IS Three D power Doppler of the endometrial and sub endometrial regions effective in predicting endometrial implantation? Prospective cohort study

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Abstract

Objective: This study aimed to evaluate the three dimension power Doppler indices together with uterine artery Doppler indices during the day of embryo transfer in predicting the outcome of ICSI cycle.

Study design: One hundred and three healthy women with singleton pregnancy werprospective cohort study.

Patient and methods: One hundred twenty patients were included in the study during ICSI cycles. This work was done at IVF unite of Dar El Teb hospital, Egypt. All patients included in the work had these criteria; age; 22–35 years, BMI; < 35 kg/m^2, oligo- or oligoasthenospermia. All patients received along agonist protocol of ovarian hyperstimulation and after follicular retrieval; embryos were transferred at the stage of blastocyst. Three D Power Doppler was done at the day of embryo transfer. Quantitative pregnancy tests were done for every patient. The rates of clinical and ongoing pregnancy were estimated. All women were categorized into two categories: with pregnancy and without pregnancy.

Results: Thirty-five percent of patients became pregnant. Our study showed non-significant differences in both groups regarding demographic, clinical and laboratory data except for some vascular parameters (endometrial VI, FI, VFI-subendometrial FI- u PI). Our study revealed a significant increase of some vascular parameters (endometrial VI, FI, VFI-subendometrial FI- u PI).and correlated to pregnancy. The endometrial VFI is the most sensitive vascular parameter correlated to pregnancy.

Conclusion: 3DPD is a useful non invasive predictor for IVF outcome.

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INTRODUCTION

Many factors determine the success in the cycle of IVF/ET; few of them are known to be directly related to the successful outcome. The implantation of good quality embryos remains a rate limiting step in IVF/ET management .In spite of the advances in ovarian stimulation protocols, improvement in culture conditions and the method of assisted fertilization, the implantation rate remains low. The success of embryo implantation depends on a dialogue between the transferred embryo and the receptive endometrium (1).

The receptivity of endometrium was investigated by different strategies like the histological dating of an endometrial biopsy (2), intra-uterine flushing for detection of endometrial cytokines (3), the genomic study of a timed endometrial sample(4). Nevertheless, ERA requires an invasive method, and high cost. Ultrasound can evaluate changes in the endometrium during stimulated cycles by non-invasive technique (5).

The uterine receptivity are controlled by many variables like the endometrial, and the sub-endometrial perfusion (6, 7).Many studies observed a positive correlation between the characteristics of endometrium, and implantation rate after IVF/ ICSI cycles, and the poor uterine receptivity was related to impaired blood flow in endometrial and sub-endometrial regions (8, 9, 10).

Ultrasonography was used as a non invasive tool to measure the endometrial thickness to show the effect of endometrial thickness on embryo implantation and endometrial receptivity but unfortunately conflicting findings were obtained. (11).

Some tried to assess the flow of blood in the uterine arteries by Doppler US and they found that uterine arteries Doppler did not represent the actual blood flow in the endometriam .Others tried to use three-dimensional power Doppler ultrasound for measurements of endometrial and sub-endometrial blood flows (1).The endometrial receptivity was evaluated in the endometrial and sub-endometrial blood supplies, especially in intrauterine insemination and IVF-ET cycles (12). This study aimed to investigate the three dimensional power Doppler indices together with uterine artery Doppler indices at the day of embryo transfer in predicting the outcome of ICSI cycle.

Patient and methods:

This prospective cohort research was done at IVF unit of Dar El Teb, Dokki, Egypt, since January 2015 till September 2019. Before the conduction of the study, the Local Ethical Committee approved the work. All women gave consent to participate in the work. One hundred twenty couples included in the work had these criteria; age; 22–35 years, BMI; < 35 kg/m2, male factor with oligo- or oligoasthenospermia. Exclusion criteria; -gross pathology in the uterus and tube, -Development of OHSS, -inadequate response to super ovulation, -failure of mature ovum to fertilize or inadequate development of the embryos to the stage of blastocyst and - If the couple refused to be included in the work at any stage of the treatment cycle.

All patients received long protocol for controlled ovarian overstimulation as described by Chang et al (13). The LHRH agonist ampoules were commenced in the prior mid-luteal phase (decapeptyl R 0.1mg, Triptorelin-Acetate, Ferring GmbH, Wittland 11, D-24109, and Kiel, Germany). After the pituitary down regulation was confirmed, the r FSH vials were given by 225 IU/day (Gonapure 75 IU, IBSA Institute Biochimique SA, Switzerland). During the follow up period of hyperstimulation, dosages were scheduled regarding the response of every woman.

When at least three dominant follicles (a size 18-20 mm) were reached in every patient, the HCG 10000 IU (Epifassi 5000 IU, Epico, Egypt) was taken. The follicles were retrieved 35 hours following HCG administration. Dydrogesterone 30 mg daily (Duphaston, Dydrogesterone 10 mg, Abbott, Pentapharma, Egypt) was used to support the luteal phase. At the day of embryo transfer (blastocyst stage), every woman underwent 3 D power Doppler US. Serum pregnancy test was done after twelve days later to embryo transfer, and if positive (chemical pregnancy), the TVS was used to detect clinical pregnancy while the ongoing pregnancy was detected at the end of first trimester.

Technique of 3D Power Doppler:

We used dedicated 3D transducers to obtain 3D US image. Firstly, determination of the volume box. Secondly, activation of the 3D probe while it was held stationary. Thirdly, the volume data were presented in multi planner display. By using 3D Power-Doppler ultrasound and the VOCAL program (the rotation angel was 30° in our study), we can evaluate the tissue vascularity. Three vascular parameters were used: the Vascularization Index (VI) represents the number of the blood vessels inside the volume box. Flow Index (FI) represents the intensity of blood flow within the area of interest. The Vascular-Flow Index (VFI) represents the number of the blood vessels and the intensity of blood flow within the area of interest. (14) (Figure 1). The "shell" function was used at different

thickness around the predetermined endometrium (in this study, it is estimated to be 5 mm) to measure the sub endometrial volume and estimate the vascularization in this region". (Figure 2)

Statistical analysis

Calculation of the sample size was done by using Open Epi (version 3, open source calculator-SSProor) depending on the number of patients fulfilling inclusion criteria in 6 months and attending to IVF unit of Dar El Teb hospital was estimated by 185 patients and percentage of ICSI success in a prior research is 32.4%(15), so to obtain a research power 80% and CI 95%, at least 120 patients must be included in the research. The variables were presented as mean ±SD. Independent t-test, Mann -Whitney-test and ROC curve analysis were used for statistical analysis. The SPSS program Version 18 was used. The statistical significance was considered when P value <0.05.

Results

Nine patients were excluded from the work from 129 women participating in the study due to; development of OHSS in 2 patients, 2 patients with inadequate ovarian response, failure of mature ovum to fertilize in 3 patients or inadequate development of the embryos to the stage of blastocyst in 2 patients. Figure 1

All included patients had demographic, clinical and laboratory data as presented in table 1. On assessment of serum pregnancy tests, it was found the chemical pregnancy was 39.2% while clinical pregnancy rate was 35%. Only 11 patients had abortions at 7-12 weeks gestation (ongoing pregnancy rate =25.8%). The included women were subdivided into two groups; group A (with pregnancy) and group B (with non pregnancy). Table 2. The no significant differences in both groups regarding the demographic data were presented in Table 1

Assessment of endometrial-sub endometrial and uterine blood flow at the day of embryo transfer, revealed significant increase of endometrial vascularity(VI,FI,VFI) in the pregnant women, significant increase of sub endometrial blood flow (FI) in the pregnant women. Also significant increase of pulsatility index of uterine artery correlated with pregnancy. The endometrial volume was comparable in both groups. Table 1

At the day of embryo transfer,3 D power Doppler of the endometrial and sub endometrial areas and uterine artery Doppler were used to predict endometrial implantation by The ROC curve analysis .The areas under the curve for E VFI, u PI,E FI ,SE FI and E VI were 0.82, 0.75. 0.66, 0.65, and 0.62 at a cut off ≥ 0.96 & ≤ 1.5, ≥ 26.7, ≥ 19.9, ≥ 19.8, ≥ 4.7 indicating that the endometrial VFI is more sensitive and specific than other vascular parameters. Table 3

In other words, the endometrial VFI is the most sensitive endometrial vascular parameter (figure 3), while the sub endometrial FI is the only sensitive sub endometrial vascular parameter (figure 4)detected by 3D PD US. On evaluation of the colour Doppler of uterine artery, it was found that only the u PI was significantly correlated to pregnancy. (Figure 5)

Discussion:

The 3D PD-US angiography is the most important diagnostic tool to evaluate restricted tissue, by showing and calculating relevant parameters (16, 17, and 18).The power Doppler ultrasound has extreme sensitivity to slight blood flow to detect overlapping vessels (19). The restricted tissue like endometrium is important for uterine receptivity (18). Our study showed that the thickness and volume of endometrium were not correlated with pregnancy.

The endometrial thickness was investigated for several years for detection of its relation to pregnancy and the results were controversial because the endometrial thickness was affected by different factors like mechanical stimulation or by the ovarian stimulation treatment method (18). For some times, the endometrial volume was considered an important index for endometrial receptivity with reporting it should be at least 2.0–2.5 ml for establishing pregnancy (20) while another research showed no pregnancy with volume less than 1ml (21). Our study, similar to several studies (22, 23, and 24), found no relation between the endometrial volume together with the endometrial thickness and pregnancy while others concluded a positive

correlation with pregnancy (17). This controversy can be seen in other view as the impact of endometrial thickness or volume on the pregnancy was favored by endometrial vascularization that should be investigated (25, 26). Because sufficient blood supply is necessary for endometrial receptivity (24), the endometrial neomicrovascularisation increases significantly in the follicular and early luteal phase (27) and is affected by different factors like age, medication, hormones (23). The endometrial neomicrovascularisation can be assessed by power Doppler combined with 3D US(17).Vascular indices like VI, FI, and VFI, can be estimated from the total number of color voxels and intensity of blood flow (28).Our study, similar to Wang et al (29) and Singh et al (1), found a positive correlation with pregnancy regarding endometrial vascular indices and sub endometrial flow index, in spite of the assessment of vascularization was questioned in different reports (30, 31,32). The clinical value of 3D-PD US has been intensively studied. Jinno et al (33) stated that the endometrial blood flow during second half of the cycle could predict the outcome in IVF cycles. Ng et al (23) found a positive correlation between flow of blood in endometrial and sub endometrial regions and pregnancy outcome. Furthermore there was a positive correlation between flow of blood in sub endometrial region and some cytokines like IL 15(34) and IL 18 and IL 18 B P (35). Our study, similar to Kim et al (16), found that the endometrial VFI was the most sensitive vascular parameter in predicting pregnancy (0.8) so it is included, recently, in Ultrasound multimodal score to assess the endometrial receptivity. The total score was 18, the lower the score, the worse the endometrial receptivity, and vice versa (36). Based on these results, it is reasonable to hypothesize that the endometrial vascularity is correlated to embryo implantation.

Othman et al (37) stated that the blood flow, in the endometrial and sub endometrial tissue, differed significantly according to BMI. It was lower in obese and overweight women. In obese women, the relatively hyperestogenemia may have negative impact on the receptivity of the endometrium (38).Also the relatively hyper insulinemia decreases the glycodelin level that reduces the fertility at the level of endometriam. (39, 40)

Numerous studies have evaluated the value of measurement of vascularity in endometrial and sub endometrial regions in predicting IVF outcome, at the day of embryo transfer and the day of HCG administration but the results were conflicting(19, 24 , 41, 42, 43, 44, 45). These conflicting results and the variations of day timing of measurement explained why still no consensus as to when these measurements should be done (24).

Different thickness of sub endometrial shell was used to assess the sub endometrial vascularity. Some used 2mm (24) and5mm (19) while others used 1mm (22, 23). Our study used 5mm shell. The difference of thickness of subendometrial shell between different studies explained the variation of measurements.

This study was limited as it included only women received long agonist protocol and shell of 5 mm in the sub endometrial region. Our protocol of COS cannot be generalized to other protocols of IVF. Also, this study did not compare other rFSH types.

Conclusion

The use of 3DPD to predict embryo implantation in IVF is of significant value.

Abbreviations

Ovarian hyperstimulation syndrome (OHSS), Estradiol (E2), gonadotropin-releasing hormone agonist (GnRH-a), Luteinizing hormone (LH), in-vitro fertilization (IVF), intra-cytoplasmic sperm injection (ICSI), trans vaginal ultrasound (TVS), human chorionic gonadotropin (hCG), interleukin (IL), embryo transfer (ET), assisted reproductive technology (ART), percent (%),kilogram per square meter Kg/m2 (Kg/m2), recombinant follicle stimulating hormone (rFSH), milli international unit (mIU), milligram (mg), millimeter (mm), number (NO), SD (standard deviation), metaphase 2 (M11) Odd Ratio (OR) confidence interval(CI) , region of interest (ROI) , virtual organ computer aided Analysis(VOCAL) , binding protein (BP) , controlled ovarian stimulation (COS) ,Three dimensions Power Doppler Ultrasound(3 DPD US) ,uterine artery pulsatility index (u PI) , Vascularization Index (VI), Flow Index (FI) Vascular-Flow

Index (VFI),endometrial(E) subendometrial(SE),Endometrial Receptivity Array(ERA).

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study were available from the corresponding author on reasonable request.

Authors' contributions

KMS: Analysis, Manuscript Drafting, Acquisition of data, Critical Discussion, Management and Follow up of cases; IIS: Study Design, Manuscript Drafting, Acquisition and interpretation of data, Management and Follow up of cases;. Both authors read and approved the final manuscript.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the Local Ethical Committee of Benha University Hospital and written informed consent was obtained from each participant before the study.

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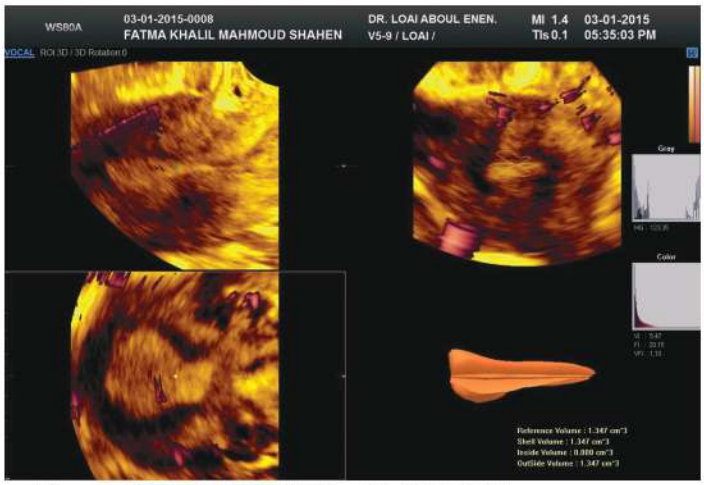

Figure (1): 3 D PD US with VOCAL programme showing endometrial VI, FI, and VFI.

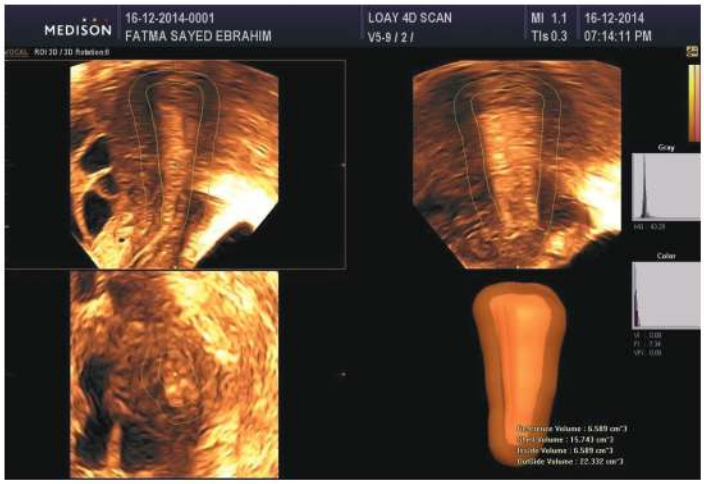

Figure (2):3 D PD US with VOCAL programme showing subendometrial VI, FI, and VFI.

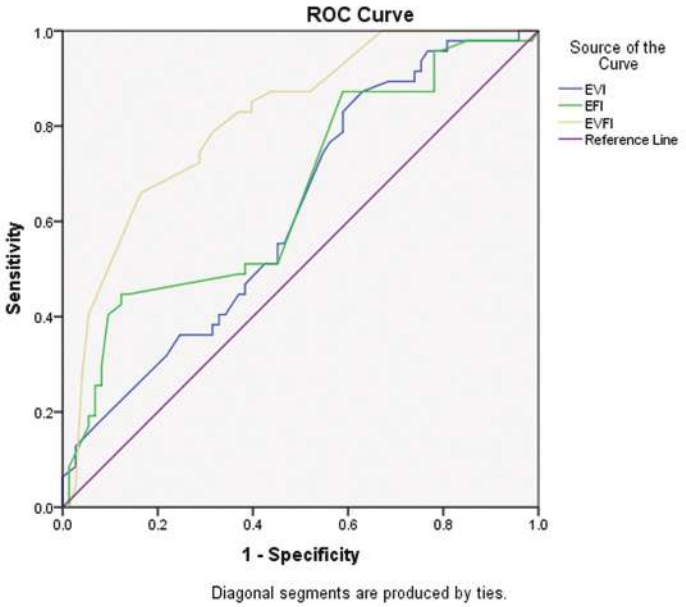

Figure (3):ROC curve of endometrial vascular indices

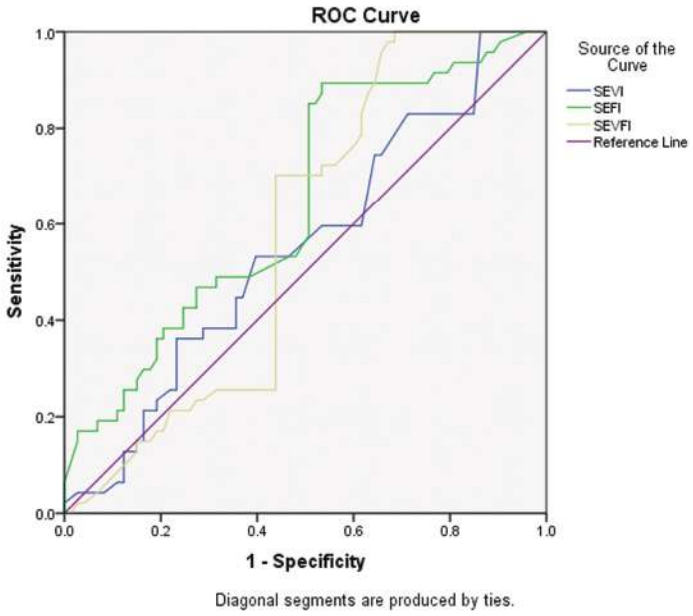

Figure (4): ROC curve of subendometrial vascular indices

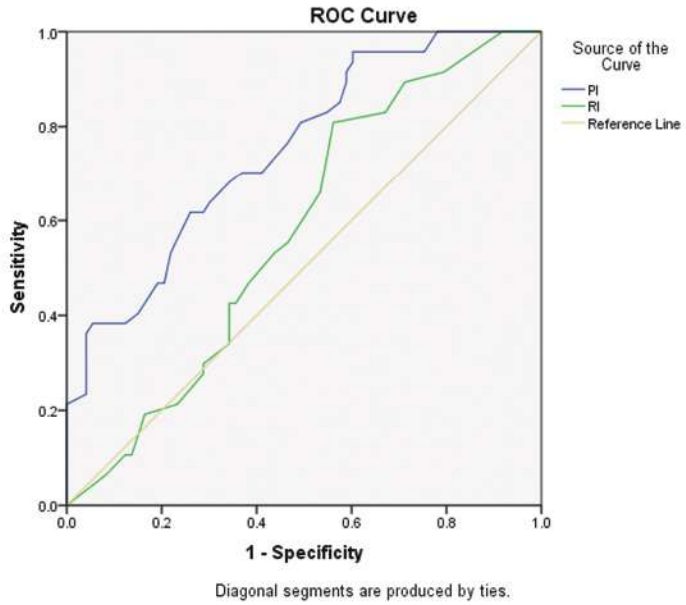

Figure (5):ROC curve of uterine artery Doppler indices

Table 1: shows demographic, clinical and laboratory data and their relations to pregnancy

Variables	Pregnant (n=47)	Non-pregnant (n=73)	Total (n=120)	t	p
Age (years)	29.87±4.2 (20.0-35.0)	30.38±4.28 (23.0-35.0)	31.52±6.48 (20.0-35.0)	0.64	0.52
BMI (kg/m^2)	30.56±3.54 (23.41-38.37)	29.92±2.35 (23.67-39.64)	30.28±3.27 (23.41-39.64)	1.18	0.24
Duration of infertility (year)	5.66 ± 1.56 (3-9)	5.6±2.11 (2-10)	5.79±2.56(2-10)	0.16	0.87
No. of HMG amp	29.94±2.38 (25-37)	30.85±1.84 (26-37)	30.49±2.62 (25-37)	1.89	0.062
Duration of induction : (day)	2.94±1.63 (11-15)	13.32±1.29 (11-15)	13.17±1.44 (11-15)	1.41	0.16
No. of follicles retrieved	15.06±5.08 (9-26)	15.22±4.25 (7-25)	15.16±4.57 (7-26)	0.18	0.86
No. of Metaphase II oocytes:	8.49±2.33 (5-15)	8.7±2.37 (5-14)	8.62±2.35 (5-15)	0.48	0.64
No. of transferred blastocyst:	2.72±0.62 (2-4)	2.68±0.72 (2-4)	2.70±0.68 (2-4)	0.30	0.76
Endometrial VI	4.69±0.89 (0.33-5.52)	4.24±1.28 (0.28-5.51)	4.41±1.16 (0.28-5.52	2.1	0.038*
Endometrial FI	20.21±1.31 (17-22)	19.44±1.22 (17-23)	19.46±1.19 (17-23)	10.72	0.001**
Endometrial VFI	1.1±0.17 (0.86-1.4)	0.90±0.19 (0.06-1.5)	0.98±0.21 (0.06-1.5)	6.26	<0.001**
Endometrial volume	5.62±1.98 (3.572-8.922)	4.94±2.41 (1.26-8.79)	5.35±2.36 (1.26-8.922)	1.6	0.112
Sub VI	2.16±1.71 (0.67-5.93)	1.95±1.78 (0.06-5.86)	2.03±1.75 (0.06-5.93)	0.64	0.53
Sub FI	36.03±20.75 (7.34-65.88)	27.34±20.07 (6.73-65.62)	30.74±20.70 (6.73-65.88)	5.22	0.024*
Sub VFI	1.26±0.67 (0.57-2.48)	1.20±0.98 (0.01-2.53)	0.83±0.78 (0.01-2.53)	0.40	0.69
PI	1.41±0.15 (1.22-1.83)	1.59±0.22 (1.29-1.90)	1.56±0.21 (1.22-1.90)	5.1	<0.001**
RI	0.83±0.06 (0.72-0.92)	0.85±0.07 (0.72-0.95)	0.84±0.07 (0.72-0.95)	1.21	0.23
Endometrial thickness	12.77±0.69 (11.3-13.9)	12.91±0.48 (11.4-14.3)	12.66±0.92 (11.3-14.3)	1.27	0.21
Basal FSH	6.78±0.49 (6.28-7.7)	6.79±0.42 (6.3-7.7)	6.79±0.45 (6.28-7.7)	0.14	0.89
Basal LH	6.07±0.91 (4.9-7.6)	5.92±0.88 (4.8-7.5)	6.09±0.93 (4.8-7.6)	0.87	0.39

Data are presented as mean±SD, and ranges are in parenthesis; *: Significant ($p<0.05$); **: Highly Significant ($p<0.01$)

Variables	(n=120)	
	No.	%
Pregnancy test		
-ve	73	60.8
+ve	47	39.2
Chemical pregnancy rate	47	39.2
Clinical pregnancy rate	42	35.0
Ongoing pregnancy rate	31	25.8
No. of gestational sac (47)		
1	27	57.4
2	15	31.9
3	5	4.2

Table 3: shows validity of some predictors in prediction of success ICSI.

Variable	Cutoff	AUC	CI	Sens.	Spec.	+PV	-PV	Accu-racy	p-value
EVI	≥4.66	0.62	0.52-0.72	40.4	67.1	44.2	63.6	56.7	0.027*
EFI	≥19.87	0.66	0.56-0.76	51.1	61.6	46.2	66.2	57.5	0.003**
EVFI	≥0.96	0.82	0.74-0.89	74.5	71.2	62.5	81.2	72.5	<0.001**
SEVI	≥1.35	0.55	0.45-0.66	53.2	60.3	46.3	66.7	57.5	0.34
SEFI	≥19.79	0.65	0.55-0.75	55.3	50.7	41.9	63.8	52.5	0.008**
SEVFI	≥1.01	0.58	0.48-0.68	63.8	56.2	48.4	70.7	59.2	0.14
PI	≤1.47	0.751	0.664-0.838	68.1	65.8	56.1	76.2	66.7	<0.001**
RI	≤0.86	0.578	0.476-0.68	61.7	49.3	43.9	66.7	54.2	0.15

AUC: Area under curve; CI: Confidence interval; +PV: Positive predictive value; -PV: Negative predictive value; Sens.: Sensitivity; Spec.: Specificity; *: Significant (p<0.05); **: Highly Significant (p<0.01)