

## Evaluation of Doppler Study of Uterine Artery and Subendometrial Blood Flow in Unexplained Recurrent Pregnancy Loss

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### ABSTRACT

**Background:** Abortion is considered recurrent when it happens spontaneously and successively at least two times. Recurrent pregnancy loss (RPL) can occur due to maternal or fetal factors. Studies recommend that uterine artery perfusion could control endometrial receptivity, and that poor uterine perfusion may be a main cause of unexplained abortion. **Objective:** The aim of the current study is to investigate the ability of uterine Doppler in assessing uterine causes of RPL.

**Patients and methods:** A case-control study was carried out on females attended to Fetal Medicine Care Unit at Mansoura University Hospital and Damietta General Hospital, from November 2019 to November 2020. The study included 160 of non-pregnant women, who were divided into 2 groups; *Group A* included 80 participants presented with a history of idiopathic recurrent pregnancy loss (RPL group), and *Group B* included 80 participants who had no history of abortion and had at least one child born at term (Control group).

**Results:** There was statistically significant higher mean mid luteal endometrial thickness detected in case group than in control group ( $P<0.001$ ). The subendometrial blood flow resistance index was increased in RPL ( $P<0.001$ ). Significant increases in right and left uterine artery pulsatility index (PI) and resistance index (RI) were recorded in RPL cases in comparison with the control group ( $P<0.001$ ).

**Conclusion:** Uterine Doppler is a simple available method that can help in evaluation of RPL, especially PI and RI that were significantly increased in women with RPL.

**Keywords:** Spontaneous abortions, Recurrent pregnancy loss, Color Doppler, Pulsatility index.

### INTRODUCTION

Spontaneous abortion has been considered as the commonest complication of pregnancy and is described as the passage of a pregnancy before termination of 20 weeks gestation. It implies delivery of all or any part of the products of conception <sup>(1)</sup>. Prior to the termination of the first trimester, 40% of conceptions end in spontaneous abortion. The majority of losses develop at implantation time. About 17.5% of clinical pregnancies end in spontaneous abortion <sup>(2)</sup>.

Recurrent abortion could be described as at least two successive pregnancy losses prior to 20 weeks of gestation, with a fetus weighing less than 500gm <sup>(1)</sup>. Though the true incidence of spontaneous abortion isn't well identified, about 50% of clinically diagnoses pregnancies and 50% of chemically diagnosed pregnancies end in spontaneous abortion. Of note, about 80% of spontaneous abortions happen before 12 weeks gestation. About 1% of women are habitual aborters. In addition, there is a substantial controversy in the context of the cause and correlation; as the actual pathophysiological mechanisms of the most identified causes haven't been accurately clarified. The majority of women with RPL probably have a lot of predisposing factors for miscarriage <sup>(3)</sup>.

Uterine perfusion is important in the context of accomplishing a normal pregnancy. Researches recommend that uterine artery perfusion could control endometrial receptivity, and that recommend uterine perfusion might a main cause of unexplained abortion <sup>(4)</sup>. Color Doppler could be utilized as a complementary approach to grayscale radiology to obtain data in the

context of the existence, direction and velocity of blood flow <sup>(5)</sup>. Prior to pregnancy, blood flow of the uterine artery reveals high resistance to absent or reversed diastolic flow. The PI of uterine artery is identified to reduce markedly throughout the luteal phase during which implantation develops <sup>(6)</sup>.

The aim of the current study is to investigate the ability of uterine Doppler in assessing the subendometrial and uterine artery blood flow (UABF) and pattern of waveform of uterine artery RPL patients, in comparison with normal controls.

### PATIENTS AND METHODS

A case-control study was carried out on females attended to Fetal Medicine Care Unit at Mansoura University Hospital and Damietta General Hospital, from November 2019 to November 2020. The study included 160 of non-pregnant women, who were divided into 2 groups; *Group A* included 80 participants presented with a history of idiopathic recurrent pregnancy loss (RPL group), and *Group B* included 80 participants who had no history of abortion and had at least one child born at term (Control group).

They presented to the clinic seeking for contraception. All females enrolled in the study had recurrent abortion (at least 2 times) and had regular cycles for the preceding 3 months before the study with no history of hormonal contraception or intrauterine devices.

**Exclusion criteria:** Cases with uterine aberrations, uterine fibroids or polypi from the study, cases with bleeding tendencies, hypercoagulable conditions,

endocrine and autoimmune disorders that might interfere with the hemodynamic indices, cases received acetyl salicylic acid or heparin and cases with medical problems which include diabetes, hypertensive heart disease, kidney disorders, and autoimmune diseases were excluded.

## Methods

Entire participants were subjected to history taking including personal history (name, age, duration and number of marriage, parity, and special habits especially smoking), menstrual history (any abnormal bleeding or amenorrhea), obstetric history (stressing on abortion, gravidity and parity), past history of any gynecological operation (e.g., cauterization for cervical erosion) and family history of any gynecologic malignancy (e.g., cancer breast or colorectal carcinoma).

### Type of ultrasound machine

Transvaginal ultrasound was carried out for whole comprised subjects. All scan was performed using Samsung H60 (South Korea) with transvaginal probe 4-9 MHz in the mid luteal phase. Evaluation comprised uterine size and dimensions: longitudinal diameter, transverse and AP diameters, myometrial evaluation, endometrial thickness, evaluation of ovarian textures, evaluation of the Douglas pouch and ruling out any abnormal conditions.

### Technique

The vaginal probe was covered with an examining glove comprising a small amount of gel. The gel ensured good contact between the transducer and the overlying glove. Care was taken to evade trapping any air bubbles that might create unwanted artifacts on the screen. Cross infection was prevented by the use of probe cover and disinfectants.

With the women lying in the lithotomy position after evacuating her urinary bladder, the transvaginal probe was introduced in a gentle manner into the vagina and positioned in the anterior fornix, and the internal cervical os and external os were identified, and uterus was examined to assess any uterine anomaly that might interfere with pregnancy such as uterine septum, bicornuate uterus, uterine myomas and to assess and measure the endometrial thickness. The probe was after that moved laterally and the right uterine artery was recognized, by utilizing color Doppler in box

magnification cursor, as an aliasing vessel running along the side of the cervix at the level of the internal OS, after that the left one was recognized in an identical manner. Pulsed wave Doppler was utilized to get clear, consistent, flow velocity waveforms of both uterine arteries. RI and PI ( $PI = S-D/\text{mean}$ ) are measured bilateral. Doppler signal was performed to evaluate subendometrial blood flow RI, type of Doppler waveform, and uterine artery PI in the midluteal stage for all cases and controls<sup>(7)</sup>.

### Ethical Consideration:

**This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Mansoura University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.**

### Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as means and standard deviation (SD) or median and range (minimum and maximum). Independent sample t-test/ Mann-Whitney U test was used for comparison of two independent groups. P value  $\leq 0.05$  was considered to be statistically significant. The diagnostic performance of a test or the accuracy of a test to discriminate diseased cases from non-diseased cases was evaluated using ROC curve assessment. Binary stepwise logistic regression analysis was utilized for prediction of independent variables of binary outcome. AOR and their 95% CI were measured.

## RESULTS

The Regarding the characters of the studied groups, there was no significant difference between both groups regarding the age, number of marriages, and number of gravidities, while there was significant difference between the both groups in regard to number of parity and number of abortion (**Table 1**).

**Table (1): Characters of the studied groups.**

Personal history	Cases (N=80)	Control (N=80)	Test of significance
Age/years Mean±SD	31.60±4.37	30.28±4.26	t=1.94 P=0.05
Number of marriage's Median (range)	1(1-2)	1 (1-2)	Z=1.91 P=0.057
<b>Obstetric history</b>			
Gravidity Median (range)	3 (2-6)	3 (1-5)	Z=0.75 P=0.45
Parity Median (range)	0 (0-3)	3 (1-5)	Z=9.72 P<0.001*
Abortion Median (range)	3 (2-4)	0 (0-1)	Z=11.20 P<0.001*

There was statistically significant higher mean mid luteal endometrial thickness detected in case group than in control group (Table 2).

**Table (2): Comparison of transvaginal ultrasound findings between cases and control groups.**

Transvaginal US	Cases N=80	Control N=80	Test of significance
Uterine volume	4.81±0.62	4.79±0.88	t=0.13, P=0.89
Mid luteal Endometrial thickness/mm	0.94±0.23	0.811±0.17	t= 3.28, P=0.001*

The mean Sub-endometrial blood flow RI, mean right uterine artery PI, mean right uterine artery RI, mean left uterine artery PI, and mean left uterine artery RI were significantly higher among cases than controls (Table 3).

**Table (3): Comparison of Doppler findings among studied groups.**

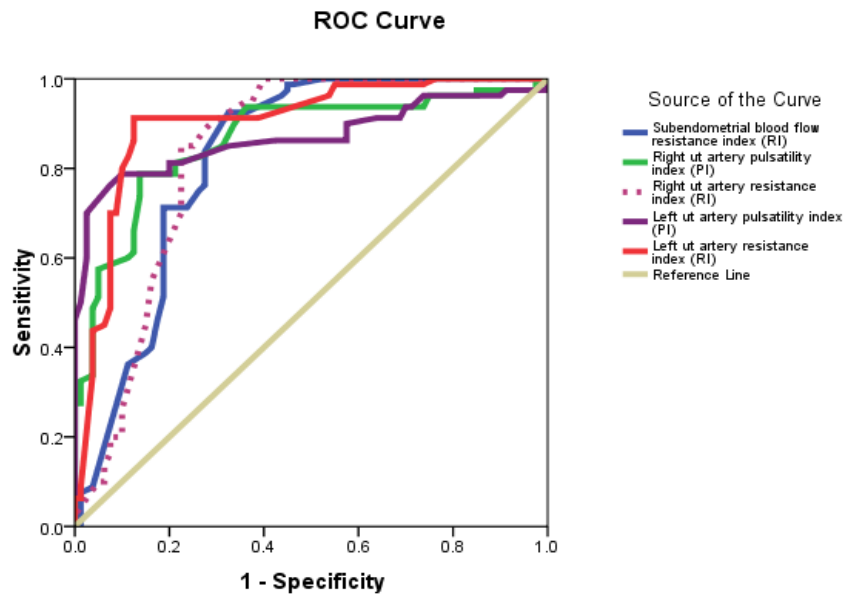
Doppler	Cases N=80	Control N=80	Test of significance
Subendometrial blood flow resistance index (RI)	0.88±0.07	0.70±0.39	t=3.92, P<0.001*
Right uterine artery pulsatility index (PI)	2.4±0.24	2.08±0.22	t= 9.38, P<0.001*
Right uterine artery resistance index (RI)	0.86±0.06	0.65±0.17	t=9.8, P<0.001*
Left uterine artery pulsatility index (PI)	2.56±0.28	2.24±0.18	t=8.58, P<0.001*
Left uterine artery resistance index (RI)	0.88±0.07	0.705±0.12	t=11.47, P<0.001*

Table 4 and Figure 1 demonstrate that ROC Curve was used to assess validity of uterine artery PI and RI in differentiating cases with recurrent abortion, and demonstrated that the most accurate index in differentiating recurrent abortion cases was left uterine artery resistance index (89.4%) followed by left uterine artery PI (80.6%), then right uterine artery PI (80.0%) and the least was for right uterine artery resistance index (79.4%). Area under ROC curve was excellent for all parameters ranging from 0.82 to 0.90.

**Table (4): Validity of Doppler findings in differentiation between cases with recurrent abortion.**

Variable	AUC (95%CI)	P value	Cut off point	Sensitivity	Specificity	PPV	NPV	Accuracy
Subendometrial blood flow resistance index (RI)	0.82 (0.75-0.89)	<0.001*	0.76	92.5%	67.5%	74%	90%	80%
Right ut artery pulsatility index (PI)	0.86 (0.80-0.92)	<0.001*	2.26	81.2%	78.8%	79.3%	80.8%	80%
Right ut artery resistance index (RI)	0.83 (0.76-0.90)	<0.001*	0.745	95%	63.8%	72.4%	92.7%	79.4%
Left ut artery pulsatility index (PI)	0.86 (0.80-0.92)	<0.001*	2.38	81.2%	80.2%	80%	81%	80.6%
Left ut artery resistance index (RI)	0.90 (0.85-0.95)	<0.001*	0.805	91.2%	87.5%	88%	90.9%	89.4%

AUC: Area Under curve, PPV: Positive predictive value, NPV: Negative predictive value.



Diagonal segments are produced by ties.

**Figure (1):** Receiver Operating Characteristics curve of Doppler resistant and pulsatility indices in prediction of recurrent abortion cases versus control group.

**Table 5** demonstrated that sub-endometrial blood flow RI, left uterine artery PI and left uterine artery RI are statistically significant predictors of recurrent abortion with the combination of these factors can predict 90% of recurrent abortion. Every increase one unit in the previous factors increases risk of recurrent abortion by 16.15, 10.95, 4.57 and 13.24, respectively.

**Table (5): Multivariate analysis for predictors of recurrent abortion among studied groups**

Doppler	B	P- value	AOR (95%CI)
Sub-endometrial blood flow resistance index (RI)	2.39	.02*	10.95 (1.43-12.58)
Right ut artery pulsatility index (PI)	2.43	.08	11.45 (0.69-13.78)
right ut artery resistance index (RI)	4.24	.13	16.1 (0.25-18.91)
left ut artery pulsatility index (PI)	3.69	.01*	4.57 (2.46-6.15)
left ut artery resistance index (RI)	16.39	<.001*	13.24 (1.24-20.54)
<b>Overall % predicted = 90%</b>			

β: regression co-efficient, AOR: Adjusted odds ratio

## DISCUSSION

Studies suggested that uterine artery perfusion could control endometrial receptivity and that poor uterine perfusion could be considered as a main cause of unexplained abortion<sup>(8)</sup>. The current study found statistically significant decreased parity among women with recurrent pregnancy (P<0.001). This goes in run with **Garhy et al.**<sup>(7)</sup> study which was conducted on 50 women with RPL in addition to 50 control to detect any change in uterine artery PI and found statistically significant decreased parity among women with RPL compared to the control group (P=0.001) which can be explained by their main problem (RPL).

The current study found statically significant decreased parity among women with RPL compared to control (P<0.001). This goes in run with a study by **Habets et al.**<sup>(9)</sup> that was conducted on 123 women with RPL and found statistically significant decreased parity compared to the control group (P<0.001)

The current study found statically significant increased abortion among women with RPL compared to control (P<0.001), this goes in run with **Güvey et al.**<sup>(10)</sup> study which was conducted to investigate the role of ferritin, CRP and WBCs as inflammatory markers for detection of RPL and found statistically significant increased abortion among women with RPL (P-value=0.004).

The current study found statistically significant increased mid luteal endometrial thickness assessed by US in women with RPL compared to controls (P-value=0.01). This goes in run with **Lazzarin et al.**<sup>(11)</sup> study which was conducted on 75 women with recurrent miscarriage to evaluate characteristics of uterine thickness using transvaginal US and revealed statistically significant increased endometrial thickness (5.8 mm) compared to control group (5 mm) with P-value <0.05.

The current study found statistically significant higher subendometrial blood flow resistance index in RPL (P<0.001). The current study found statistically significant higher Rt and Lt uterine artery PI in RPL cases compared to control group (P<0.001). This goes in run with **El-Mazny et al.**<sup>(12)</sup> study which was conducted to assess UABF using uterine Doppler for 40 women with unexplained infertility in addition to 40 control and found statistically significant higher uterine artery PI (P-value=0.003). Another study by **Habara et al.**<sup>(4)</sup> reported a statistically significant increased uterine artery PI in women with RPL compared to control group (P-value<0.01).

**Ferreira et al.**<sup>(13)</sup> study was conducted on 43 patients with unexplained recurrent abortion in addition to control group to evaluate uterine artery Doppler and found statistically significant higher PI in case group (2.71) than control group (2.3).

In contrast to **Yildiz et al.**<sup>(14)</sup> study which was conducted on 28 cases of RPL, in addition to 28 control

group to evaluate the relationship between RPL and uterine artery Doppler flow and revealed no statistically significant difference between both groups as regards PI and RI (P-values 0.703 and 0.333, respectively).

The current study found statistically significant higher Rt and Lt uterine artery RI in RPL women compared to control (P<0.001). This goes in run with **El-Mazny et al.**<sup>(12)</sup> study which found statistically significant higher RI in infertile women compared to fertile women (P-value=0.007). **Bao et al.**<sup>(15)</sup> study was performed on 139 women with RPL to assess if blood flow measurements by Doppler US of uterine radial artery and found RI was significantly greater in women with RPL (0.51) compared to women who had a live birth (0.42) (P<0.001).

**Ozkam et al.**<sup>(16)</sup> have recorded no significant differences in Doppler findings of uterine arteries of cases with first trimester threatened abortion, and control and this can be explained by different inclusion criteria.

The current study revealed that ROC curve analysis showed that subendometrial PI at cutoff point 0.765 had 92.5% sensitivity, 67.5% specificity for prediction of RPL. Another study by **Rifat**<sup>(17)</sup> was conducted on 39 women with normal intrauterine pregnancy, 28 females with threatened miscarriage and 18 with missed miscarriage to assess the role of uterine artery Doppler in prediction of miscarriage and revealed that PI at cutoff point 2.64 had 91% sensitivity, 81% specificity for miscarriage denoting that it can be used to predict the adverse pregnancy outcomes.

The current study revealed that ROC curve analysis shows that subendothelial RI at cutoff point 0.765 had 92.5% sensitivity, 76.5% specificity for prediction of RPL. **Bao et al.**<sup>(15)</sup> study also found that UA RI at cutoff point 0.45 had the most optimum balance of sensitivity (83.33%) and specificity (87.78%).

## CONCLUSION

Uterine Doppler is a simple available method that can help in evaluation of RPL being especially PI and RI being significantly increased in women with RPL.

**Conflict of interest:** The investigators declare no conflict of interest.

**Sources of funding:** The current study didn't receive any specialized grant from funding agencies.

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