and 40 years; normal endocrine status; no use of hormonal contraception or intrauterine devices; and serum levels of TSH, free thyroxin (T4), a glucose tolerance test, and progesterone were measured between days 19 and 21 of the menstrual cycle.

Criteria for inclusion in control group:

Having a normal obstetric history, which includes at least one full-term pregnancy and no history of abortions, as well as a 20–40 year age range, normal menstrual cycles in the three cycles before the trial, no intrauterine devices or hormonal contraception were used.

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.

Examination of the chest, abdomen, and pelvis for general thyroid and autoimmune disease symptoms, and cardiovascular diseases were examined. Breast examination, abdominal inspection, palpation, and percussion were conducted. Pelvic examination was performed to assess uterine size as well as existence of adnexal masses.

Ultrasound Machine Used:

Sonography was conducted utilizing a Mindray DC-70 Exp ultrasound machine possessed by a vaginal transducer. Transvaginal examinations were done 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 enveloped in a gel-coated examination glove to ensure proper contact and prevent the formation of air bubbles. Measures were taken to prevent cross-infection by employing probe covers and disinfectants. With the patient positioned in lithotomy posture and an empty bladder, transvaginal probe was carefully introduced into the vaginal canal. The probe was positioned within the anterior fornix to identify both the internal and external cervical os. Subsequently, a thorough examination of the uterus was performed, including the measurement of endometrial thickness. The probe was then laterally repositioned, allowing for identification of both uterine arteries through the use of color Doppler imaging.

Pulsed wave Doppler technology was utilized to obtain well-defined flow velocity waveforms from both uterine arteries. Bilateral measurement of PI (calculated as PI = SD/mean) was conducted, and reported PI value was derived from arithmetic mean of three previous heartbeats.

Statistical analysis:

The data were determined by computing mean and standard deviation. (mean ± SD). To compare the RPL cases with the control groups, an independent samples t-test was used. The relationships between different variables were evaluated using the Pearson correlation coefficient for linear associations. A *p-value* below 0.05 demonstrated statistical significance. Statistical calculations were conducted with the assistance of computer software, which included Microsoft Excel 2010 (developed by Microsoft Corporation, located in NY, USA) and SPSS (Statistical Package for the Social Sciences, produced by SPSS Inc. in Chicago, IL, USA), specifically version 15 tailored for the Microsoft Windows platform.

RESULTS

All of the study's participants' demographic information was displayed in Table 1. Women in control group had mean parity and serum progesterone levels that were significantly greater than those in RP group. (Table 1).

A marked statistical distinction was observed in PI of the right uterine artery when contrasting RPL group to control group. The average PI values were 2.000 (±0.451) and 2.248 (±0.322) for the two groups, respectively. This suggests a heightened impediment to blood flow within the right uterine artery among individuals in the RPL group. (Table 2).

A substantial difference was seen when the left uterine artery's PI was contrasted between the RPL group and control group. (Table 3)

Concerning PI of both the right and left uterine arteries, a statistically notable distinction was identified when contrasting the RPL group to the control group. (Table 4)

Endometrial thickness measured 9.7 mm ±1.8 mm within study group and 9.7 mm ±1.4 mm within control group; however, the variance between the two was not statistically significant (with a *P-value of 0.95*). (Table 5)

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)*

RPL: Recurrent Pregnancy Loss, **N:** Number, *P value*: Probability value, **SD:** Standard Deviation, **NS:** Not Significant, **S:** Significant.

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)*

PI: Pulsatility Index, **RPL:** Recurrent Pregnancy Loss, **n:** Number, ***P value:*** Probability value, **S:** Significant.

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)*

PI: Pulsatility Index, **RPL:** Recurrent Pregnancy Loss, **n:** Number, *P value:* Probability value, **S:** Significant.

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)*

PI: Pulsatility Index, **RPL:** Recurrent Pregnancy Loss, **n:** Number, *P value:* Probability value, **S:** Significant.

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 main goal of this study with non-pregnant women was to find out whether individuals with a history of unexplained RPL had increased uterine blood flow impedance in comparison to those who had no history of spontaneous abortions but at least one living child.

While some research have hypothezised that unexplained infertility may be caused by inadequate uterine perfusion, there are fewer studies that have investigated the correlation between RPL and uterine artery Doppler flowmetry[8].

Numerous investigations have delved into uterine artery blood flow among patients experiencing recurrent pregnancy loss[9], revealing a correlation between heightened uterine arterial impedance and recurrent pregnancy loss.

PI of uterine arteries is recognized to gradually decline during the crucial luteal phase, which has a crucial role in the implantation process[7]. Ideal uterine receptivity seems to be associated with a mean PI value ranging between 2 and 3. A notable decline in implantation and pregnancy rates is observed when the PI surpasses 3 or 4 or when diastolic flow is absent in Doppler waveform[10].

However, it is worth emphasizing that while insufficient blood flow might impede implantation, the presence of optimal uterine perfusion does not guarantee pregnancy. Furthermore, fewer than 10% of non-conception cycles show evidence of strong uterine resistance, suggesting that this component only sometimes causes implantation failure[11].

Considering absence of disparities between right and left sides, it seems that the most effective interpretation of Doppler data pertaining to uterine arteries entails considering the mean PI value derived from both sides combined.

Roughly 10-15% of pregnancies recognized clinically culminate in spontaneous miscarriages, and this risk amplifies with advancing maternal age. The decrement in endometrial receptivity, linked to reduced uterine perfusion, may contribute to diminished implantation rates as women age[2].

In our present study, we conducted measurements of uterine artery PI during luteal phase of spontaneous menstrual cycles. Uterine artery PI was found to be significantly greater in recurrent miscarriage group (2.6 ± 0.36) than in control group (1.7 ± 0.27) ($p = 0.000$). Within the study group, there was a strong positive connection found between UAPI and recurrent miscarriage ($r = 0.8$, $p = 0.00$). This discovery is consistent with prior research concerning patients grappling with recurrent pregnancy loss[9]. Furthermore, a study revealed escalated impedance in ovarian and uterine blood flow among women dealing with RPL as compared to individuals without this concern[12].

A comprehensive study involving 230 women experiencing RPL and 50 fertile controls unveiled that uterine artery PI values among RPL patients (2.42 ± 0.79) were significantly greater in contrast to those in control group (2.08 ± 0.47). Remarkably, maximum PI values were recorded in patients exhibiting uterine abnormalities (2.82 ± 1.0), antiphospholipid antibody syndrome (2.70 ± 1.1), and unexplained RPL (2.6 ± 0.7). This underscores the potential adverse influence of impaired uterine perfusion on reproductive function and underscores the importance of considering therapeutic interventions to enhance uterine perfusion[10].

A proposition has been made to assess uterine perfusion by considering both the endometrial and subendometrial regions as a unified entity, given the absence of significant disparities in blood flow between these areas concerning the probability of achieving pregnancy[13].

In a research investigation that examined uterine artery blood flow utilizing pulsed Doppler, along with an assessment of microvascularization of the endometrium and subendometrium in women with unexplained infertility a comparison was made between 40 women with unexplained infertility and an equal number of fertile parous controls[9].

The study revealed a notable increase in uterine artery PI (*p = 0.003*) within the unexplained infertility group, while there was no significant variation in endometrial thickness between the two groups. This finding underscores compromised endometrial perfusion during the peri-implantation phase in women facing unexplained infertility. Consequently, Doppler examinations of uterine hemodynamics needs to be integrated into infertility assessments.

In the context of in vitro fertilization (IVF) cycles, instances of implantation failure have been linked to the lack of subendometrial blood flow[14]. Conversely, expectant patients who go on to achieve successful live births exhibit considerably elevated levels of endometrial and subendometrial vascularity in contrast to those who experience miscarriages[15].

These outcomes suggest that enhanced endometrial and subendometrial vascularity may contribute to improved placental development during pregnancy, thereby mitigating the risk of miscarriage and augmenting the prospects of successful live births following assisted reproductive technology (ART) procedures[15].

Lack of color mapping in endometrium and subendometrial myometrium is indicative of either complete failure of implantation or a substantial reduction in the implantation success rate[13].

In a study involving 75 IVF cycles, it was demonstrated that all three-dimensional subendometrial power Doppler flow indices done during the start of ovarian stimulation, with subendometrial flow index (FI) being the most influential predictive factor, played a crucial role in distinguishing between cycles that led to pregnancy and those that did not[16].

Another study noticed that subendometrial vascularization flow index (VFI) on the day of human chorionic gonadotropin (HCG) administration was significantly greater in pregnant group and exhibited superior predictive capabilities in comparison to endometrial volume, subendometrial vascularization index (VI), and FI in forecasting outcomes[17].

Although various studies have aimed to connect these discoveries to uterine receptivity with the goal of optimizing embryo implantation and IVF success, there remains uncertainty regarding the intricate relationship between uterine receptivity and modifications to the endometrium and subendometrium. Discrepancies in the timing of ultrasounds, patient characteristics, ovarian stimulation protocols, and employed techniques have likely contributed to the divergent results.

The use of a binary logistic regression analysis model inside our study demonstrated that the addition of factors did not considerably improve our capacity to predict the occurrence of miscarriages. Even though we saw substantial differences between the two groups, this observation might be explained by the small sample size.

Unfortunately, we were unable to pinpoint specific threshold values for predicting miscarriage, possibly due to the restricted sample size, the relatively short follow-up period, and the study's focus on patients with normal uterine cavities as confirmed by hysteroscopy. These patients were between the ages of 20 and 40, exhibited regular cycles falling between days 18 and 23, and displayed normal thyroid function. To establish precise predictive values, larger prospective studies are imperative for validation. Furthermore, providing emotional support and closely monitoring early pregnancies can contribute to enhanced pregnancy outcomes. It is worth noting that empirical treatments involving exogenous progesterone or low-dose aspirin have not been found to be effective for women suffering from unexplained recurrent pregnancy loss[18].

CONCLUSION

According to the study, there was a significant variation between the RPL group's uterine artery PI (2.513 ± 0.415) and the control group's (2.278 ± 0.325), indicating greater blood flow resistance. This suggests that transvaginal ultrasonography with Doppler flowmetry may be helpful for evaluating uterine artery blood flow in women at risk of spontaneous abortion during the second menstrual cycle phase.

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.

CONFLICT OF INTEREST

There are no conflicts of interests.

REFERENCES

1. Garhy, I. T. E., Mohamed, A. H., & Sultan, A. S. (2018). Uterine and subendometrial arteries Doppler in patients with recurrent first trimestric abortion. The Egyptian Journal of Hospital Medicine, 73(5), 6683-6690.

2. Papas, R. S., & Kutteh, W. H. (2020). A new algorithm for the evaluation of recurrent pregnancy loss redefining unexplained miscarriage: review of current guidelines. Current Opinion in Obstetrics and Gynecology, 32(5), 371-379.

3. Dimitriadis E, Menkhorst E, Saito S, Kutteh WH, Brosens JJ. Recurrent pregnancy loss. Nature reviews disease primers. 2020;6:98..

4. Vomstein, K., Feil, K., Strobel, L., Aulitzky, A., Hofer-Tollinger, S., Kuon, R. J., & Toth, B. (2021). Immunological risk factors in recurrent pregnancy loss: guidelines versus current state of the art. Journal of Clinical Medicine, 10(4), 869.

5. Ma J, Gao W, Li D. Recurrent implantation failure: A comprehensive summary from etiology to treatment. Front Endocrinol (Lausanne). 2022;13:1061766.

6. Kale RM, Tirupathi RG, Sheela SR. Role of Ultrasonography and Color Doppler in the Assessment of High-Risk Pregnancies and Their Accuracy in Predicting Fetal Outcome. Cureus. 2023;15:e39017.

7. Guedes-Martins L, Gaio R, Saraiva J, Cerdeira S, Matos L, Silva E, et al. Reference ranges for uterine artery pulsatility index during the menstrual cycle: a cross-sectional study. PLoS One. 2015;10:e0119103.

8. Singh, M., Acharya, N., Shukla, S., Shrivastava, D., & Sharma, G. (2021). Comparative study of endometrial & subendometrial angiogenesis in unexplained infertile versus normal fertile women. The Indian Journal of Medical Research, 154(1), 99.

9. Neykova, K., Tosto, V., Giardina, I., Tsibizova, V., & Vakrilov, G. (2022). Endometrial receptivity and pregnancy outcome. The Journal of Maternal-Fetal & Neonatal Medicine, 35(13), 2591-2605.

10. Elswah, H. A., Mohamed, E., & AYMAN, A. (2018). Doppler Study of Uterine and Ovarian Arteries in Cases of Unexplained Infertility(Case Control Study). The Medical Journal of Cairo University, 86(September), 3197-3202.

11. Li, J., Ming-Der Chow, R., Vadivelu, N., & Kaye, A. D. (Eds.). (2021). Ultrasound Fundamentals: An Evidence-Based Guide for Medical Practitioners. Springer Nature..

12. El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet PE. (2017): Recurrent pregnancy loss: current perspectives: Devopress; 331—345.

13. Nori, W., Shallal, F., & Zghair, M. A. G. (2020). Aspirin Effect on Mid Luteal Phase Doppler Indices in Patients with Recurrent Pregnancy Loss. International Journal of Pharmaceutical Research, 12(3), 2929-2934.

14. Yuan, B., Luo, S., Mao, J., Luo, B., & Wang, J. (2022). Effects of intrauterine infusion of platelet-rich plasma on hormone levels and endometrial receptivity in patients with repeated embryo implantation failure. American Journal of Translational Research, 14(8), 5651..

15. Mayer, R. B., Ebner, T., Weiss, C., Allerstorfer, C., Altmann, R., Oppelt, P., & Shebl, O. (2019). The role of endometrial volume and endometrial and subendometrial vascularization parameters in a frozen embryo transfer cycle. Reproductive Sciences, 26(7), 1013-1018.

16. Neumann, K., Depenbusch, M., Schultze-Mosgau, A., & Griesinger, G. (2020). Characterization of early pregnancy placental progesterone production by use of dydrogesterone in programmed frozen–thawed embryo transfer cycles. Reproductive BioMedicine Online, 40(5), 743-751.

17. Zhang, C. H., Chen, C., Wang, J. R., Wang, Y., Wen, S. X., Cao, Y. P., & Qian, W. P. (2022). An endometrial receptivity scoring system basing on the endometrial thickness, volume, echo, peristalsis, and blood flow evaluated by ultrasonography. Frontiers in Endocrinology, 13, 907874.

18. Varla-Leftherioti, M., Keramitsoglou, T., & Tsekoura, C. (2020). The Immunobiology of Recurrent Miscarriage. In Recurrent Pregnancy Loss (pp. 89-100). CRC Press.