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Uterine Artery Doppler and Subendometrial Vascularity in Unexplained Recurrent Pregnancy Loss

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Abstract

Background

Recurrent pregnancy loss (RPL) affects approximately 1–2% of couples; in some cases, a definite cause may not be found after complete evaluation. Impaired uterine and subendometrial vascularity has been suggested as a possible reason for failed implantation in these women.

Aims and Objectives

1. To assess uterine artery pulsatility index (PI) and resistance index (RI) in unexplained RPL cases and fertile parous controls during the mid-luteal phase.
2. To evaluate subendometrial vascularity using a four-zone colour Doppler grading system.
3. To compare above parameters between the two groups.

Methods

A case-control study was done at the Department of Radiodiagnosis, JJM Medical College over 6 months, with ethical approval and informed consent. Forty females aged 20–35 years were included, 20 with unexplained RPL (≥2 consecutive losses, no identifiable cause) and 20 age-matched fertile parous controls. Bilateral uterine artery PI &RI and subendometrial vascularity were assessed by Transvaginal colour Doppler ultrasound (GE Voluson E8) during the mid-luteal phase. Independent samples t-test and Fisher's exact test were used.

Results

The unexplained RPL group showed higher uterine artery PI (2.52 ± 0.13 vs 1.866 ± 0.17) and RI (0.84 ± 0.05 vs 0.739 ± 0.05) compared to controls ($p < 0.001$ for both). Subendometrial vascularity was limited to Zones 1–2 in 90% of RPL women and 20% of controls, while 80% of controls had Zones 3–4 vascularity compared to 10% in the RPL group ($p < 0.001$).

Conclusion

The RPL group showed higher uterine artery resistance and poor subendometrial vascularity compared to non RPL group, suggesting impaired uterine perfusion and reduced endometrial receptivity in them. Transvaginal colour Doppler assessment of these parameters can aid to identify women at risk and plan to improve pregnancy outcomes.

Keywords: Endometrial receptivity, recurrent pregnancy loss, subendometrial vascularity, uterine artery Doppler.

1a. Introduction

Recurrent pregnancy loss (RPL) is defined as loss of two or more consecutive pregnancies spontaneously occurring before the age of 20 weeks' gestation, which affects around 1–2% of couples. [1] Despite its low

prevalence it is one of the challenging conditions in reproductive medicine.

The etiology of RPL is heterogeneous, varies from genetic, anatomical, endocrine, immunological and thrombophilic causes. However, even with detailed evaluation a definite cause is not defined in some the number of cases, and is described as "unexplained RPL". [1] This subgroup is a diagnostic and therapeutic dilemma, as lack of detectable causes leaves with no clear pathway of management.

Recently, impaired endometrial receptivity is thought to be potential underlying mechanism in unexplained RPL. Optimal uterine perfusion and subendometrial vascularity are believed to be necessary for successful implantation and early placental formation. Decreased blood flow in uterine arteries, seen as high pulsatility index (PI) and resistance index (RI), have been shown as a marker of impaired uteroplacental perfusion in these women. [2] Habara et al. showed significantly increased uterine artery resistance in women with unexplained RPL at the non-pregnant phase of the midluteal phase, showing this as a persistent vascular abnormality independent of the pregnancy itself. [2]

Subendometrial vascularity, evaluated by colour Doppler ultrasound, adds information about endometrial blood supply at the level of implantation. Different studies reported significantly lower subendometrial blood flow in women with RPL compared to fertile controls, attributing impaired endometrial receptivity as contributing factor [3,4,5]. Three-dimensional power Doppler was employed to assess subendometrial vascularity quantitatively, and showed significantly lower vascularisation indices, in women with unexplained recurrent miscarriage [5]. However, the assessment of subendometrial vascularity on two-dimensional colour Doppler, by zonal grading system, is a more reproducible and readily available evaluation method for routine clinical practice.

Transvaginal colour Doppler ultrasound provides a non-invasive method to assess the hemodynamics of uterine arteries and subendometrial vascularity, at a non-pregnant phase, without the confounding effects in presence of pregnancy. The goal of the study was to evaluate uterine artery Doppler indices and subendometrial vascularity based on four-zone colour Doppler grading system, at midluteal phase, in women with unexplained RPL and to compare these parameters in fertile parous controls.

1b. Aims and Objectives

1. To assess uterine artery pulsatility index (PI) and resistance index (RI) in unexplained RPL cases and fertile parous controls during the mid-luteal phase.

2. To evaluate subendometrial vascularity using a four-zone colour Doppler grading system.

3. To compare above parameters between the two groups.

2. Materials And Methods

2a. Study Design: Case-control study

2b. Study Period: Six months, May 2025 to October 2025

2c. Study Area: The study was conducted at Department of Radiodiagnosis, JJM Medical College and Hospital, Davangere, Karnataka, India.

2d. Sample Size: Total of 40 women aged 20–35 years were included - 20 women with unexplained RPL (cases) and 20 age-matched fertile parous women (controls).

2e. Inclusion Criteria

RPL Group (n=20)

- Women with a history of recurrent pregnancy loss, defined as two or more consecutive spontaneous abortions with no identifiable cause after RPL workup, were included in the study.
- This workup included uterine cavity assessment by ultrasound and hysterosalpingography. thyroid function test, coagulation profile and antiphospholipid antibody syndrome screening.

Control Group (n=20)

Age-matched fertile parous women with at least one successful live birth and no history of pregnancy loss were included.

Both Groups: Regular menstrual cycles of 25–35 days duration.

2f. Exclusion Criteria

The following were excluded from both groups:

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1. Uterine abnormalities - congenital malformations, fibroids, adenomyosis.
2. Polycystic ovarian syndrome
3. Active pelvic inflammatory disease
4. Systemic diseases which affect vascular function - diabetes mellitus, hypertension, thrombophilias and connective tissue disorders.
5. Hormonal medications or intrauterine devices

2g. Methodology

All participants underwent transvaginal ultrasound examination (GE Voluson E8) during the mid-luteal phase (cycle days 19–23), corresponding to the presumed implantation window following written consent and ethical approval.

Uterine Artery Doppler Assessment

Bilateral uterine arteries were identified at the level of the internal cervical os using colour doppler. Spectral Doppler waveforms were obtained and mean values of pulsatility index (PI) and resistance index (RI) were calculated.

Subendometrial Vascularity Assessment

Subendometrial vascularity was assessed in the mid-sagittal plane using a four-zone colour Doppler grading system as described by Malhotra et al. [6]

The zones were defined as follows

1. **Zone 1:** myometrium surrounding the endometrium
2. **Zone 2**: hyperechoic endometrial edge
3. **Zone 3:** internal hypoechoic endometrial zone
4. **Zone 4:** endometrial cavity.

Higher zone indicates deeper subendometrial vascular penetration which reflects better endometrial receptivity.

2h. Statistical analysis

Data were analysed using MedCalc statistical software, version 23.5. Continuous variables (PI and RI) were compared between groups using independent samples Student's t-test. Categorical variables (subendometrial zone distribution) were analysed using Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

3.Results

40 women were included case-control study, 20 cases unexplained recurrent pregnancy loss (RPL group) and 20 age-matched fertile parous controls.

3a. Uterine Artery Doppler Indices

Mean uterine artery PI was higher in the RPL group 2.52 ± 0.13 compared to 1.866 ± 0.17 in the control group, with mean difference of 0.654 ($p < 0.001$). Mean uterine artery RI was higher in the RPL group (0.84 ± 0.05) compared to controls (0.739 ± 0.05), with mean difference of 0.101 ($p < 0.001$). (Table 1)

These parameters indicate impaired/poor uterine perfusion in women with unexplained RPL during the mid-luteal phase.

Table 1. Uterine Artery Doppler Indices between RPL and Control Groups

Parameter	RPL Group (n=20) Mean ± SD	Control Group (n=20) Mean ± SD	Mean Difference	p-value
Uterine Artery PI	2.52 ± 0.13	1.866 ± 0.17	0.654	**<0.001**
Uterine Artery RI	0.84 ± 0.05	0.739 ± 0.05	0.101	**<0.001**

PI = Pulsatility Index; RI = Resistance Index; SD = Standard Deviation. p-values derived from independent samples t-test. Statistical significance set at $p < 0.05$.

3b. Subendometrial Vascularity

Subendometrial vascularity was assessed mid-sagittal plane using a colour Doppler zonal grading system (Zones 1–4), with higher zones indicating deeper vascular penetration into the endometrium.

In the RPL group, 8 women (40%) showed vascularity confined to Zone 1 alone, and 10 women (50%)

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showed vascularity reaching Zone 2, 90% of RPL patients (n=18) having poor subendometrial vascularity confined to Zones 1–2.

In contrast to RPL group, control group showed no cases where vascularity is restricted to Zone 1. Only 4 controls (20%) showed Zone 2 vascularity, while the majority 10 controls (50%) showed Zone 3 vascularity and 6 controls (30%) showed Zone 4 vascularity. Controls demonstrated good vascular penetration, with 80% of controls (n=16) reaching Zones 3–4 vascularity.

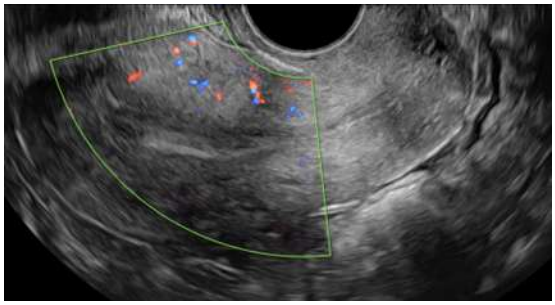
On Fisher's exact test, RPL group had higher odds of poor subendometrial vascularity (Zones 1–2) compared to controls (OR = 36.00, 95% CI: 5.80–223.55, p < 0.001). The wide confidence interval reflects the small sample size of this study. (Table 2)

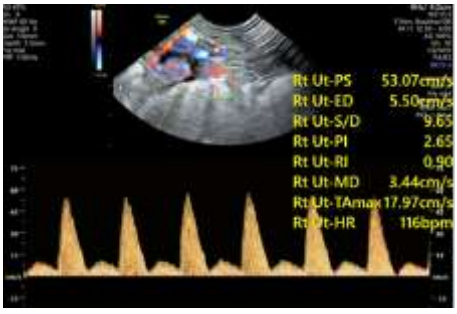
Table 2. Subendometrial Vascular Zone Distribution in RPL and Control Groups

Zone	RPL Group (n=20) n (%)	Control Group (n=20) n (%)
Zone 1	8 (40%)	0 (0%)
Zone 2	10 (50%)	4 (20%)
Zone 3	2 (10%)	10 (50%)
Zone 4	0 (0%)	6 (30%)

Zone grading based on colour Doppler signal penetration depth. Zones 1–2 = poor vascularity; Zones 3–4 = good vascularity.

Fig 1. TVS in a 28-year-old woman with recurrent pregnancy loss demonstrating (a)Zone 1 subendometrial vascularity and (b & c) uterine artery Doppler evaluation shows a mean pulsatility index (PI) of 2.6 and mean resistance index (RI) of 0.89.





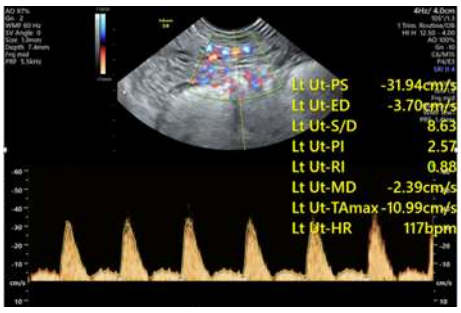


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Fig 2. Transvaginal colour Doppler ultrasound in a 30-year-old woman with unexplained RPL demonstrating (a)Zone 2 subendometrial vascularity. (b & c) Uterine artery Doppler assessment shows a mean PI of 2.56 and mean RI of 0.88.

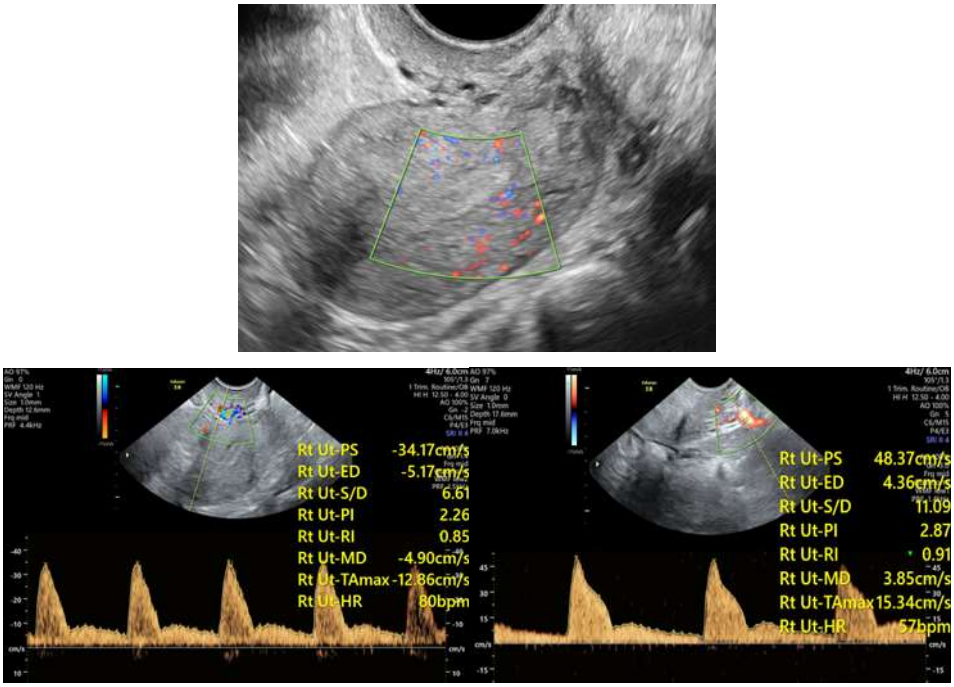
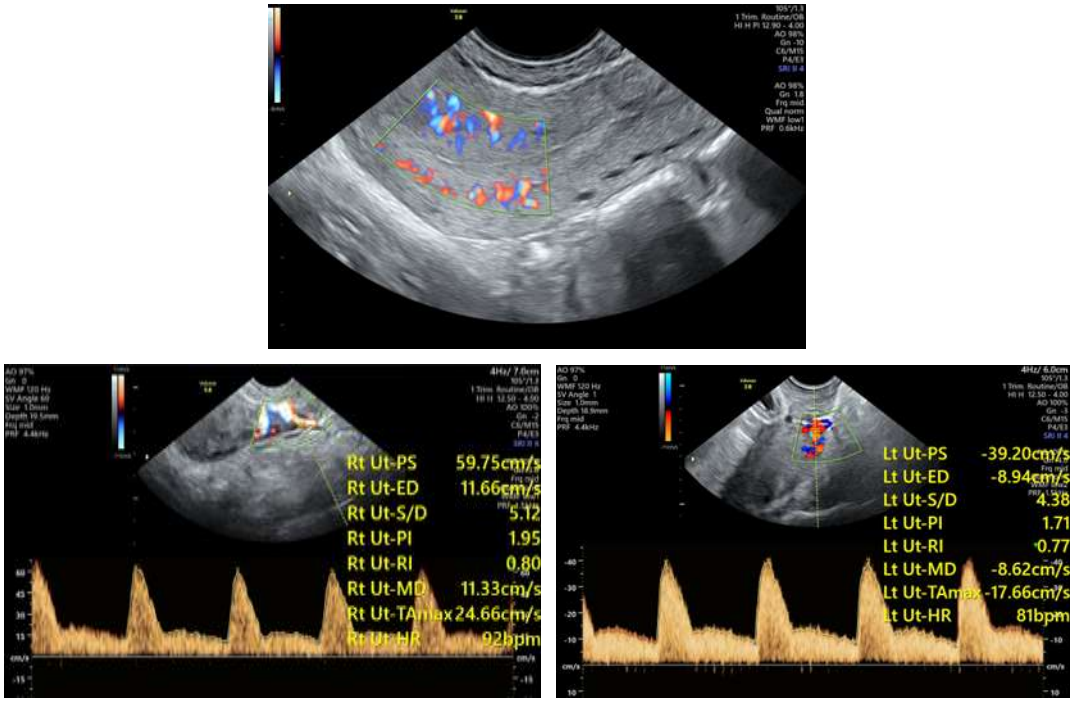


Fig 3. TVS in a normal fertile woman demonstrating (a) Zone 3 subendometrial vascularity, with vessels penetrating into the middle one-third of the endometrium. (b & c) Uterine artery Doppler shows mean pulsatility index (PI) of 1.8 and mean resistance index (RI) of 0.78, consistent with optimal uterine perfusion.



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4. Discussion

Both parameters uterine artery doppler indices and subendometrial vascularity demonstrated significant differences between the two groups, suggesting impaired uterine perfusion. Reduced uterine perfusion as potential contributing factor for reduced endometrial receptivity in unexplained RPL.

Mean uterine artery PI was higher in the RPL group compared to the controls (2.52 ± 0.13 vs 1.866 ± 0.17, p <0.001), these findings align with Habara et al., which was the first study to demonstrate significantly elevated uterine artery resistance in women with unexplained RPL during non-pregnant mid-luteal phase, and concluded that reduced uterine perfusion during the luteal phase compromises endometrial receptivity and leads to unfavourable environment for implantation. [2]

Ferreira et al. also reported that higher uterine artery PI in RPL women compared to controls (2.71 ± 0.54 vs 2.30 ± 0.44, p <0.05), suggesting reduced uterine perfusion, as persistent vascular abnormality in the non-pregnant state. [7] Yang et al. studied mid-luteal phase uterine artery hemodynamics in RPL and reported significantly higher PI and RI in the RPL group compared to controls, which is similar to present study. [8]

The mean uterine artery RI was also higher in the RPL group comparted to the controls (0.84 ± 0.05 vs 0.739 ± 0.05, p <0.001). These findings align with Zhong et al., demonstrated higher resistance indices in RPL patients with adverse pregnancy outcomes compared to controls, and Cao et al., similarly reported elevated uterine artery resistance in women with recurrent spontaneous abortion. [9,10] El-Mashad et al. and Anwar et al. also reported significantly higher PI and RI values in RPL women compared to controls. [11,12]

The elevated PI and RI values observed in the RPL group suggests increased resistance to uterine blood flow, which reflects inadequate uteroplacental perfusion, which may represent a pre-existing vascular insufficiency that contributes to recurrent implantation failure.

On subendometrial vascularity assessment, 90% of RPL women showed colour flow restricted to Zones 1–2 compared to only 20% of controls, these findings indicate reduced endometrial vascular penetration in women with unexplained RPL.

Wahab et al. similarly reported significantly impaired subendometrial blood flow in RPL patients compared to fertile controls using colour Doppler assessment, supporting reduced endometrial vascularity as a feature of unexplained RPL. [3] Mansour et al. found reduced subendometrial vascularity alongside abnormal uterine artery flow velocity waveforms in RPL women, demonstrating that macrovascular and microvascular impairment coexist in this condition. [4] Elhessy et al. and Mostafa et al. similarly reported significantly reduced subendometrial blood flow in RPL women compared to controls, consistent with present study findings. [13,14]

Chen et al. used three-dimensional power Doppler to demonstrate significantly lower vascularisation indices in the subendometrial zone in women with unexplained recurrent pregnancy loss compared to fertile controls. [5] Three-dimensional power Doppler provides more quantitative assessment of subendometrial vascularity, the four-zone colour Doppler grading system used in the present study is simpler, reproducible, and accessible alternative. El Garhy et al. similarly used two-dimensional colour Doppler assessment of subendometrial vascularity in RPL and demonstrated findings consistent with our results, supporting the utility of this approach. [15]

The odds ratio of 36.00 for poor subendometrial vascularity in the RPL group suggests a strong association between reduced endometrial vascular penetration and unexplained RPL. The wide confidence interval (5.80–223.55) is acknowledged and is due to small sample size of this study. Larger studies are needed to provide more precise estimates.

Most published studies have assessed either parameter in isolation. Impaired macrovascular flow (elevated PI and RI) with reduced microvascular penetration (poor subendometrial zone distribution) provides complete picture of uterine vascular insufficiency in unexplained RPL. The mid-luteal phase was chosen, as it corresponds to the implantation window, when subendometrial vascularity is most physiologically relevant and endometrial receptivity is at its peak.

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Impaired uterine perfusion in women with unexplained RPL is further supported by interventions targeting to increase the uterine blood flow and have shown beneficial effects in RPL group. Abdel-Razik et al. demonstrated nitric oxide donors significantly improved uterine artery blood flow and subendometrial vascularity in RPL group, suggesting that vascular impairment represents modifiable contributing factor in this condition. [16] Similarly, Al-Thuwaynee et al. demonstrated improved endometrial blood flow and thickness with sildenafil and nifedipine in women with recurrent first-trimester miscarriage. [17] These findings together suggests that impaired uterine perfusion is not merely an association but play a pathophysiological role in unexplained RPL.

Limitations

The sample size of 20 women per group represents a convenience sample; larger studies with adequate power are needed to confirm and assess these findings. Uterine cavity assessment was done by hysterosalpingography and ultrasound rather than hysteroscopy, and minor intracavitary abnormalities may have been missed. Parental karyotyping was not performed, possibility of chromosomal causes contributing to RPL in some cases cannot be entirely excluded.

5. Conclusion

Present study demonstrated that women with unexplained recurrent pregnancy loss have higher uterine artery doppler indices and markedly reduced subendometrial vascular penetration during the mid-luteal phase compared to controls. Both macrovascular and microvascular parameters suggests that uterine vascular insufficiency may represent a contributing mechanism in women with otherwise unexplained recurrent pregnancy loss.

Transvaginal colour Doppler assessment of uterine artery PI and RI with four-zone subendometrial vascularity grading is non-invasive and clinically accessible means for evaluating endometrial receptivity in the non-pregnant state. These parameters may serve as useful adjuncts in the evaluation of women with unexplained RPL and may help guide targeted therapeutic interventions at improving uterine perfusion.

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