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Uterine Artery Doppler and Sub Endometrial Blood Flow in Patients with Unexplained Recurrent Miscarriage

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Abstract

It is our goal to determine if Doppler is involved in unexplained miscarriage by comparing the endometrial thickness, uterine artery Doppler indices, and power Doppler assessment of the endometrial-sub endometrial vascularity of the RPL group and control group. Doppler and power Doppler evaluations of the endometrial-sub endometrial vascularity of fifty women with a history of two or more recurrent miscarriages were compared to fifty women who served as controls. Findings: In comparison to the control group, participants in the research had substantially greater PI and RI in the uterine artery (p0.001). There is no statistically significant difference between the recurrent abortion (study) group and the control group in the power Doppler detection rate of sub endometrial vascularity (p .05). However, as compared to the control group, the study group exhibits a statistically significant difference in good vascularity. While 75% of the control group had great vascularity, only 13% in study group had poor vascularity (24%) compared to 9.4% in the control group. Therefore, it is possible that poor endometrial-sub-endometrial vascularity is the cause of unexplained RPL and may be utilised as a risk factor for miscarriage on its own.

Keywords: Unexplained recurrent pregnancy loss, uterine blood flow, sub endometrial zones, power Doppler, uterine receptivity.

1. Introduction

Miscarriage, especially repeated ones, remains a medical concern despite decades of study. The number 43 is defined as: At 24 weeks gestation or less, a clinically proven intrauterine pregnancy is considered to be miscarriage when it is spontaneously lost. Approximately 15% to 20% of clinically identifiable pregnancies are affected by miscarriage [14].

According to the American Society for Reproductive Medicine ("Definitions of Infertility and Recurrent Pregnancy Loss: A Committee Opinion" 2013), recurrent miscarriage (RM) is defined as two or more consecutive pregnancy losses of a clinically developed intrauterine pregnancy (in this scenario Ultrasound or histological confirmation of pregnancy is required).

Primary and secondary recurrent miscarriage. Primary RM refers to several pregnancies that fail in a woman who has never given birth, while secondary RM refers to many pregnancies that fail in a woman who has given birth before [3]. RM Affects 0.5% to 2.3% of the population [11]. RM is a disorder with a wide range of symptoms (Ali et al., 2020). In addition to the several recognised causes of RM, such as parental chromosomal abnormalities, uterine anomalies, viral illnesses, endocrinopathies, and autoimmune disorders, around half of all instances of RM are still idiopathic [24].

Type 1: It seems to be the result of pure chance, whereas Type II: It looks to be caused by some other factor. The prognosis for these ladies is excellent. There is no need for any surgical or pharmacological interventions, and treatment with LMWH does not improve live birth rates in these women, according to the research. A healthy pregnancy can only be achieved with the help of a supportive therapist (tender loving care). In Type 2 cases, the underlying disease was not discovered by normal testing, resulting in the condition.

To determine whether or not an IVF procedure will be successful, doctors might utilise the endometrial perfusion test [46], a painless, noninvasive uterine receptivity test. It is preferable to perform an endometrial biopsy, which may cause trauma and bleeding at the implantation site, to assess uterine receptivity by Doppler, as most of the blood that passes via uterine arteries never reaches the endometrium; therefore, it is preferable to use Doppler rather than endometrial biopsy. So, in order to assess uterine receptivity, we must quantify vascularization surrounding the endometrium directly using Doppler of the endometrium and subendometrial area. The thin hypoechoic layer between the echogenic endometrium and myometrium may be seen as a separate subendometrial area on ultrasound at the myometrial–endometrial junction [42]. If vascularization in this area affects endometrial perfusion and, eventually, endometrial function, then we will examine the endometrium and subendometrial region alongside uterine artery Doppler throughout our research. The primary goal of this research is to compare the endometrial thickness, uterine artery Doppler indices, and power Doppler assessment of endometrial-subendometrial vascularity between the RPL group and the control group.

2. Patient and method

One hundred patient were enrolled in this case-control study in benha university hospital.50 patient with history of two or more recurrent miscarriage (Study group, no. = 50), and 50 with no history of abortion and had at least 1 child born at term (Control group, no. = 50). The participants signed an informed consent

Form. Inclusion criteria in study group were; not being pregnant, two or more recurrent miscarriage, age 20-40 years old, regular cycle, no hormonal contraception or intra uterine device, normal endocrinal status including serum thyroid-stimulating hormone, free thyroxin (T4), glucose tolerance test and progesterone levels between days 19 and 21 of the menstrual cycle, autoimmune diseases ruled out, normal hystrosalpingography with normal endometrial cavity.

For both groups the exclusion criteria were having cervical incompetence or uterine anomalies and systemic diseases that may affect Doppler indicies.

All patients were subjected firstly to full history and examination, then Doppler study was evaluated via a 7.5 MHz vaginal probe with a Doppler facility (Voluson 730 PRO V, GE Healthcare, USA). Ultrasound checks were done by the same sonographer to avoid inter-observer variability. The participant was examined between days 18 and 23 of menstrual cycle with an empty bladder. Doppler examination was done between 8.00 and 10.00 A.M. to eliminate the impacts of circadian rhythmicity on the uterine perfusion and relaxed for 20 min before the Doppler examination to reduce the impacts of exercises on uterine Doppler indices.

On each examination;

The endometrial thickness was measured in the midsagittal plane in the fundus of the uterus (point of maximal thickness) from the echogenic interface at the junction of the endometrium and myometrium.

The uterine vessels were visualized using color Doppler, and the ascending branch was identified lateral to the cervix, at the level of the internal os before they entered the uterus. The blood velocity waveform was gained by employing the Doppler gate on the target vessel. The mean values of bilateral uterine artery RI and PI were used for statistical analysis.

When a longitudinal view of the uterus was obtained, applying 2 d Power Doppler with machine adaption for endometrium, vascular signals were quantified. Endometrial- Subendometrial vascularity was evaluated in four zones;

Zone 1 vascularity (Subendometrial region) described blood vessels reached the hypoechoic endometrial–myometrial junction,

Zone 2 vascularity described blood vessels reached the outer hyperechoic line of the endometrium,

Zone 3 vascularity described blood vessels reached the intervening hypoechoic area and

Zone 4 vascularity described blood vessels reached the central echogenic line.

Endometrial vascularity was classified according to the power Doppler signals into:

Excellent vascularity by the presence of at least five signals in zones 3 and 4, Modest vascularity with up to 4 signals reaching zones 3 and 4, and Poor vascularity with less than one signal in zones 3 and 4.

2.1. Statistical analysis

Quantitative variables are expressed as mean ± standard devi- ation (SD) and comparisons were performed using the t-test for independent samples if the samples were normally distrib- uted or by the Mann–Whitney test otherwise. The significance level was 0.05 and p-values less than 0.05 were considered sig- nificant. Binary logistic regression analysis model has been per- formed to predict a categorical variable from a set of predictor variables.

3. Results

There was no significant difference between the control and the study groups regarding the mean age, parity and the mean body mass index (p>0.05).

Both PI &RI of the uterine artery are significantly higher in the study group compared to the control group (p<0.001). However there was no significant difference regarding endometrial thickness in both groups (p 1.0.) table (1).

Table (1) Comparison between study and control groups regarding uterine artery Pulsatility Index (PI), Resistance index (RI), and Endometrial thickness (ET).

	Case group (50)		Control group (50)		Statistical test (st t)	P value
	Mean	±SD	Mean	±SD		
PI	2.28	0.86	1.42	1.43	3.66	<0.001**
RI	0.93	0.22	0.73	0.13	5.46	<0.001**
ET	7.90	1.0	7.90	1.0	0.0	1.0

PI and RI were significantly higher in study group than control group with increased number of abortion p= 0.005, p<0.001 respectively table (2).

Table (2) Comparison between study group scaled according to number on miscarriage (2, 3, 4, and 5) and control group regarding PI, RI and ET

			Miscarriage								Statistical test	P value
	No (control group)(50)		2 (21)		3 (12)		4 (9)		5 (8)			
	Mean	±sd	Mean	±sd	Mean	±sd	Mean	±sd	Mean	±sd	F test	
PI	1.42	1.43	2.08	0.85	2.30	0.72	2.20	0.85	2.88	0.95	4.02	0.005**
RI	0.73	0.13	0.87	0.22	0.98	0.21	0.87	0.18	1.10	0.20	11.21	<0.001**
ET	7.90	1.0	8.17	1.01	7.79	1.12	7.72	1.0	7.56	0.78	0.71	0.585

But, there was no statistical difference among cases of the study group scaled according to number of abortion 2, 3,4and 5 according to PI, RI and ET (p>0.05) table (3).

Table (3) Comparison of cases of the study group scaled according to number of abortion 2, 3,4and 5 according to PI, RI and ET.

	MISCARRIAGE(n)								Statistical test	P value
	2 (21)		3 (12)		4 (9)		5 (8)			
	Mean	±sd	Mean	±sd	Mean	±sd	Mean	±sd		
PI	**2.08**	**0.85**	**2.30**	**0.72**	**2.20**	**0.85**	**2.88**	**0.95**	**1.81**	**0.158**
RI	**0.87**	**0.22**	**0.98**	**0.21**	**0.87**	**0.18**	**1.10**	**0.20**	**2.79**	**0.051**
ET	**8.17**	**1.01**	**7.79**	**1.12**	**7.72**	**1.0**	**7.56**	**0.78**	**0.95**	**0.424**

The power Doppler detection rate of sub endometrial vascularity has no statistically significant difference between both the recurrent abortion (study) group compared to control group($p < .05$) table (4). However; the study group shows high significant statistical difference compared to control group regarding excellent vascularity pattern. The majority of cases in the study group had poor vascularity 24% versus to 9.4% in control group while 75% of control group had excellent vascularity versus 12% in case group figure (1).

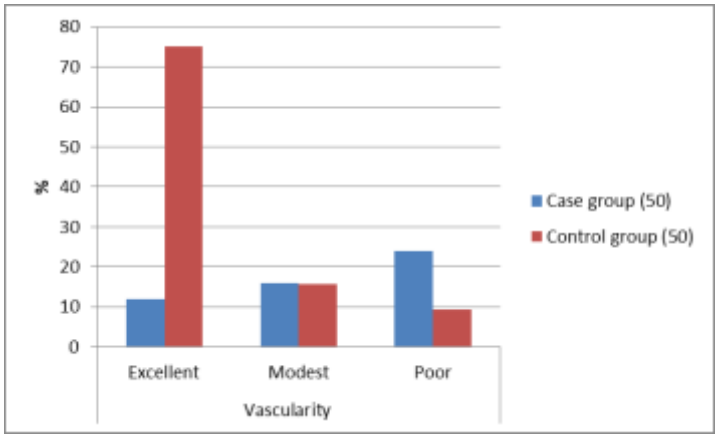

Fig. (1) Comparison between case and control groups according to vascularity**.**

With increased number of abortion in the study group, There were significantly high excellent vascularity pattern in control group compared to each miscarriage subgroups. ($p<0.001$).

Table (4) Comparison between case and control groups according to Power Doppler sub endometrial vascularity pattern**.**

	Case group (50)		Control group (50)		Statistical test	P value
	No	%	No	%		
Vascularity detection Pattern	28	56%	32	64%	X2= 0.6667	P < .05.
– **Excellent**	6	12.0	24	75.0		
– **Modest**	8	16.0	5	15.6	X2= 18.43	<0.001**
– **Poor**	14	24.0	3	9.4		

4. Discussion

Endometrial receptivity is required for a successful embryo implantation, and it is characterised by a short time period during which endometrium is suitable for embryo adhesion and the following attachment and invasion processes [4] where vascular development is critical. Pregnancy losses may be related to implantation, which shows that endometrial receptivity is a major component in the success of the pregnancy [44]. When excellent quality embryos are transplanted as standard of care in assisted reproductive technologies (ART), implantation failure remains an unresolved issue [4].

Endometrial thickness, endometrial pattern, and blood flow Doppler indices are all often included in sonographic assessments of the endometrium. The vascularity of the endometrium seems to be more essential in predicting implantation than endometrial thickness or pattern, according to many studies [19]. The resistance index (RI), pulsatility index (PI), and systolic/diastolic (S/D) ratio are the most often utilised Doppler indices for assessing uterine artery blood flow impedance [29]. It has been hypothesised that analysing the pulsatility index (PI) of uterine artery in mid-luteal phase of spontaneous cycles might help identify patients who have recurrent pregnancy loss due to uterine

circulation problems (Casikar et al., 2012; Mohamed and Sultan, 2018) (Guedes-Martins et al., 2014).

The study's objectives were to compare the endometrial thickness, uterine artery Doppler indices, and power Doppler assessment of endometrial-subendometrial vascularity between the RPL group and the control group.

RPL patients had substantially greater midluteal uterine artery mPI and mRI values (p 0.001) compared to the control group. Our study group had considerably greater rates of PI and RI than the control group with an increased number of abortions, which was statistically significant (p=0.005 and p0.001 respectively).

According to Yang et al. [8] investigation, which showed high measurement of RI and PI in the prior findings, It was concluded that a retrospective study of 870 RPL and 237 non-RPL patients had been completed. Patients with RPL had substantially higher mean PI, RI, and S/D values for uterine arteries than those without RPL (P 0.001).

Recurrent pregnancy loss is associated with a higher resistance to blood flow in the anterior uterine artery (AUA) in RPL patients compared to controls, according to several studies (seven).

As a result, we found no statistically significant change in the mPI, mRI, and ET values of RPL patients with increasing numbers of miscarriages (p>0.05).

Previous studies have shown that uterine artery impedance is an excellent predictor of future pregnancy, but the data from the IVF–embryo transfer programme shows that this component is responsible for implantation failure in only a few cases(9). (9) However, a 23-year-old research found no connection between uterine artery blood perfusion and spontaneous foetal demise. 25 investigated the values of Doppler indices in 81 women with a history of RSA and 19 healthy women in the control group A on the 21st day of a typical menstrual cycle. Even more strikingly, both the mean UTAPI and average IOARI values in control groups A were substantially lower than in the total study group B as well as all of its subgroups (p! 0.001 respectively). (9) a research showing that uterine artery pulsatility and resistance indices had an adverse association with the chance of conception There was no significant difference in the mean pulsatility index and the resistance index between conception and non-conception cycles, although the statistical significance was modest because of a large sample size. It's worth noting that RPL patients with no known cause had much greater uterine artery blood flow resistance than controls, which is in line with earlier studies (21) Because of this, inadequate uterine perfusion in individuals with unexplained RPL may be one of the root causes.

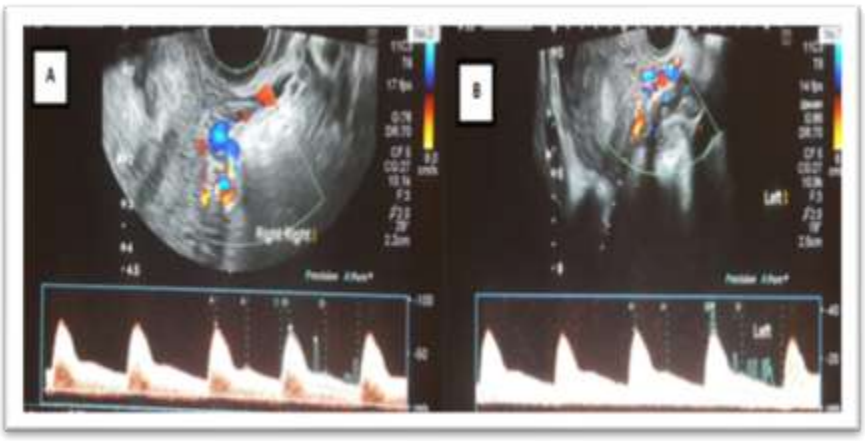

Fig. (2) a, **b** Transvaginal Doppler ultrasound of both uterine arteries (**a** right, **b** left) of fertile female (control group) aged 25 years old shows RI of right and left uterine arteries were 0.58 and 0.58 with mean RI 0.58 and PI of right and left uterine arteries were 1.1 and 1.96 respectively with mean PI 1.53***.[3]***

According to our findings, there was no significant difference in endometrial thickness between the two groups, which is supported by [18] which found that Although most clinicians empirically prefer endometria >7 mm, available evidence does not support any specific thickness, as pregnancies with similar success have been described from 5 mm to more than 15 mm.

As a last step, we examined the power Doppler sub endometrial vascularity pattern, which was classified according to Applebaum's zones of vascularity in the endometrium (figure 2). It is defined as zone 1 when Doppler power Doppler shows vascularity at endometrium myometrium junction, zone 2 when vessels penetrate the hyperechogenic endometrial edge, zone 3 when it reaches an intervening hypoechogenic zone and reaches the endometrial cavity, and zone 4 when vessels exit the endometrial cavity [41]. Excellent vascularity was defined as having at least five zones 3 and 4 signals, mild vascularity as having up to four zones 3 and 4, and poor vascularity as having fewer than one zone 3 and 4 signals.

Endometrial perfusion and, eventually, endometrial thickness and function may be linked to vascularization in the sub endometrial region, given that blood supply to the endometrium must travel via the sub endometrial area [30].

Invasion of interstitial and intravascular trophoblasts into the junctional zone but not the outside myometrium is said to occur according to [8], which means that the decidual process may also include the junctional zone, despite the fact that this is still poorly understood. Sub endometrial blood flow was shown to be the most sensitive indicator of uterine receptivity in the segmental uterine artery perfusion.

Ending our analysis, we found that there was no statistically significant difference in the power Doppler detection rate of sub endometrial vascularity between the study group and the control group. However, as compared to the control group, the study group exhibits a statistically significant difference in good vascularity. While 75% of the control group had great vascularity, only 13% in study group had poor vascularity (24%) compared to 9.4% in the control group. RPL patients were found to have higher excellent vascularity patterns in control groups compared to each abortion subgroup (p0.001), highlighting the link between poor endometrial-sub endometrial vascularity in study group and their unexplained recurrent miscarriage. Also, similar results were found when RPL patients were scaled according to different numbers of miscarriage.

According to our findings

There was an approximately two-fold increase in conception rates when vascularity was seen in zones 3 and 4 of the endometrium, compared to zones 1 and 2, in a retrospective analysis of 500 ovum donation-embryo transfer cycles reported by [32].

It was shown that the existence of endometrial vascularity in frozen embryo transfer cycles considerably improved the result for the women who were studied [36].

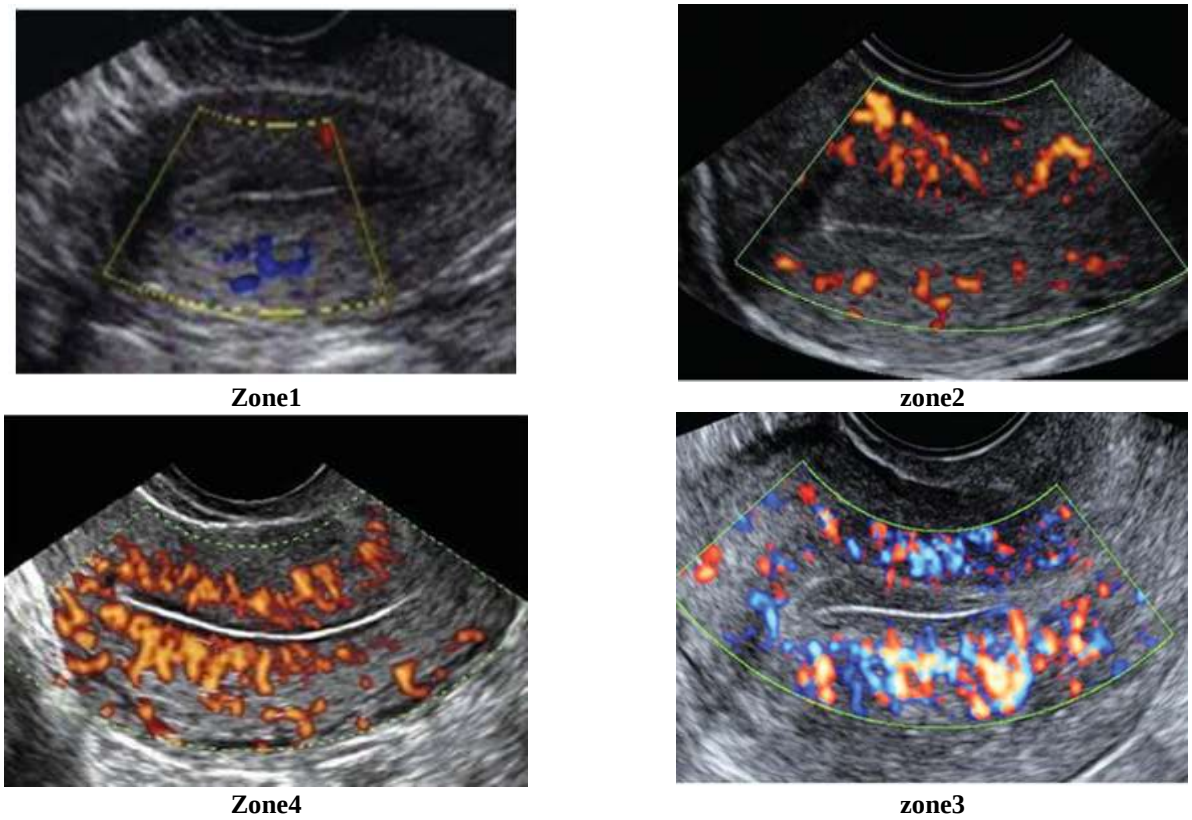

Fig. (3) Applebaum's zones of vascularity(1, 2 ,3 and 4)

However, in IVF-related studies, our findings are consistent. The endometrium and subendometrium of pregnant women who had a live birth after stimulated IVF and frozen embryo transfer (FET) treatment had higher vascularity on the day of oocyte retrieval than those who had a miscarriage, and failure of implantation was linked to absent sub endometrial blood flow [47], and pregnant women who had a live birth had significantly higher endometrial vascularity than those who had a miscarriage. If the endometrium and subendometrial myometrium are not mapped in colour, then the implantation rate is either zero or significantly decreased. We found that Doppler ultrasonography does not provide accurate information on uterine receptivity and the likelihood of pregnancy, in contrast to the findings of our research [15].

There were no reliable predictors for pregnancy in ICSI cycles of endometrial vascularization.

According to the results of recurrent miscarriage, which is marked by higher uterine artery blood flow resistance and lower endometrial blood flow, as well as patients with unexplained RPL, it is clear that adequate blood flow to the uterus and the endometrium is essential for successful implantation and continued pregnancy. The small sample size and short period of follow up may explain why we were unable to find any

cut off values that could accurately predict the likelihood of a miscarriage, but larger prospective studies are needed to confirm these findings and reach cutoff values that can accurately predict such cases.

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