Study of uterine artery Doppler velocity waveforms in patients with recurrent early pregnancy loss

A.I.Elmashad [١], Y.M.Edris [١], H.E.Abdel raziq [١], M.M.Elrab[١]

[١] Obstetrics and Gynecology, Dept., Faculty of Medicine, Benha Univ., Benha, Egypt

Abstract

Background: Unexplained Recurrent miscarriage remains a frustrating problem for the clinician and a distressing condition for the affected couple. Recurrent pregnancy loss is defined as three or more successive spontaneous abortion. The incidence of recurrent pregnancy loss is ١-٢٪ in the fertile population. The etiology is often unclear and may be multifactorial, with much controversy regarding diagnosis and treatment. This study aimed to find out any difference in uterine artery pulsitility index (PI) between women with history of recurrent unexplained first trimestric abortion and women without this history. Methods: This study was a case-controlled study which included ١٠٠ women attended to outpatient clinic of obstetrics and Gynecology Benha university hospitals to find out any difference in uterine artery pulsitility index (PI) between women with history of recurrent unexplained first trimestric abortion and women without this history. Results: The mean age in all women was ٢٩.٧٤ . in Study group, the mean age was ٣٠.١٨ ± ٤.٨٣ ranged between ٢١ to ٣٨ years while in Control group the mean age was ٢٨.٩٤ ± ٥.٧٧١ ranged between ٢٠ to ٣٧ years. There were no statistically significant differences between Study group and control group regarding the mean age. In Study group, the mean BMI was ٢٨.٤٧ ± ٤.٩٧ while in Control group the mean BMI was ٢٧.٥٨ ± ٣.٢١. The mean times of previous parity in study group was ٢.٠٢ ± ١.٠٢٣ while it was ٢.٦٢ ± ١.٣٣٨ in control group. There were no statistically significant differences between Study group and control group regarding the mean BMI and parity. There were no statistically significant differences between Study group and control group regarding the mean Serum Progesterone level which was Serum Progesterone ng/ml in study group and was ١٤.٤ ± ٢.١٤ ng/ml in control group.Regarding Pulsatility index (PI) in right uterine artery in Study group and control group there was a statistically significant difference with mean value ٢.٣٣ ± ٠.٤٩ and ٢.٧٢ ± ٠.٦٩ respectively which reflected increased resistance to blood flow in the right uterine artery in Study group. Comparing PI of left uterine artery in Study group and control group, revealed a significant difference, this indicated increased blood flow resistance in left uterine artery in Study group. As regards PI of both right and left uterine arteries in Study group and control group a statistically significant difference was found. Also we found a statistically significant difference between Study group and control group regarding RI. Based on ROC, the area under the curve was ٠.٩١٨ with a standard error of ٠.٠٣ (٩٥٪ CI: ٠.٨٦-٠.٩٨), which implied that the PI could perfectly predict the occurrence of the adverse outcome among pregnant women. Similarly, the cut-off value for PI was ٢.٦٥ at ٩٢٪ sensitivity and ٨١٪ specificity for miscarriage. Conclusion: Transvaginal ultrasonography colour Doppler flowmetry can be used to Assess uterine perfusion through measurement of uterine artery Doppler (PI) is recommended as routine investigation for women with Unexplained Recurrent miscarriage which helps in managements and treatment protocols.

Key words: uterine artery Doppler velocity waveforms - recurrent early pregnancy loss

١.Introduction:

Abortion is considered habitual or recurrent when it occurs spontaneously and consecutively at least ٣ times . Recurrent pregnancy loss (RPL) affects ٢٪ to ٥٪ of women, and its etiology can be categorized into fetal and maternal. The most common fetal causes are genetic, with autosomal trisomy responsible for about ٥٠٪ of abortions. However, many cases of abortion remain with no defined etiology. [١]

. The risk of recurrence increases with the maternal age and number of successive losses. Recurrent pregnancy losses may be attributable to treatable conditions such as hypercoagulable states, autoimmune diseases, endocrine disturbances or maternal anatomic abnormalities, and the high proportion of cases (up to ٤٠–٥٠٪) have unidentifiable causes. [٢]

Color Doppler is used in obstetrical ultrasound as a complementary tool to gain information about the presence, direction and velocity of blood flow. The pulsatility index (PI) of uterine artery has been known to diminish progressively during the luteal phase during which implantation occur. [٣]

Measurement of the uterine artery pulsatility index (PI) in the midluteal phase of spontaneous cycles might isolate patients with RPL associated with impaired uterine circulation. Transvaginal three-dimensional (٣D) power Doppler ultrasonography can detect subendometrial blood flow presented by the following indices: vascularization index (VI), flow index (FI), and vascular flow index (VFI) [٤]

Therefore, it has been proposed that measurement of uterine artery pulsatility index (PI) in the mid luteal phase of spontaneous

cycles might isolate patients with recurrent pregnancy loss associated with impaired uterine circulation [٥]

Studies suggest that uterine artery perfusion may regulate endometrial receptivity, and that poor uterine perfusion could be one of the causes of unexplained abortions and, probably, of faulty implantation. In an effort to elucidate the vascular changes that occur in women with recurrent abortion, and identify women with poor uterine perfusion, we compared uterine artery pulsatility index (PI) and flow velocity wave (FVW) patterns between women with no history of abortion and women with a history of unexplained RPL. [٦]

A poor uterine perfusion might be one of the causes of unexplained infertility, however, fewer studies correlates RPL and uterine arteries Doppler flowmetry . Some studies have been conducted to study uterine artery blood flow in patients with recurrent pregnancy loss, and it was found that elevated uterine arterial impedance is associated with recurrent pregnancy loss [٧]

The aim of this work was to find out any difference in uterine artery pulsitility index (PI) between women with history of recurrent unexplained first trimestric abortion and women without this history.

٢.Patients and methods

Type of study case-control study included one hundred women attending Outpatient Clinic of Obstetrics and Gynecology department, Benha University Hospitals. A written informed consent was obtained from each participant before participation and the study was approved by the hospital ethics committee of Benha University.

Subjects: this study was conducted from June ٢٠٢١ to june٢٠٢٢

٢.١Number of the patients:

The sample size were calculated by using Epi Info program version ٧ by adjusting the confidence interval to ٩٥٪, the margin of error accepted to ٥٪, the power of the test was set to ٨٠٪ and was found to be ١٠٠ women divided into two groups, each group consisted of ٥٠ patients:

١) **Group A (study group):** ٥٠ participants presented with a history of unexplained recurrent pregnancy loss.

٢) **Group B (control group):** ٥٠ participants who had no history of abortion and had at least ١ child born at term. They presented to the clinic seeking for contraception.

٢.٢Patient selection:
The following inclusion and exclusion criteria were applied to all patients:

٢.٣Inclusion criteria:

١. Three or more successive unexplained first trimestric abortion.
٢. Age between ٢٠-٤٠ years old.
٣. Regular menstrual cycles for the previous three cycles before the study.
٤. No hormonal contraception or intrauterine devices.
٥. Normal endocrinal status including serum thyroid-stimulating hormone, free thyroxin (T٤), glucose tolerance test and progesterone levels between days ١٩ and ٢١ of the menstrual cycle.

٢.٤Exclusion criteria:
The exclusion criteria were:

١. Systemic diseases that might affect the hemodynamic indices e.g. thrombocytopenia, thyroid disease, autoimmune disease cardiovascular disease, DM.etc.
٢. History of consanguinity.
٣. Family history of chromosomal abnormalities (e.g. trisomy ٢١, trisomy ١٣, Turner's disease …etc.).
٤. Patient age less than ٢٠ years or more than ٤٠ years old.
٥. Women in the follicular phase or menstrual phase.
٦. Women having uterine alterations on office hysteroscopy.
٧. Women having cervical incompetence on transvaginal ultra sonography.

٢.٥Study procedure:

All patients recruited give an informed consent and were subjected to the following:
Complete history:
Detailed history taken from women included:

- *Personal history* including their names, age, addresses, occupations, special habits, and history of consanguinity.
- *Present history:* Ask about any complaint, use of any medication.
- *Menstrual history* including regularity of cycles frequency, duration and amount of bleeding of each cycle, and date of the last menstrual period.
- *Obstetric history* including parity and method of previous deliveries, time at which previous abortions had been occurred and whether they had been followed by surgical evacuation or not, and ask about date of the last delivery or abortion.
- *Past history:* Past history of systemic diseases such as diabetes mellitus, hypertension, renal disease, past history of

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infants with chromosomal abnormalities such as trisomy ٢١, history of consanguinity, and past history of thyroid troubles.

- *Family history:* They were asked about family history of diabetes mellitus, hypertension, history of autoimmune disorders and history of chromosomal anomalies in the family.
- *Contraceptive history* with focus on use of oral contraceptive pills.

Clinical examination:

Clinical examination had been done including general, abdominal and pelvic examination.

- *General examination* included general appearance, weight and height (to calculate body mass index), vital signs (pulse, blood pressure, temperature and respiratory rate), signs of of thyroid disease, autoimmune disease, cardiovasculardisease, etc….
- *Breast examination* for swelling or nipple discharge.
- *Abdominal examination* to assure freedom of any organic clinically detectable pathologic lesions.
- *Pelvic examination* included inspection of the external genitalia, speculum examination of the vagina to rule out infection, and bimanual assessment of uterine size and position as well as exclusion of adnexal masses.

Technique of examination:

- The vaginal probe is covered with an examining glove containing a small amount of gel.
- The gel ensured good contact between the transducer and the overlying glove.
- Care is taken to avoid trapping any air bubbles, which might create unwanted artifacts on the screen.
- Cross infection is 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 is inserted gently into the vagina and placed in the anterior fornix, and the internal cervical os and the external one are identified, and uterus is examined to asses any uterine anomaly that might interfere with pregnancy such as uterine septum, bicornuate uterus, uterine myomas..etc.; and to assess and measure the endometrial thickness.
- The probe is then moved laterally and the right uterine artery is identified, using color Doppler, as an aliasing vessel running along the side of the cervix at the level of the internal OS, then the left one is identified by the same way.
- Pulsed wave Doppler is used to obtain clear, consistent, flow velocity waveforms of both uterine arteries. Pulsatility index (PI) and RI were calculated electronically for both uterine arteries and mean values were applied (PI=SD/mean) is measured bilaterally.
- The PI reported was the arithmetic mean for the last three cardiac cycles.
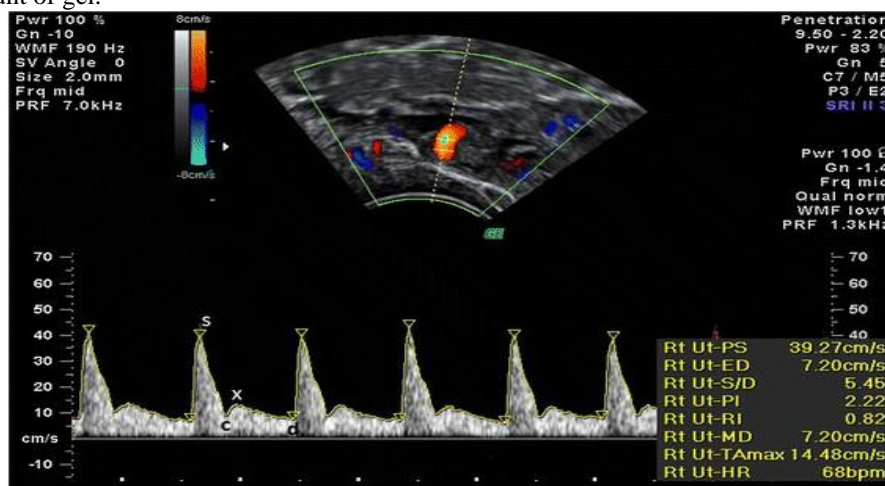
Doppler spectra of uterine artery flow. Pulsatility index (PI) is used as a measure of impedance of the flow of blood distal to the sampling point and is automatically calculated according to the formula PI = s − d mean where s is the peak d is the minimum and the average is the mean maximum Doppler shift frequency over the cardiac cycle. Resistance index (RI) is automatically calculated using the formula R I = s − d s s, peak systolic; d, end-diastolic; c, early diastolic; x, maximum diastolic frequency.

٣.Results:

The mean age in all women was ٢٩.٧٤ . in Study group, the mean age was ٣٠.١٨ ± ٤.٨٣ ranged between ٢١ to ٣٨ years while in Control group the mean age was ٢٨.٩٤ ± ٥.٧٧١ ranged between ٢٠ to ٣٧ years. There

were no statistically significant differences between Study group and control group regarding the mean age.

In Study group, the mean BMI was ٢٨.٤٧ ± ٤.٩٧ while in Control group the mean BMI was ٢٧.٥٨ ± ٣.٢١. the mean times of previous

parity in study group was ٢.٠٢ ±١.٠٢٣ while it was ٢.٦٢ ±١.٣٣٨ in control group. There were no statistically significant differences between Study group and control group regarding the mean BMI and parity.

Table (١) ases properties in both groups

Variable	Study group N=٥٠	Control group N=٥٠	P value
Age(years)			٠.١٦٤
-Range:	٢١:٣٨	٢٠:٣٧	
-Mean ± SD:	٣٠.١٨ ± ٤.٨٣	٢٨.٩٤ ±٥.٧٧١	
BMI			٠.٢٧٩
-Range:	٢٢.٥-٣٠	٢١-٣٢	
-Mean ± SD:	٢٨.٤٧ ± ٤.٩٧	٢٧.٥٨ ± ٣.٢١	
Parity			٠.٠٧
-Range:	١:٤	١:٥	
-Mean ± SD:	٢.٠٢ ±١.٠٢٣	٢.٦٢ ±١.٣٣٨	

There were no statistically significant differences between Study group and control group regarding the mean **Serum**

Progesterone level which was **Serum Progesterone ng/ml** in study group and was ١٤.٤ ±٢.١٤ ng/ml in control group.

Table (٢) Cases presentation in both groups

Variable	Study group N=٥٠	Control group N=٥٠	P value
Serum Progesterone(ng/ml)			
-Range:			٠.٠٦
-Mean ± SD:	١١.٥:١٦	١٢.٥:١٨	
	١٣.٩ ±٢.١٧	١٤.٤ ±٢.١٤	

Regarding Pulsatility index (PI) in right uterine artery in Study group and control group there was a statistically significant difference with mean value ٢.٣٣ ± ٠.٤٩ and ٢.٧٢ ± ٠.٦٩ respectively which reflected increased resistance to blood flow in the right uterine artery in Study group

Comparing PI of left uterine artery in Study group and control group, revealed a

significant difference, this indicated increased blood flow resistance in left uterine artery in Study group.

As regards PI of both right and left uterine arteries in Study group and control group a statistically significant difference was found. Also we found a statistically significant difference between Study group and control group regarding RI

Table (٣): Comparison of uterine artery (right , left and mean) PI between Study and control groups

PI	Study group n=٥٠	Controls n=٥٠	p value
right uterine artery	٢.٣٣ ± ٠.٤٩	٢.٧٢ ± ٠.٦٩	٠.٠٠٤
left uterine artery	٢.٢٦ ± ٠.٥٢	٢.٧٠ ± ٠.٥٧	< ٠.٠٠١
mean uterine artery	٢.١٠ ± ٠.٤٣	٢.٤٩ ± ٠.٥٩	٠.٠٠١
Average (٣ arteies)	٢.٣٠ ± ٠.٤٤	٢.٧١ ± ٠.٥٤	< ٠.٠٠١

Table (٤): Comparison of uterine artery (right , left and mean) RI between Study and control groups

RI	Study group n=٥٠	Controls n=٥٠	p value
right uterine artery	٠.٨٧ ± ٠.٢١	٠.٩٩ ± ٠.١٨	٠.٠٠٤
left uterine artery	٠.٨٩ ± ٠.١٩	١ ± ٠.١٥	< ٠.٠٠١
mean uterine artery	٠.٩١ ± ٠.١٥	١ ± ٠.١٣	٠.٠٠١

Based on ROC, the area under the curve was ٠.٩١٨ with a standard error of ٠.٠٣ (٩٥٪ CI: ٠.٨٦-٠.٩٨), which implied that the PI could perfectly predict the occurrence of the adverse

outcome among pregnant women. Similarly, the cut-off value for PI was ٢.٦٥ at ٩٢٪ sensitivity and ٨١٪ specificity for miscarriage.
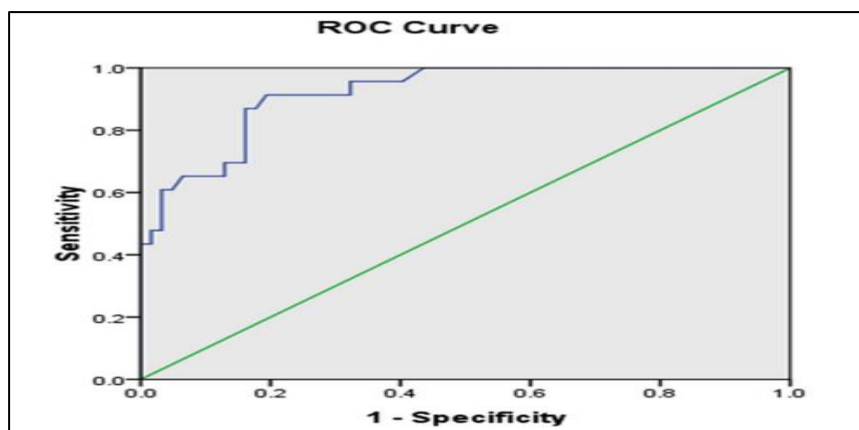
Fig (١) ROC curve

٤.Discussion

The mean age in all women was ٢٩.٧٤ . in Study group, the mean age was ٣٠.١٨ ± ٤.٨٣ ranged between ٢١ to ٣٨ years while in Control group the mean age was ٢٨.٩٤ ± ٥.٧٧١ ranged between ٢٠ to ٣٧ years. There were no statistically significant differences between Study group and control group regarding the mean age.

It was similar to Garhy et al., [٣] study the age of the patients in the recurrent miscarriage group and the control group was not significant (٢٨.٦ ± ٤.٦ years and ٢٦.٢ ± ٤.٧ years, respectively) (p = ٠.٠٦)

In The mean ± SD age was ٢٩.٨ ± ٦.٥ years in the RPL group and ٣٢.٧ ± ٤.٤ years in the control group. Most women had a history of ٣ (٧٦.٧٪) or ٤ (٢١.٠٪) abortions in the RPL group whereas most were primiparas (٤٤.١٪) or secundiparas (٤٨.٨٪) in the control group.

In Ferreira et al., [١] study, The mean ± SD age was ٢٩.٨ ± ٦.٥ years in the RPL group and ٣٢.٧ ± ٤.٤ years in the control group. Most women had a history of ٣ (٧٦.٧٪) or ٤ (٢١.٠٪) abortions in the RPL group whereas most were primiparas (٤٤.١٪) or secundiparas (٤٨.٨٪) in the control group.

In the present study, In Study group, the mean BMI was ٢٨.٤٧ ± ٤.٩٧ while in Control group the mean BMI was ٢٧.٥٨ ± ٣.٢١. the mean times of previous parity in study group was ٢.٠٢ ± ١.٠٢٣ while it was ٢.٦٢ ± ١.٣٣٨ in control group. There were no statistically significant differences between Study group and control group regarding the mean BMI and parity.

In the present study, there were no statistically significant differences between Study group and control group regarding the mean Serum Progesterone level which was Serum Progesterone ng/ml in study group and was ١٤.٤ ± ٢.١٤ ng/ml in control group.

In the present study, Regarding Pulsatility index (PI) in right uterine artery in Study group and control group there was a statistically significant difference with mean value ٢.٣٣ ± ٠.٤٩ and ٢.٧٢ ± ٠.٦٩ respectively which reflected increased resistance to blood flow in the right uterine artery in Study group

In the present study, Comparing PI of left uterine artery in Study group and control group, revealed a significant difference, this indicated increased blood flow resistance in left uterine artery in Study group. As regards PI of both right and left uterine arteries in Study group and control group a statistically significant difference was found . Also we found a statistically significant difference between Study group and control group regarding RI

A study done by Ziegler et al. [٨] concluded that low levels of progesterone during the luteal phase cause the uterine vascular impedance to increase. Therefore, the secretory endometrium was used as an inclusion criterion in women with RPL.

Inadequate blood flow would thus prevent implantation, although optimal uterine perfusion does not always mean pregnancy In Taher et al., [٤] study, they measured uterine artery PI in the luteal phase of spontaneous cycles. We found that uterine artery PI was significantly higher in the recurrent miscarriage group (٢.٣١٩ ± ٠.٥٣٠٩) compared with the control group (١.٦٨٩ ± ٠.٤٨٣٢) (P = ٠.٠٠٠). This finding is in agreement with many previous studies carried out on patients with RPL who reported mean PI values of ٢.٤٤ ± ٠.٤١ in their RPL group and ٢.١٩ ± ٠.٤٠ in their control group as reported by Habara et al., [٦].

On the other hand, no statistically significant difference between the PI of the right and left uterine arteries could be found within the groups, just as was reported by Steer et al. [٥] . Because no difference between the right and left sides could be detected, it seemed possible to confirm that the best way

to interpret Doppler data for uterine arteries would be through the mean PI of both sides combined.

In the present study, Based on ROC, the area under the curve was ٠.٩١٨ with a standard error of ٠.٠٣ (٩٥٪ CI: ٠.٨٦-٠.٩٨), which implied that the PI could perfectly predict the occurrence of the adverse outcome among pregnant women. Similarly, the cut-off value for PI was ٢.٦٥ at ٩٢٪ sensitivity and ٨١٪ specificity for miscarriage.

About ١٠-١٥٪ of clinically recognized pregnancies end in spontaneous miscarriage and there is an increasing risk of spontaneous miscarriage with maternal age. Decline in endometrial receptivity which is associated with a decrease in uterine perfusion may play an important role in the decrease of implantation rate with age [١٠]

Likewise Jirous et al. [١١] found increased ovarian and uterine flow impedance in women with RPL than in controls. Also in a study conducted by Lazzarin et al. [١٢] on ٢٣٠ women with RPL and ٥٠ fertile controls, they found that uterine arteries PI values in RPL patients (٢.٤٢ ± ٠.٧٩) were significantly higher with respect to those found in the control group (٢.٠٨ ± ٠.٤٧), and when patients were grouped according to different causes of RPL the highest PI values were found among patients with uterine abnormalities (٢.٨٢ ±١.٠), antiphospholipid antibodies syndrome (٢.٧٠ ± ١.١), and unexplained RPL (٢.٦ ± ٠.٧).

This suggested that an impaired uterine perfusion can negatively influence the reproductive function. So, the authors suggested that these data should be considered of importance as specific therapeutic approaches improving the uterine perfusion may lead to better pregnancy outcome. So, in the completion of this previous work Lazzarin et al. [١٣] conducted a study on sixty women with unexplained RPL and impaired uterine perfusion to determine the effect of different therapeutic approaches on uterine artery PI in those women, patients were randomly assigned to three different therapeutic regimens; ٢٠ patients received a daily dose of ١٠٠ mg of aspirin (LDA); ٢٠ patients were treated with omega-٣-fatty acids ٤ mg daily; and ٢٠ patients received LDA and omega-٣-fatty acids, they found that all therapeutic regimens induced an improvement in uterine perfusion with a significant reduction in uterine artery PI values. But they recommended further studies to ascertain whether such improvement in uterine perfusion can effectively lead to better pregnancy outcome in these women .

٥.Conclusion:

Transvaginal ultrasonography colour Doppler flowmetry can be used to Assess uterine perfusion through measurement of uterine artery Doppler (PI) is recommended as routine investigation for women with Unexplained Recurrent miscarriage which helps in managements and treatment protocols.

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