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# ASSESSING UNEXPLAINED INFERTILITY: THE ROLE OF UTERINE ARTERY DOPPLER ULTRASOUND PARAMETERS

*Original Research*

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## ABSTRACT

**Background:** The objective of the study was to assess the diagnostic value of uterine artery Doppler in unexplained infertility

**Objective**: The objective of this study was to evaluate the diagnostic effectiveness of uterine artery Doppler ultrasound parameters in distinguishing unexplained infertility from fertile controls in women.

**Methods**: We conducted a case-control study on unexplained infertility at a Public Tertiary Hospital in Rawalpindi from April 2023 to March 2024. The study included 105 cases of women with unexplained infertility and 35 control women with documented fertility. Women in the case group met specific criteria for unexplained infertility, while controls had successful pregnancies and no known fertility issues. Both groups underwent transvaginal ultrasound and uterine artery Doppler assessments using the Xario 200 ultrasound machine, with experienced radiologists analysing the results.

**Results**: In our study comparing women with unexplained infertility to fertile women, significant differences were found in vascular resistance (P= 0.00), endometrium thickness (P= 0.01), and systolic/diastolic ratio (P= 0.00). The Resistance Index and Systolic/Diastolic ratio had perfect discriminatory power (AUC=1.000), indicating strong diagnostic accuracy, while the Pulsatility Index also showed good performance (AUC=0.986).

**Conclusions**: Uterine artery Doppler indices were higher in unexplained infertile women. The sensitive and specific uterine artery Doppler indices identify excessive uterine blood flow impedance. Uterine artery Doppler may identify high uterine blood flow impedance, helping diagnose unexplained infertility.

**Keywords**: Uterine artery Doppler, Infertility diagnosis, Unexplained infertility, Fertility assessment, Blood flow impedance, Pulsatility index, Resistance index, Transvaginal ultrasound, Fertility treatment, Endometrial receptivity, Systolic/Diastolic ratio, Reproductive health.

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## INTRODUCTION

Infertility is characterized as the inability to achieve conception after one year or more of regular and non-protected sexual intercourse (1). Unexplained infertility is the inability to conceive even after one year of frequent unprotected sexual intercourse, and all tests indicating that the woman's cycle is normal and all factors supporting fertility are present (2).

Around 1 in 6 individuals, or approximately 17.5% of the adult global population, are afflicted with infertility; this underscores the critical need to increase the accessibility of affordable, high-quality fertility treatments (3). Between 10 and 25% percent of women experiencing infertility encountered an enigma: no specific cause could be identified, leading to a diagnosis of unexplained infertility (4).

The implantation of an embryo into the uterus is mainly dependent on the receptivity of the uterine endometrium and the content of the ovum. Optimal endometrial growth is of paramount importance in attaining successful implantation, given the association between endometrial atrophy and reduced rates of pregnancy. Uterine artery blood flow and endometrial perfusion are elements that exert an influence on uterine endometrial receptivity. A sufficient supply of blood to the uterus is critical for promoting healthy endometrial receptivity and growth. Conversely, compromised endometrial growth and thinning may result from impaired blood flow through the uterine arteries (2,5). Reduced uterine artery blood flow and endometrial perfusion may potentially be factors in unexplained infertility, recurrent abortions, and in vitro fertilization (IVF) failures, according to several studies (6,7). Research has noted that uterine artery impedance is greater in women experiencing inexplicable infertility than in fertile women. This finding suggests that reduced uterine artery blood flow and perfusion may play a role in cases of unexplained infertility (8,9).

Ultrasound serves as a highly effective tool in comprehensively studying the female reproductive system, playing a crucial role in monitoring functional changes in the menstrual cycle (either spontaneous or artificially induced). In particular, transvaginal ultrasound emerges as an important diagnostic tool in finding the causes of Infertility by evaluating endometrial vascularity, assisting in embryo transfer timing, and predicting pregnancy outcomes (10).

Doppler ultrasonography is important in the monitoring of the changes in blood flow that occur throughout the menstrual cycle. Doppler ultrasonography of the uterine arteries is particularly important, the flow of blood to the ovaries, uterus, and the endometrium is highly associated with pregnancy outcomes of assisted reproduction technology. As such the increase in the degree of blood flow and the decrease in the amount of resistance within the said body parts is always quite high in the luteal phase, to access the degree of previous, the uterine arteries impedance is usually assessed (11,12, 13). Doppler analysis of endometrial perfusion and uterine artery blood flow is especially beneficial in determining the cause of unexplained infertility. Comparing uterine artery Doppler parameters, such as resistance and pulsatility indices, between fertile controls and women with unexplained infertility was the objective of the present study.

## METHODS

A case-control study was conducted in the Department of Radiology at Public Tertiary Hospital in Rawalpindi. The study was conducted between April 2023 to March 2024.

The study population was divided into controls and cases. The Case Group comprised Women diagnosed with unexplained infertility according to established criteria (e.g., failure to conceive after one year of regular unprotected intercourse, normal semen analysis, patent fallopian tubes, ovulatory cycles, and normal uterine cavity assessed via hysterosalpingography or hysteroscopy) (2). The Control Group included fertile women with a history of at least one successful conception and delivery and visiting the department for any other gynecology issue.

Married women aged ≥ 18 years were included in the study. For the cases group, women who had been actively attempting to conceive for at least one year without success were eligible. In contrast, parous non-lactating women, indicated by at least one successful pregnancy, were included in the control group. Participants with known causes of infertility, including conditions like tubal obstruction, endometriosis, or polycystic ovary syndrome (PCOS), were excluded from the study. Additionally, individuals with a history of recurrent pregnancy loss or pregnancy complications were not included. Women with significant medical conditions known to impact fertility were also excluded from the study to ensure a more homogeneous study population for the investigation of uterine artery Doppler in assessing unexplained infertility.

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The sample size determination was derived from a reported 10.1% prevalence of unexplained fertility based on findings by Fenning et al., (4). By employing a 95% confidence interval and 5% margin of error, the total required sample size amounted to 140 as calculated using an online sample size calculator.

To identify cases, we collaborated closely with the gynecology department, screening potential participants for eligibility based on our inclusion criteria. Women diagnosed with unexplained infertility, met specific criteria such as unsuccessful attempts to conceive for at least one year despite regular unprotected intercourse and absence of known fertility-affecting conditions, were approached to join the case group. On the other hand, recruiting controls involved reaching out to women with documented fertility, typically through community outreach programs and routine gynecological consultations. These women had a history of successful pregnancies and were visiting the department for general gynecological issues unrelated to infertility. By recruiting controls from a diverse pool of fertile individuals, we aimed to create a balanced comparison group for our study.

Our study required specific criteria for the control group, such as documented fertility, successful pregnancies, and no known fertility issues. However, finding enough eligible controls was challenging due to the rarity of participants meeting these criteria. Adding to this challenge was the recommendation for fewer transvaginal ultrasound assessments for the control group. This procedure, though commonly used, is typically advised less for women with documented fertility and no ongoing fertility concerns. This reduced use of transvaginal ultrasound further limited our pool of eligible participants, making it harder to meet all the criteria for inclusion in the control group.

We aimed for a 1:1 ratio of cases to controls but faced limitations in achieving this goal despite extensive recruitment efforts. Thus 3: a 1 ratio of cases to controls were recruited. The total cases were 105 and 35 married women. Both cases and controls were provided with detailed information about the study objectives, procedures, and potential benefits and risks before obtaining informed consent. Ethical considerations and privacy were considered throughout the recruitment process, ensuring confidentiality and respect for participants' autonomy.

Transvaginal ultrasound examinations and bilateral uterine artery Doppler assessments were conducted utilising the “Xario 200 ultrasound device”, manufactured by “Toshiba” in Japan under the “Canon Medical System” brand. The apparatus was equipped with an endovaginal instrument operating at 7.5 MHz. The sagittal plane was utilized by the seasoned radiologists to create images of the uterus and determine the thickness of the endometrium. Following this, the transducer was positioned laterally to traverse the external iliac vessels and detect the uterine artery. To assess the Doppler waveforms of the uterine artery, three consecutive identical waveforms were captured after the insonation angle being adjusted and the Doppler waveform being activated. The Doppler waveform was assessed using straightforward semi-quantitative techniques. The evaluation primarily focused on form analysis and the measurement of Doppler spectral parameters, including the “systolic/diastolic ratio” (S/D ratio), “resistance index” (RI), and “pulsatility index (PI)”.

## RESULTS

Our study sample was based on two groups: the Case group (Group 1) and the Control group (Group 2). The initial cohort (referred to as the case group) consisted of 105 females, aged 30.6 ±3.97 years on average, who had been diagnosed with unexplained infertility. The mean age of the 35 fertile women comprising the control group was 29.6 ± 4.47 years. Regarding age, no statistically significant difference was observed between the study groups (P = 0.38).

Comparisons between the two groups were conducted using an independent T-test across several parameters. The case group exhibited a significantly higher Resistance Index (RI) at 0.80 ± 0.03 compared to the Control Group, RI of 0.51 ± 0.03 (p-value = 0.00), suggesting notable differences in vascular resistance between the groups. Additionally, the Systolic/Diastolic (S/D) ratio was markedly higher in Group 1 at 8.66 ± 1.2 compared to Group 2's 2.84 ± 0.23 (p-value = 0.00*), further highlighting distinct vascular function profiles between the two groups. Conversely, the Pulsatility Index (PI) did not exhibit a significant difference (p-value = 0.13) despite numerical disparities, suggesting similar pulsatility trends across both groups (Table 1).

**Table 1. Comparison of Doppler findings in cases and controls**

| Variables | Group 1 (Cases) N=105 | Group (Controls) N=35 | P value |
|---|---|---|---|
| RI | 0.80± 0.03 | 0.51± 0.03 | 0.00* |
| PI | 2.77±.26 | 1.60± 0.08 | 0.13 |
| S/D | 8.66±1.2 | 2.84±0.23 | 0.00* |

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"RI= Resistance index, PI=Pulsatility index, S/D = systolic/diastolic ratio"; An Independent T-test was used; * P-value <0.05 is significant. The Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the diagnostic accuracy of Uterine Artery Doppler Ultrasound parameters in unexplained fertility. The results indicate strong discriminatory power for the "Resistance Index (RI) and Systolic/Diastolic (S/D) ratio", with both variables achieving a perfect Area Under the Curve (AUC) of 1.000. This suggests that RI and S/D ratio measurements are highly effective in distinguishing between individuals with unexplained fertility and those without. Additionally, the Pulsatility Index (PI) showed a high AUC of 0.986, indicating very good diagnostic performance in differentiating between the groups. These results underscore the potential utility of Uterine Artery Doppler Ultrasound parameters, particularly RI, PI, and S/D ratio, in aiding the diagnosis of unexplained fertility, while also highlighting the importance of considering potential biases in diagnostic statistics (Figure 1).

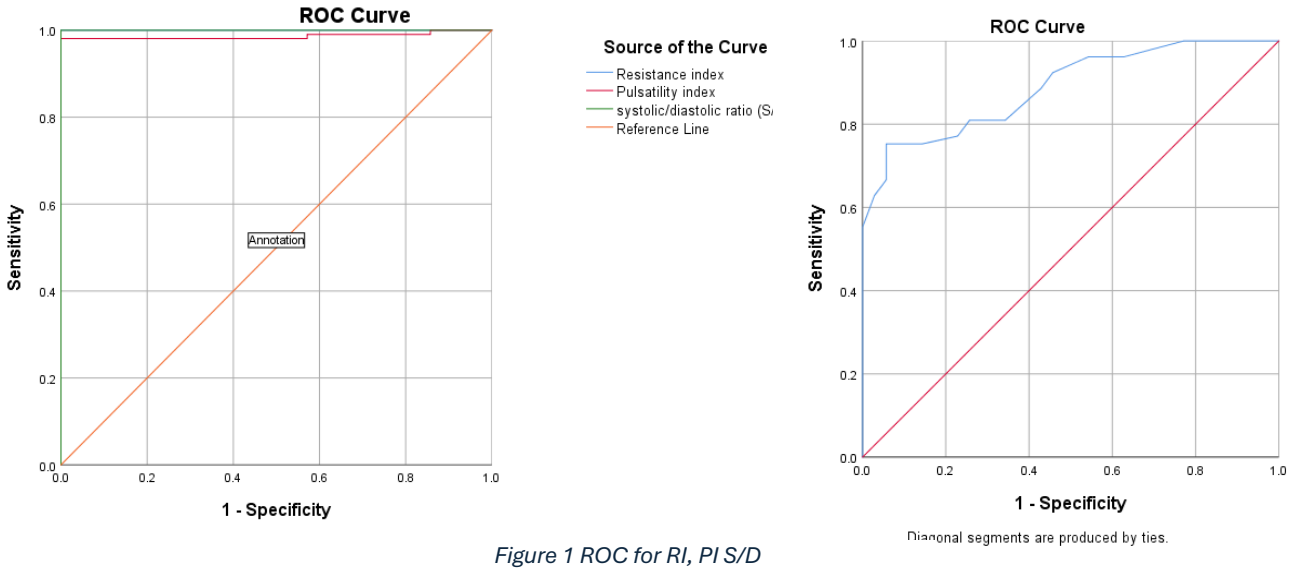


*Figure 1 ROC for RI, PI S/D*

## DISCUSSIONS

This research compared uterine artery indexes (specifically, RI, PI, and S/D) during the mid-luteal phase via transvaginal ultrasound to ascertain whether a statistically significant distinction can be identified between women experiencing unexplained infertility and fertile controls. There was no significant statistical difference observed in the age distribution of infertile women compared to their fruitful counterparts. The age of the two groups being comparable precluded age from being a confounding variable in this inquiry. Endometrium primary function is to provide temporary facilitation of embryo implantation. Resistance to obstetric implantation is a condition that persists in the uterine endometrium for the majority of the menstrual cycle. During the "luteal phase" of the menstrual cycle, the endometrium demonstrates distinctive receptive properties known as the implantation window (4). Multiple growth phases occur in the endometrium of the uterus during the course of the menstrual cycle. Endometrial proliferation initiates during the follicular phase of the menstrual cycle, after the menstrual period that precedes it. The endometrium experiences growth and endures a transition from the "proliferative phase" to the secretory phase during the luteal phase of the menstrual cycle. Endometrial growth continues until menstruation is induced by an abrupt decline in hormone levels (14).

During the course of a typical menstrual cycle, the blood flow impedance of the uterine and spiral arteries undergoes periodic changes. During "mid-luteal", the greatest resistance to blood flow occurs over the course of the menstrual cycle. During this phase, increased uterine blood flow enhances endometrial receptivity, which consequently raises the probability of embryo implantation being successful. Endometrial receptivity is evaluated via immunohistochemical analysis and endometrial biopsy, among other methods. Doppler ultrasonography is considered a simple and non-intrusive method for assessing the impedance of blood circulation in the arteries of the uterus. Moreover, it provides an indirect method for assessing the receptivity of the endometrium (4,5).

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In women experiencing unexplained infertility, endometrial perfusion is abnormally low during the pre-implantation phase, irrespective of endometrial measurement or hormonal profile (15). The relationship between sub-endometrial blood flow resistance and the onset of unexplained infertility has been the subject of numerous studies (15, 16, 17). The research methodology encompassed the assessment of transvaginal uterine artery Doppler indices in women who had been diagnosed with unexplained infertility during the pre-implantation phase of the mid-luteal phase of the menstrual cycle. The obtained data were compared to those of control groups consisting of fertile women. The results of the study revealed that uterine artery "resistance index (RI) and pulsatility index (PI")" values were significantly higher in women with unexplained infertility than in fertile women. When assessing the impedance of blood flow in the uterine artery, the "systolic/diastolic (S/D) ratio, resistance index (RI), and pulsatility index (PI)" are the Doppler indices of choice (18). The mean resistance index (RI) for the case group was 0.80 ± 0.03 SD, while for the control group it was 0.51 ± 0.03 SD. These results suggest that there is a statistically significant distinction between the two groups. These results are consistent with those of Zarad et al. (18), who documented mean RI values of 0.75 and 0.51, respectively, for the infertile and reproductive groups, indicating a substantial disparity in RI.

The case group displayed an average pulsatility index (PI) of 2.77 ± 0.26 standard deviations, whereas the control group averaged 1.6 ± 0.08 standard deviations; this disparity between the two groups was statistically significant. Consistent with the conclusions reached in prior research (16, 18, 19), these results provide additional evidence for the substantial discrepancy between fertile and infertile groups in terms of the mean pulsatility index (PI). Prior research by Chien et al. (20) revealed that resistance index (RI) and pulsatility index (PI) measurements of the uterine artery were diminished during menstrual cycles that culminated in conception as opposed to those that did not. Furthermore, an additional investigation revealed that 35% of in vitro fertilization (IVF) candidates with a mean pulsatility index (PI) of the uterine artery exceeding 3 were unsuccessful in conceiving (21). The findings of our research indicated that the average systolic/diastolic (S/D) ratio of the uterine artery was 8.66 ± 1.2 SD for the case group and 2.84 ± 0.23 SD for the control group. A statistically significant difference was observed in the systolic/diastolic (S/D) ratio between the case and control groups. Consistent with prior research, these findings provide additional evidence for their validity (18).

## CONCLUSIONS

In comparison to fertile women, uterine artery Doppler indices were greater in women with unexplained infertility. When it comes to detecting excessive uterine blood flow impedance, uterine artery Doppler indices are quite sensitive and specific. An important part of diagnosing unexplained infertility is uterine artery Doppler, which may detect excessive uterine blood flow impedance. Uterine artery Doppler should be part of any evaluation for unexplainable infertility.

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