OPEN AIMJ ORIGINAL ARTICLE

Mid-Secretory Uterine Artery Doppler Indices and Endometrial Thickness in Patients with Unexplained Recurrent Pregnancy Loss

Obstetrics & Gynecology

Eshraq Arabi Mohammed [1,*] M.B.B.Ch, Ahmed A.M. Nasr [1] MD and Wael Mohamed Hamed [1] MD.

**Corresponding Author:*

Eshraq Arabi Mohammed

Eshrak.Arabi2020@gmail.com

Received *for publication October 10, 2022;* ***Accepted*** *December 31, 2022;* ***Published online*** *December 31, 2022.*

doi: *10.21608/aimj.2023.166045.2215*

Citation: *Eshraq A. , Ahmed A. and Wael M. Mid-Secretory Uterine Artery Doppler Indices and Endometrial Thickness in Patients with Unexplained Recurrent Pregnancy Loss. AIMJ. 2022; Vol.3-Issue12 : 110-116.*

[1]Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University, Assiut, Egypt.

ABSTRACT

Background: Recurrent loss of pregnancy known as 2 or more sequential fetal losses before twenty weeks from the total gestational age. Potential uterine predictors for implantation measurable by ultrasound include endometrial thickness and volume, endometrial pattern, as well as blood flow in the uterine and sub-endometrial arteries.

Aim of the work: To evaluate endometrial thickness and uterine artery blood flow using Transvaginal color Doppler ultrasound during the midluteal phase of the menstrual-cycle for female with unexplained recurrent pregnancy loss (RPL).

Patients and methods: Pospective controlled clinical trial was conducted on 90 non pregnant women ; 45 Patient group and 45 Control group. All participants underwent comprehensive examinations and were scanned by transvaginal Doppler ultrasonography during the midluteal phase to measure endometrial thickness, the pulsatility index (PI), resistance index (RI) and systolic/diastolic ratio (S/D) values of the left and right main uterine arteries. P value less than 0.05 was considered statistically significant.

Results: No statistically significant difference between the studied groups as regard to endometrial thickness. There is highly statistically significant increased right and left uterine arteries S/D ratio ,RI and PI in the cases group when compared with the control group (p-value < 0.001).

Conclusion: Normal blood flow to uterus plays an important role in pregnancy outcome while endometrial thickness has less important role. Colour Doppler ultrasound can be used to detect abnormal uterine Doppler indices that can predict pregnancy outcome.

Keywords: *Midsecretory; Uterine artery; Doppler; endometrial thickness; RPL.*

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

Authorship: *All authors have a substantial contribution to the article.*

INTRODUCTION

Recurrent loss of pregnancy known as 2 or more sequential fetal losses before twenty weeks from the total gestational age.[1] Potential uterine predictors for implantation measurable by ultrasound include; endometrial thickness and volume, endometrial pattern, as well as blood flow in the uterine and sub-endometrial arteries.[2]

Chromosomal aberrations were observed in 3.2% of RPL cases. Chromosome analysis is an important etiological study in couples with RPL.[3] Balanced translocations are the most common chromosomal aberrations found in these pairs. Therefore, these couples are the best candidates for prenatal genetic diagnosis, leading to better reproductive outcomes.[4]

Hormones such as progesterone, human chorionic gonadotropin, normal thyroid levels, and prolactin levels play an important role in preventing RPL.[4] Endocrine causes of LPR include luteal phase deficiency, untreated hypothyroidism, hyperprolactinemia, hyperandrogenism, insulin resistance, and decreased ovarian reserve. While diagnostic criteria for LPD remain controversial, treatment of LPD and LPD patients with a progestogen in early pregnancy is the most commonly used treatment, although its role is controversial. Hyperprolactinaemia, polycystic ovarian syndrome, and overt or subclinical hypothyroidism with or without the presence of thyroid antibodies are associated with poor obstetric outcomes and should be treated.[5]

Congenital malformations of the uterus, including scalloped, scalloped, one-horned, bicorneal, and uterine dysplasia, are more common in women who have lost a pregnancy than in the general population.[5] Recurrent pregnancy loss 4.6% compared to women with 9% primary recurrent pregnancy loss. Acquired

uterine abnormalities such as uterine fibroids, endometrial polyps, intrauterine adhesions, or Asherman syndrome may be associated with an increased risk of miscarriage.[6]

The quality of the gametes and embryos and the good viability of the endometrium form the basis for a pregnancy that can last until childbearing. The receptivity of the endometrium has been widely recognized through extensive research in recent years. 3D Doppler ultrasound measurements of endometrial volume and central muscle vascular flow parameters can be used to predict miscarriage.[6]

Potential uterine indices of implantation that can be measured by ultrasound include endometrial thickness and size, endometrial pattern and uterine blood flow and endometrial arteries.[6] However, the vascular changes associated with RPL have not been sufficiently studied. While defects in the ovum, sperm, embryo, and systemic or local factors have been noted, the role of endometrial sensory defects in unexplained and often unexplained recurrent pregnancy loss has not been well studied.[7]

Therefore; this study purpose to evaluate endometrial thickness and uterine artery blood flow using transvaginal color Doppler ultrasound during the midluteal phase of the menstrual-cycle for female with unexplained recurrent pregnancy loss (RPL).

PATIENTS AND METHODS

This study is prospective controlled clinical trial that conducted a total number of 90 non pregnant female 45 with history of unexplained RPL and 45 normal fertile (control group) retrieved from Gynaecology clinic of Al-Azhar university hospital during a period from Januray 2021 to December of the same year.

The study approved by Ethics Committee of AL-Azhar University (Assuit) faculty of medicine , an informed written consent was obtained from all participants. The study is conducted in accordance with Helsinki standards as revised in 2013.

All studied female undergoe Proper history taking (personal, menstrual history ,obstetric history, past history, surgical history and present history),Examinations: general, abdominal and PV examination and routine investigations (CBC, chemistry) and Trans vaginal 2-D ultrasound scan for assessment of uterus (including measuring of endometrial thickness) and adnexa Uterine artery Doppler study assessment of uterine-blood-flow during the mid-secretory phase of the menstrual cycle using 7.5 MHz trans-vaginal convex probe (voloson E 6 ultrasound machine). The uterine arteries were identified lateral to cervix trans-vaginally and measurements. The pulsatility index, resistance index and Systole/Diastolic ratio were calculated

Non pregnant women age; 20-35 years. With history of 2 or more successive spontaneous abortion. Unexplained recurrent pregnancy loss with normal serum PRL, normal thyroid function, normal HbA1c, normal pelvic ultrasound, normal HSG or hystroscopy , negative tests for antiphospholipid antibody syndrome (ACL, Lupus anticoagulant and anti B2 glycoprotein 1) were included. Induced abortion , Less than 2 successive spontaneous abortion or patient refused to participate in the study were excluded. All findings of this study was statistically calculated using SPSS (V. 20, Echosoft Corp., USA). Statistical analyzed data were calculated and tabulated as quantitative and qualitative with percentage for catgorized data.

RESULTS

The mean ± SD age of cases were27.87 ±3.87 and mean ±SD of control 28.53 ± 4.5 p value 0.455, regard to body mass index, Endometrium thickness was no statistically significant between both group. Mean ±SD (11.5 ± 1.67 mm versus 12.08 ± 1.8 mm) for cases and control respectively. Parity were significant between both groups cases and control respectively < 0.001 . As regard to Doppler blood flow studies of right and left uterine arteries we found that : systole / diastole ratio (S/D) for both uterine arteries higher in patients group (7.23 ± 1.05 & 6.8 ± 1.8) for right and left uterine arteries for patients group versus (4.7± 1.15 &4.7 ±1) for control group respectively (p-value < 0.001). Resistance index (RI) for both uterine arteries higher in patients group (0.86 ± 0.06 & 0.86 ± 0.7) for right and left uterine arteries for patients group versus (0.75± 0.05 &0.76±0.06) for control group respectively (p-value < 0.001). Pulsatility index for both uterine arteries was statistically significantly in patients group (2.21 ± 0.09 & 2.2 ± .08) for right and left uterine arteries for patients group versus (1.65± 0.03 &1.69 ±0.03) < 0.001. Diagnostic performance right/ left uterine arteries S/D ratio at a cutoff level of (> 6.2 & > 5.7) with sensitivity (84.4% & 90.9 %), specificity (93.3% &80%) , PPV (92.6%&82 %) , NPV (85.7%&89.8%) and AUC (0.94& &0.93) for right and left uterine arteries respectively p-value < 0.001). As regard to diagnostic performance of right and left uterine arteries RI at a cutoff level of (> 0.81 & > 0.78) with sensitivity (66.7% & 80 %), specificity (88.9% &75.6%) , PPV (85.7%&76.6 %) , NPV (72.7%&79.1%) and AUC (0.87& 0.84) for right and left uterine arteries respectively (p-value < 0.001). As regard to diagnostic performance of right and left uterine arteries PI at a cutoff level of (> 1.95 & > 1.89) with sensitivity (66.7% & 68.9 %), specificity (95.6% &91.1%) , PPV (93.8%&88.6 %) , NPV (74.2%&74.6%) and AUC (0.78& &0.77) for right and left uterine arteries respectively (p-value < 0.001).

		Cases (N = 45)		Control (N = 45)		Stat test	P-value
Age (years)	**Mean**	27.87		28.53		T=0.750	0.455
	±SD	3.87		4.5			
Age categories#	**20 – 25 y (N %)**	11	24.4%	14	31.1%	$X^2 = 0.6$	0.740
	25 – 30 y (N %)	10	22.2%	8	17.8%		
	30 – 35 y (N %)	24	53.3%	23	51.1%		
BMI (kg/m²)	**Mean**	20.9		21.4		T=1.2	0.236

	±SD	1.9		1.7			
		N	**%**	**N**	**%**		
BMI categories #	**Normal**	31	68.9%	34	75.6%	$X^2 = 0.95$	0.740
	Underweight	7	15.6%	4	8.9%		
	Overweight	7	15.6%	7	15.6%		
Residence #	**Rural**	32	71.1%	34	75.6%	$X^2 = 0.22$	0.634
	Urban	13	28.9%	11	24.4%		
Education #	**Illiterate**	13	28.9%	11	24.4%	$X^2 = 1.11$	0.773
	Primary	9	20%	13	28.9%		
	Secondary	13	28.9%	13	28.9%		
	University	10	22.2%	8	17.8%		

Table 1 : Sociodemographic characteristics of the studied groups

		Cases (N = 45)		**Control (N = 45)**		**Test**	**P-value**
Parity	**Median**	1.0		2.0		MW	**<0.001**
	IQR	(0.0-2.0)		(2.0-3.5)			
Abortions	**Median**	3.0		0.0		MW	
Mode of delivery	**IQR**	**Cases (N=24)**		**Control (45)**		**X^2**	**<0.001**
		Count	**%**	**count**	**Percent**		
Vaginal	(2-4)	**14**	**58.3%**	**25**	(0.0-0.0) **55.6%**	**0.116**	
CS		**4**	**16.7%**	**9**	**20%**		
Both		**6**	**25%**	**11**	**24.4**		

Table 2: Obstetric data of the studied groups.

		Cases (N = 45)	**Control (N = 45)**	**T**	**P-value**
Endometrial thickness	**Mean**	11.5	12.08	1.53	0.129
	±SD	1.67	1.8		

Table 3: Comparison between studied groups as regard to endometrial thickness.

S/D ratio		**Cases (N=45)**	**Control (N=45)**	**T**	**P- value**
Right uterine artery	**Mean**	7.23	4.7	10.8	<0.001
	SD	1.05	1.15		
Left uterine artery	**Mean**	6.8	4.7	10.1	<0.001
	SD	1.8	1.0		

Table 4: Comparison between studied groups as regard to right and left uterine arteries S/D ratio

		Cases (N = 45)	**Control (N = 45)**	**T**	**P-value**
Right RI	**Mean**	0.86	0.75	7.98	<0.001
	±SD	0.06	0.05		
Left RI	**Mean**	0.86	0.76	6.77	<0.001
	±SD	0.07	0.06		

Table 5 : Comparison between studied groups as regard to right and left uterine arteries RI

		Cases (N = 45)	Control (N = 45)	T	P-value
Right PI	Mean	2.21	1.65		<0.001
	±SD	0.09	0.03	5.2	
Left PI	Mean	2.20	1.69		<0.001
	±SD	0.08	0.03	5.18	

Table 6: Comparison between studied groups as regard to right and left uterine arteries PI.

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	p-value
Rt uterine artery S/D	> 6.2	0.94	84.4%	93.3%	92.6%	85.7%	< 0.001
Lt uterine artery S/D	> 5.7	0.93	90.9%	80%	82%	89.8%	< 0.001

Table 7: Diagnostic performance of right and left uterine arteries S/D ratio in discrimination of cases & control groups

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	p-value
Rt uterine artery RI	> 0.81	0.87	66.7%	88.9%	85.7%	72.7%	< 0.001
Lt uterine artery RI	> 0.78	0.84	80%	75.6%	76.6%	79.1%	< 0.001

Table 8: Diagnostic performance of right and left uterine arteries resistance index in discrimination of cases & control groups

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	p-value
Rt uterine artery PI	> 1.95	0.78	66.7%	95.6%	93.8%	74.2%	< 0.001
Lt uterine artery PI	> 1.89	0.77	68.9 %	91.1%	88.6%	74.6%	< 0.001

Table 9: Diagnostic performance of right and left uterine arteries pulsatility index in discrimination of cases & control groups

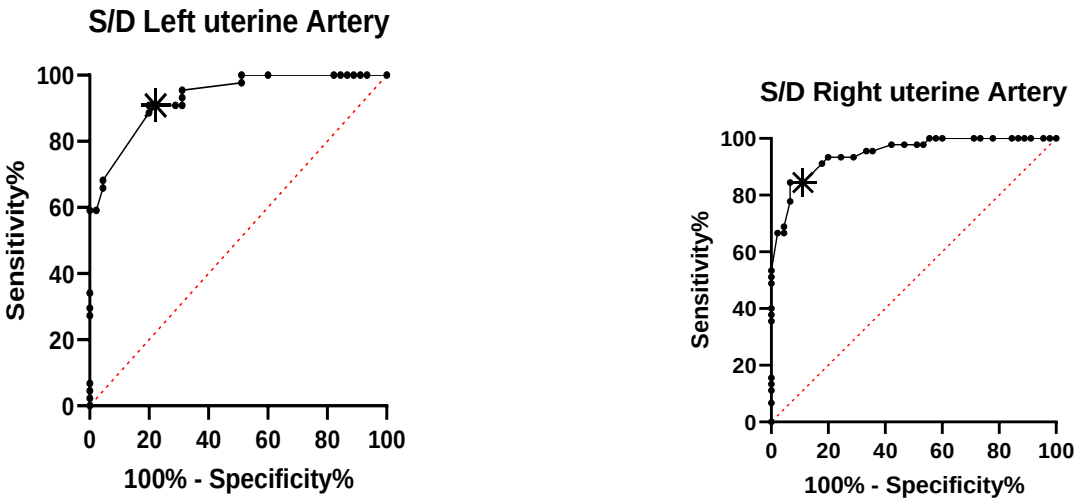

Fig. 1: ROC curve of systole /diastole(S/D) (AUC = 0.94 & p-value < 0.001).

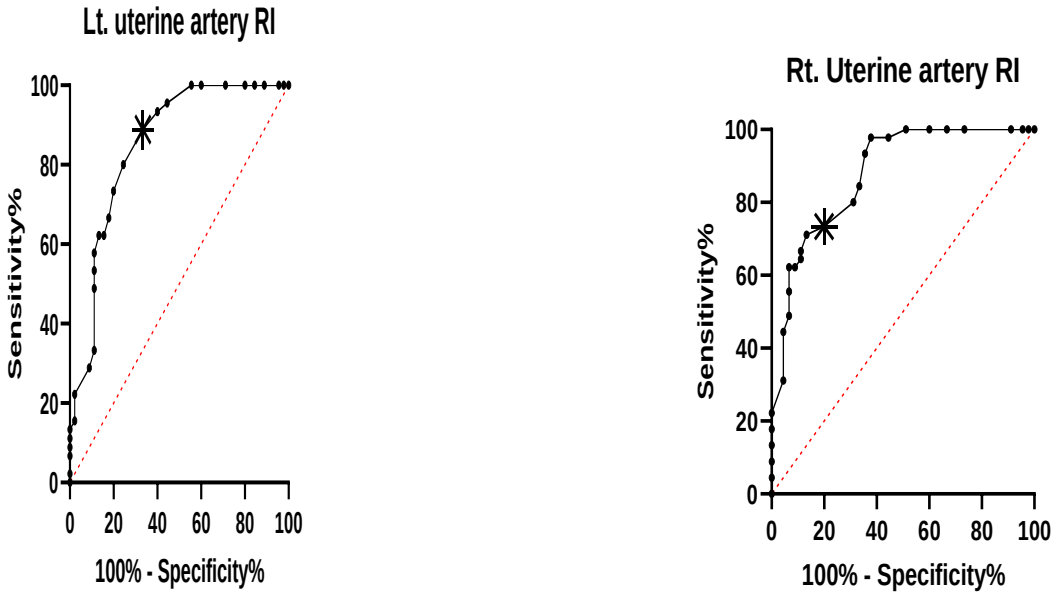

Fig. 2: ROC curve Rt. uterine artery RI (AUC = 0.87 & p-value < 0.001) and left uterine artery resistance index (AUC = 0.84 & p-value < 0.001)

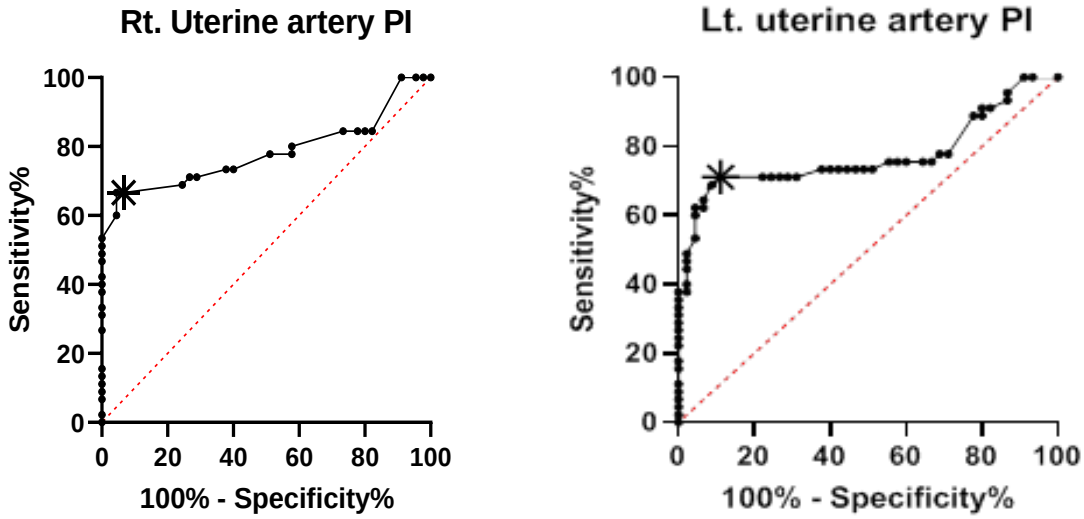

Fig. 3: ROC curve of right uterine artery PI (AUC = 0.78 & p-value < 0.001). and Lt. uterine artery PI (AUC = 0.77 & p-value < 0.001).

DISCUSSION

This study is prospective controlled clinical trial that conducted to assess UAD indices endometrial thickness-in-cases-with of-unexplained RPL. Among total number of 90 non pregnant female 45 with history of unexplained RPL and 45 normal fertile (control group) retrieved from Gynecology clinic of Al-Azhar university hospital during aperiod from Januray 2021 to December of the same year. Therefore; this study purposes to evaluate endometrial thickness and uterine artery Doppler indices using Transvaginal color ultrasound during midluteal-phase of pre-implantation phase in female diagnosed with unexplained RPL.

As per our findings; endometrium thickness was non-statistically differences among groups. Mean ±SD (11.5 ± 1.67 mm versus 12.08 ± 1.8 mm) for cases and control respectively (p-value > 0.05) . this finding was similar to what was found by Hala *et al* [7] and El Garhy *et al* [8] who found that endometrium thickness was non-statistically differences among groups p value > 0.05.

In contrary to our finding; Tan *et al* [6] and Funda *et al* [9] who found that endometrial thickness was statistically significant between cases and control groups p value less than p value > 0.05.

In the present study regarding to Doppler blood flow studies of right and left uterine arteries we found that : systole / diastole ratio (S/D) for both uterine arteries was statistically significantly in patients-group (7.23 ± 1.05 & 6.8 ± 1.8) for right and left uterine arteries for patients group versus (4.7± 1.15 &4.7 ±1) for control group respectively < 0.001 this finding was similar to what was found by Yang *et al* [10] who found that S/D ratio was siginifantly-higher in RPL group compared to control p-value < 0.001.

In the present study resistance index (RI) for both uterine arteries was statistically significant in patients group (0.86 ± 0.06 & 0.86 ± 0.7) for right and left uterine arteries for patients group versus (0.75± 0.05 &0.76±0.06) for control group respectively (p-value < 0.001) this finding was similar to what was found by Yang *et al* [10] who found that RI was siginifantly higher in RPL group p-value < 0.001.

In current study Pulsatility index for both uterine arteries were significantly higher in patients group compared to control (2.21 ± 0.09 & 2.2 ± .08) for right and left uterine arteries for patients group versus (1.65± 0.03 &1.69 ±0.03) for control group respectively (p-value < 0.001) this finding was similar to what was found by Yang *et al.,* [10] Funda *et al.,* [9] Hala *et al.,* [7] and EL- Garhy *et al* [8] who found that PI was siginifantly higher in RPL group compared to control p-value < 0.001**.**

In current study diagnostic performance of right and left uterine arteries S/D ratio at a cutoff level of (> 6.2 & > 5.7) with sensitivity (84.4% & 90.9 %), specificity (93.3% &80%) , PPV (92.6%&82 %) , NPV (85.7%&89.8%) and AUC (0.94& &0.93) for right and left uterine arteries respectively p-value < 0.001).

According to previous study Zard *et al* [11] reported that the best systolic/diastolic (S/D) ratio resistance were increased to uterine blood flow more than 3, 100% with a sensitivity, 96.7% with specificity and predictive positivity and 100% negative predictive value.

Regarding the diagnostic performance of the IR of the uterine artery at the cut-off threshold (> 0.81 and > 0.78) with sensitivity (66.7% and 80%), specificity (88.9% and 75.6 %), PPV (85.7% and 76.6%), VPN (72.7% and 79.1%) and AUC (0.87 and 0.84), respectively (p-value < 0.001).

As per previous study Zard *et al* [11] reported that the best cut-off value for both indices of uterine arterial resistance (RI) to predict increased resistance to uterine blood flow was RI > 0.67 with 100% sensitivity, 96.7% specificity, and a positive predictor. the value was 97.5%, the negative predictive value was 100%, and the diagnostic accuracy was 98.6%.

According to Hashad *et al* [12] reported that the best cut-off value of uterine arterial resistance index (IR) to predict increased resistance to uterine blood flow was greater than 0.67 with a sensitivity of 70%, a specificity of 75%, and a positive predictive value of 85% was. , a negative predictive value of 60% and a diagnostic accuracy of 69.7%.

Regarding the diagnostic performance of the right and left uterine arteries at the cutoff threshold (> 1.95 and > 1.89) with sensitivity (66.7% and 68.9%), specificity (95.6% and 91.1%) and VPP (93.8% and 88.6) . %), NPV (74.2% and 74.6%) and AUC (0.78 and 0.77) respectively (p<0.001). S/D at threshold (> 6.2 and > 5.7), sensitivity (84.4% and 90.9%) and specificity (93.3% and 80%) relate to the right uterine artery and the left. 0.81 and >0.78) were the sensitivity (66.7% and 80%) and specificity (88.9% and 75.6%) respectively. 66.7% and 68.9% were the specificities (95.6% and 91.1%), respectively.

In addition to Zard *et al* [11] reported that the best PI (shear pulse index) value to predict increased resistance to uterine blood flow was 95% with sensitivity, 86.7% with specificity, 90.47% with positive predictive value and 92.86% with negative predictive value and 91.42% with diagnostic accuracy.

As mentioned by Hashad *et al* [12] reported that the best cut-off value for uterine arterial pulse index (PI) to predict increased resistance to uterine blood flow was greater than 1.37, with a sensitivity of 77.5%, a specificity of 85%, and a positive predictive factor of 87 % and a negative predictive value 66%, diagnostic accuracy 85.3.

CONCLUSION

Normal blood flow to uterus deduce a vital role in pregnancy outcome while endometrial thickness has less important role Also impedance of blood flow have a role in recurrent unexplained miscarriage. Colour Doppler ultrasound is safe, non invasive , cost effective and available facility that can be used to detect abnormal uterine Doppler indices that can predict pregnancy outcome.

Conflict of interest : none

REFERENCES

1. Van Dijk M, Kolte AM, Limpens J, Kirk E, Quenby S, van Wely M, Goddijn M. Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses?: A systematic review of the literature and meta-analysis. *Hum Reprod Update*. 2020; 26(2): 356-67.
2. Chelsea W, Ricardo F, Jae-Wook J, Tae H, Paul B, Creighton E, David P, Steven L, Bruce A. Unexplained recurrent pregnancy loss and unexplained infertility: twins in disguise, *Human Reproduction Open*. 2020;27(1): 5 - 10.
3. Hong Li Y, Marren A.Recurrent pregnancy loss: A summary of international evidence-based guidelines and practice: *Aust J Gen Pract*. 2018;47(7):432-6.
4. Priya K, Mishra V, Roy P, Patel H. A study on balanced chromosomal translocations in couples with recurrent pregnancy loss: *Journal of Human Reproductive Sciences*. 2018;11(4):327- 37

5. Agarwal N & Kulshrestha V (2018):. Hormones in Recurrent Pregnancy Loss: In Recurrent Pregnancy Loss. Springer, *Singapore*. 2018;32(1):22- 30

6. Tan S, Hang F, Purvarshi L, Meng H, Huang L. Decreased endometrial vascularity and receptivity in unexplained recurrent miscarriage patients during midluteal and early pregnancy phases: *Taiwanese Journal of Obstetrics and Gynecology*. 2015;54(5):522-6.

7. Hala A, Doaa S, Eman Z, Mohamed A, Mohamed A. uterine artery Doppler and subendometrial blood flow in patients with unexplained recurrent miscarriage : *Middle East Fertility society Journal*. 2011;16(3):209- 14

8. EL Garhy T, Ashraf H, Mohamed F, Ahmed S. Uterine and subendometrial Arteries Doppler in Patients with Recurrent First Trimestric Abortion :*The Egyptian Journal of Hospital Medicine*. 2018;73(5):6683-90 .

9. Funda A, Gunlunar O, Ozdemir M, Mustafa E, Aycag Y, Cihan O. Midluteal phase Doppler assessment of uterine artery blood flow in patients with history of recurrent pregnancy loss:*MITTEILUNGEN KLOSTERNEUBURG* .2015 ; 65(1):100 - 10.

10. Yang W, Wu Z, Peng X, Lu W, Feng W, Kang X. Characteristics of midluteal phase uterine artery hemodynamics in patients with recurrent pregnancy loss: *Journal of Obstetrics and Gynaecology Research*. 2019;45(7): 1230 -35.

11. Zarad A, Hafez M, Said A. Role of uterine artery Doppler in assessment of unexplained infertility : *Egyptian Journal of Radiology and Nuclear Medicine*. 2021; 56(3):52:9.

12. Hashad A, Ibrahim I, Etman M. A study of endometrial perfusion in unexplained infertility:*Egyptian J Hosp Med*. 2018;72(6):4673–80.