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A STUDY ON THE EFFECTIVENESS OF TRANSVAGINAL SONOGRAPHY AND COLOR DOPPLER IN THE ASSESSMENT OF ENDOMETRIUM IN SUBFERTILE WOMEN COMING TO A TERTIARY CARE HOSPITAL.

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Abstract

Background

Ultrasonography (USG) is a very important imaging modality for the diagnosis, treatment, and monitoring of subfertility. Grayscale USG provides structural information about the pelvic organs and color Doppler USG provides functional information along with its vascularity. Adequate blood flow via the uterine arteries and good endometrial perfusion plays a very important role in endometrial receptivity.

Objectives

The aim and objective of this study is to assess the mid-luteal phase endometrial spiral artery blood flow by TVS including Doppler, in women coming for the treatment of subfertility to a tertiary care hospital.

Results

Out of 50 patients, primary subfertility comprised 36 individuals while 14 were categorized under secondary subfertility. Most of the patients belonged to the age group of 20-30 years. Of the total number of females 56% conceived, among them 46.43% of patients conceived naturally, followed by IUI (32.14%) and then IVF (21.43%). In our study, 58% of patients presented with an endometrial thickness of over 7 mm, out of which 93.1% conceived successfully. The mean peak systolic velocity in conceived women was 13.18 ± 3.62 cm/s which was higher as compared to 11.55 ± 3.47 cm/s in non-conception menstrual cycles. Similarly, the EDV, Tmax, and Tmin were significantly higher as compared to the not-conceived group. 96.3% of the women who conceived had a lower pulsatility index (< 2.5). The best cut-off value of the resistive index was less than 0.9 for predicting conception status.

Conclusion

The combination of endometrial thickness and Doppler examination of endometrial and sub-endometrial blood flow can be used as a quick and efficient way to enhance the success of assisted reproductive techniques.

Recommendation

Due to rapid advancement in Doppler technology, it is highly recommended to perform transvaginal USG including Doppler for assessment of Doppler indices mid-luteal phase in subfertile women coming for treatment.

Keywords: *Transvaginal Sonography, Color Doppler, Endometrium, Subfertile Women.*
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Introduction

World Health Organization estimates a 3.9% to 16.8% range in the overall prevalence of primary infertility1. While Indian states range greatly from 3.7% in Uttar Pradesh, Himachal Pradesh, and Maharashtra to 5% in Andhra Pradesh to 15% in Kashmir2. Infertility is a condition defined by the inability to achieve a successful pregnancy determined by a patient's medical, sexual, and reproductive history and diagnostic testing, or any of these factors in combination. Unexplained subfertility is a condition that occurs in couples despite the results of all routine investigations, including ovulation tests, tubal patency tests, checks for any anatomical or developmental defects, and semen analysis, being normal3. In these cases, abnormal uterine perfusion may have a role in the etiopathology of infertility 4. Adequate blood flow via the uterine arteries and good endometrial perfusion control the uterine endometrial receptivity. Ultrasonography is

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one of the important key components of current fertility therapy. This study aims to assess the mid-luteal phase endometrial spiral artery blood flow in women coming for the treatment of subfertility to a tertiary care hospital by TVS including Doppler.

Materials & Methods

Study design
Prospective observational study

Study setting/area
Department of Radiodiagnosis, IGIMS, Patna. This study has been conducted for a period of 1.5 years from January 2021 to July 2022

Participants
Patients coming to the Department of Reproductive Medicine for fertility treatment and then referred to the Radiodiagnosis department for TVS

Variables
Endometrial wall thickness, endometrial echogenicity & endometrial-myometrial border regularity

Data sources/Measurement
The equipment used was a SAMSUNG H60 Ultrasound machine with transvaginal transducer of frequency 5-7.5 Hz. TVS was performed in the late follicular phase (between 14-20 days) of the menstrual cycle.

Bias
Unavailability of control groups

Study size
50 patients with primary or secondary infertility

Statistical methods
Data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0. For statistical significance, p p-value of less than 0.05 was considered statistically significant.

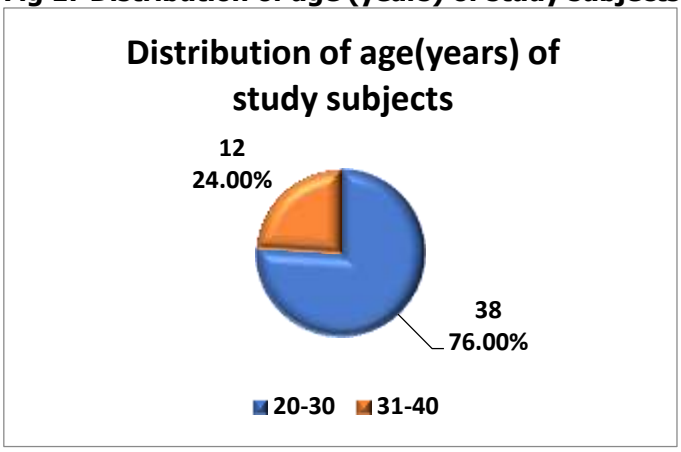
Ethical consideration
Approved by the Institute Ethical Committee. IEC No. is 1932/IEC/ IGIMS/2020

Inclusion criteria
- Age: between 20 - 45 years
- Females with Primary or Secondary Infertility
- Minimum of 3 years of marriage
- Clinical features/diagnosis: Patients in whom the Blood and hormonal profile is normal.
- Endometrial pathology – polyp, fibroid, adenomyosis

Exclusion criteria
- Females with Pelvic inflammatory disease(PID), cervicitis, vulvovaginitis
- Females who are HIV, hepatitis B, Hepatitis C, and COVID Positive
- Patients with Co- co-morbidities like Diabetes mellitus and hypertension.
- Tubal and ovarian factors causing infertility

Results and observations

Fig 1:-Distribution of age (years) of study subjects



More number of patients were present 20-30 years of age.
The mean value is 27.8 ± 4.6.

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Table 1:-Distribution of type of infertility. † Chi-square test

Primary infertility was the most common cause. There were more chances of conception in females with primary infertility than secondary infertility. There was no significant association between types of infertility and conception.

Type of infertility	Frequency (n=50)/ Percentage	Conceived 28 (56%)	Not conceived 22 (44%)	P value
Primary infertility	36 (72%)	22 (44%)	14 (28%)	0.243†
Secondary infertility	14 (28%)	6 (12%)	8 (16%)	

Table 2:-Association of age (years) with conception.

Age(years)	Conceived(n=28)	Not conceived(n=22)	Total	P value
Range	20-40	22-38	20-40	0.874‡
Mean ± SD	27.89 ± 4.76	27.68 ± 4.49	27.8 ± 4.6	

‡ ***Independent t test****. There is no significant association between the age of the females and conception.*

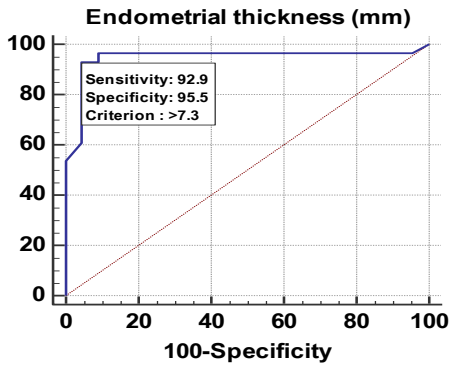
Table 3:-Distribution of method of the conception of study subjects.

Method of conception	Frequency (n=28)/ Percentage
Natural	13 (46.43%)
IUI	9 (32.14%)
IVF	6 (21.43%)

Most of the patients conceived naturally, however, among assisted reproduction IUI gave better results.

Table 4:-Distribution of endometrial thickness and its ROC curve.

Endometrial thickness (in mm)	Conceived 28 (56%)	Not conceived 22 (44%)	P value
<7	1 (2%)	20 (40%)	<.0001*
>=7	27 (54%)	2 (4%)	
Mean ± SD	9.88 ± 1.61	5.73 ± 1.23	<.0001‡



* ***Fisher's exact test,*** ‡ ***Independent t-test Receiver operating characteristic curve***

Endometrial thickness was equal to or more than 7 in most of the study subjects. It was significantly associated with conception.

The area under the ROC curve showed that the performance of endometrial thickness (AUC 0.946; 95% CI: 0.842 to 0.990) was outstanding.

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Table 5:-Association of systolic and diastolic velocity with conception.

Systolic and diastolic velocity	Conceived(n=28)	Not conceived(n=22)	Total	P value
Peak systolic velocity (cm/s)				
Range	5.8-19.9	4.5-19.1	4.5-19.9	0.113‡
Mean ± SD	13.18 ± 3.62	11.55 ± 3.47	12.46 ± 3.61	
End diastolic velocity (cm/s)				
Range	2.6-6.4	0.6-3.8	0.6-6.4	<0.0001‡
Mean ± SD	4.31 ± 1.17	1.7 ± 0.74	3.16 ± 1.64	
S/D ratio				
Range	1.5-5.4	3.6-12.2	1.5-12.2	<0.0001‡
Mean ± SD	3.15 ± 0.9	7.26 ± 1.81	4.96 ± 2.47	

‡ **Independent t-test**. ***A significant association was seen in end-diastolic velocity and S/D ratio with conception. (p-value <0.001)***

Table 6:-Association of Tmax and Tmean (cm/s) with conception.

Tmax and Tmean(cm/s)	Conceived(n=28)	Not conceived(n=22)	P value
Tmax(cm/s)			
Range	2.5-11.2	1.3-5.2	0.0006‡
Mean ± SD	5.25 ± 2.25	3.42 ± 1.13	
Tmean(cm/s)			
Range	1.3-5.3	0.6-3.3	0.005‡
Mean ± SD	2.63 ± 1.1	1.9 ± 0.64	

‡ **Independent t-test**, ***Significant association was seen in Tmax (cm/s) &Tmean (cm/s) with conception. (p-value <0.005)***

Table 7:-Distribution of the resistive index (RI) & pulsatility index (PI) of study subjects and their ROC curve.

Doppler indices		Frequency/ (percentage %)	Frequency/ (percentage %)	P value
		Conceived(n=28)	**Not conceived(n=22)**	
Resistance index (RI)	<1	28 (56%)	0	<.0001*
	>=1	0	22 (44%)	
		Frequency/ (percentage %)	**Frequency/ (percentage %)**	**P value**
		Conceived(n=28)	**Not conceived(n=22)**	
Pulsatile index (PI)	<2.5	26 (52%)	1 (2%)	<.0001*
	>=2.5	2 (4%)	21 (22%)	

* ***Fisher's exact test***

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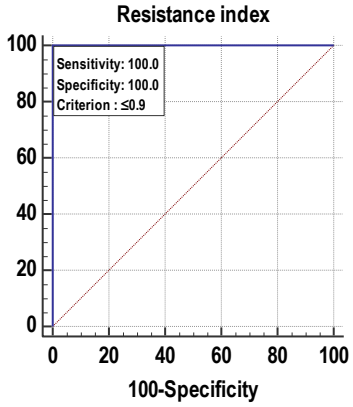

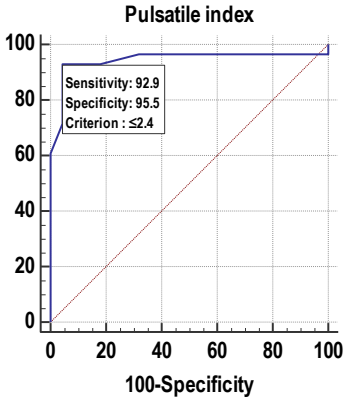

Receiver operating characteristic curve

In the majority [28(56.00%)] of patients, the resistance index was <1. The resistance index was >=1 in only 22 out of 50 patients (44.00%). The mean value of the resistance index of study subjects was 0.92 ± 0.31.

In the majority [27(54.00%)] of patients, the pulsatile index was <2.5. The pulsatile index was >=2.5 in only 23 out of 50 patients (46.00%). The mean value of the pulsatile index of study subjects was 2.52 ± 1 . Proportion of patients conceived was significantly higher in resistance index<1(100%) as compared to resistance index >=1(0%). (p-value <.0001) and in pulsatile index <2.5(96.30%) as compared to pulsatile index >=2.5(8.70%). (p-value <.0001)

The area under the ROC curve showed that the performance of the resistance index (AUC 1; 95% CI: 0.929 to 1.000) and pulsatile index (AUC 0.943; 95% CI: 0.839 to 0.989) was outstanding.

Table 8:- Multivariate logistic regression to find out significant independent risk factors of conception.

Variables	Beta coefficient	Standard error	P value	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
End diastolic velocity (cm/s)	0.176	0.825	0.831	1.192	0.236	6.010
S/D ratio	0.125	0.485	0.797	1.133	0.438	2.929
Tmax(cm/s)	-0.116	0.768	0.880	0.890	0.197	4.014
Tmean(cm/s)	-0.152	1.500	0.919	0.859	0.045	16.233
Endometrial thickness (mm)						
<7				1.000		
>=7	0.927	1.948	0.634	2.527	0.056	115.041
Resistance index						
<1				1.000		
>=1	-4.130	2.816	0.142	0.016	0.000	4.008
Pulsatile index						
<2.5				1.000		
>=2.5	-1.122	2.049	0.584	0.326	0.006	18.052

On performing multivariate logistic regression, none of the factors was an independent factor affecting conception.

Discussion

The present study showed that 76 % of patients belonged to the age group of 20-30 years while the remaining belonged to the group of 31-40 years. No significant

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association was noted between age and conception status. Hashad et al 5 and El-Shourbagy et al6 found a similar result in different studies. Although increasing age has been linked with declining fertility, according to a meta-analysis done by Chua SJ et al **7**.

Of the total individuals enrolled in this study, 56% conceived while the rest did not. The distribution of conception was comparable between the types of infertility. Primary infertility comprised 61.11% of individuals while 42.86% were categorized under secondary infertility. Naturally conceived patients were 46.43%, followed by the same through IUI (32.14%) and IVF (21.43%).

In this study, 58% of patients presented with an ET of over 7 mm, out of which 93% conceived successfully (Image 1**).** The mean ET in conceived individuals was (9.88 ± 1.61) mm which was significantly higher as compared to those who were not conceived (5.73 ± 1.23) mm. The results were consistent with the different studies conducted by Khan et al8, Noyes et al.9**,** and Kovacs et al.10**.** They found that women with ET greater than 7 mm had considerably increased pregnancy rates, and those with endometrial thickness less than 7 mm had no reported pregnancies. According to Okohue et al 11a higher rate of conception was associated with an endometrial thickness of at least 6.5 mm. Casper RF12 hypothesized that oxygen tension might be connected to thinner endometrium which leads to implantation failure. The functional layer is thin or missing when the thickness assessed by ultrasound is less than 7 mm, which places the embryo considerably closer to the spiral arteries and the basal endometrial increased vascularity and oxygen concentrations.

The mean peak systolic velocity in conceived women was 13.18 ± 3.62 cm/s which was higher as compared to (11.55 ± 3.47) cm/s in non-conception menstrual cycles (Image 2)**.** This was no significant association between them. Similar results were obtained by Ivanovski et al**.**13 while Zollner et al 14 and Engmann et al**.**15. They did not find any significant association between the two. A statistically significant association was observed between conception and end-diastolic velocity. In conception cycles it was (4.31 ± 1.17) cm/s which was significantly higher as compared to non-conception cycles (1.7 ± 0.74) cm/s. Similarly, the S/D ratio also showed a statistically significant association with conception where the mean S/D ratio in not conceived was (7.26 ± 1.81) which was significantly higher as compared to conceived (3.15 ± 0.9). Similar results were observed by Hassan et al16. Whereas Zarad A et al17 showed a higher S/D ratio in the infertile group compared to the fertile group.

A significant association was noted between conception status and Tmax and between conception status and Tmin (Image 3)**.** Tmax and Tmin in conceived women were (5.25 ± 2.25) cm/s and (2.63 ± 1.1) cm/s respectively which was significantly higher as compared to not conceived, in which it was (3.42 ± 1.13)cm/s and (1.9 ± 0.64)cm/s respectively. Wang et al. 18 showed a favorable link between the success of IVF/ET and endometrial and as well as sub endometrial blood flow. According to Sardana et al.19, regular clinical practice should include the combination of endometrial thickness and Doppler examination of endometrial blood flow as a quick and efficient way to enhance the success of IVF/ET.

In the current study, 96.3% of the women who conceived had a lower PI (pulsatility index) (< 2.5); whereas the majority of women who did not conceive had a higher PI (>=2.5) (Image 4). This was consistent with studies done by Tohma et al 20 and Czekierdowski et al 21 who observed elevated uterine artery impedance in cases of unexplained infertility and attributed that to a diminished uterine response to circulating ovarian hormones.

The RI (resistive index) showed a statistically significant relation with the conception status; in which it was observed that irrespective of the type of infertility, 100% of women who conceived showed the RI to be less than 1 whereas in women who did not conceive presented with the RI to be more than 1 (Image 4)**.** The studies by Selda et al22, El-Mazny23, andUysalet al 24 revealed that, compared to fertile women, women with unexplained infertility had considerably higher uterine artery PI and RI. The best cut-off value of RI was less than 0.9 for predicting conception status with sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 100% each. However, none of the Doppler indices behaved as independent factors affecting conception on multivariate logistic regression analysis.

Conclusion

Transvaginal Doppler ultrasound examination of the mid-luteal phase spiral artery of the sub-endometrial region has a very important role in clinical practice as well as in research settings. There are various research articles on this, some of them showing a significant correlation between the blood flow to the endometrium and pregnancy outcome in subfertile women and some of them didn't show a significant correlation. In this study, sub endometrial spiral artery various Doppler indices like ET, EDV, S/D, RI, PI, Tman & Tmin showed significant association with conception.

Limitation

This study did not include a healthy control group as a comparison group. The samples were mainly from the women visiting the tertiary care center seeking treatment hence the sample cannot be representative of the entire population. Various treatment modalities were employed for different individuals such as IVF, IUI, or a natural conception. The above-mentioned parameters were not compared with each group separately.

Recommendation

Due to rapid advancement in Doppler technology, it is highly recommended to perform transvaginal USG including Doppler for assessment of Doppler indices mid-luteal phase in subfertile women coming for treatment. The inclusion of a control group will further increase the accuracy of pregnancy outcome prediction based on TVS including color Doppler study.

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Conflict of interest

No conflict of interest.

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