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Evaluation of The Role of 3D Power Doppler in Predicting the Viability of The Endometrium to Receive Embryos for ICSI Patients

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ABSTRACT

Background: Embryo implantation is an important event in both natural and assisted human reproduction. The benefit of 3D power Doppler is that it can measure endometrial blood flow and endometrial volume (EV) at the same time. We wanted to check whether 3D power Doppler characteristics might be utilized to predict pregnancy and implantation on the day of HCG injection during an intracytoplasmic sperm injection (ICSI) and embryo transfer procedure.

Methods: This was a cross-sectional study done on 100 women EVF unit. Study was conducted in Al-Hussein University Hospital, Al-Azhar University, between May 2021 and February 2022. Before the conduction of the study, the Local Ethical Committee approved the work. All women gave consent to participate in the work.

Results: There was significant increase in endometrial VI, FI, VFI and thickness in injection day in cases became pregnant compared to those who did not fulfill pregnancy. PI and RI were significantly decreased in pregnant group. No significant difference between pregnant and non-pregnant groups concerning endometrial volume.

Conclusion: 3D power Doppler is a useful noninvasive predictor for predicting the viability of the endometrium to receive embryos for ICSI patients.

Key words: 3D power Doppler, ICSI, Viability of endometrium, Receive of embryo**.**

INTRODUCTION

The procedures employed in assisted reproductive technologies (ART) have substantially evolved since the first IVF birth in 1978 [(1)]. There are now techniques for assessing endometrial condition and identifying high-quality embryos. Furthermore, ART processes are constantly improving in order to achieve greater pregnancy rates, fewer multiple births, and healthier offspring from genetically modified progenitors [(2)]. Despite these gains, birth rates remain low and have not grown much over the recent decade. This implies that implantation rates in stimulated cycles will continue to be poor [(3)].

Embryo implantation is an important event in both natural and assisted human reproduction. Embryo apposition, adhesion to the maternal endometrial epithelium, and penetration into the endometrial stroma are all part of the dynamic process of blastocyst implantation. Implantation failure during IVF may occur for a variety of reasons, including poor embryo quality, which has been recognised as a substantial cause of implantation failure [(4)]. A poorly formed endometrium is another well-known impediment to effective blastocyst implantation. Embryos cannot implant in a poorly developed endometrium, which might explain why implantation rates are low when "high grade" embryos are transferred [(5)]. Furthermore, communication between the embryo and a receptive endometrium is essential for embryonic implantation to be effective. Endometrial receptivity may be assessed through histological analysis of an endometrial sample, identification of endometrial proteins in uterine flushes, or, more often, noninvasive ultrasonography screening of the endometrium [(6)].

Angiogenesis is clearly involved in a variety of female reproductive processes, including the establishment of a dominant follicle, the formation of the corpus luteum, endometrial expansion, and implantation. As a result, several studies have focused on ovarian and endometrial vascularization to predict the efficacy of IVF therapy. Endometrial blood flow accurately portrays uterine receptivity since the endometrium is the location of embryonic implantation [(7)]. However, when vessels can be seen reaching the subendometrial halo and the endometrium, the pregnancy rate rises [(8)].

Endometrium ultrasonography and uterine and endometrial blood flow analysis have long been utilized to predict implantation in IVF and embryo transfer cycles [(9)]. Their findings, however, are contested when utilized to predict IVF outcomes. False-positive findings have been reported for endometrial receptivity markers such as a triple-layer endometrial pattern and an endometrial thickness of more than 7 millimeters [(10)].

The benefit of 3D power Doppler is that it can measure endometrial blood flow and endometrial volume at the same time (EV). When utilized to evaluate endometrial receptivity, it also exhibits high intraobserver and interobserver repeatability for all endometrium ultrasound and 3D Doppler characteristics [(11)]. Our objective was to examine 3D power Doppler parameters as putative implantation indicators and pregnancy predictions on the day of HCG injections as part of an ICSI and embryo transfer program.

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MATERIAL AND METHODS

This was a cross-sectional study done on 100 women EVF unit. Study was conducted in Al-Hussein University Hospital, Al-Azhar University, between May 2021 and February 2022.

Inclusion criteria: Age; 22-35 years, BMI; < 35 kg/m^2, male factor with oligo- or oligoasthenospennia.

Exclusion criteria: Gross pathology in the uterus and tube, Development of DHSS, 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.

In all instances, **Chang *et al.*** [12] designed a protracted procedure for controlled ovarian overstimulation. During the prior mid-luteal period, the luteinizing hormone-releasing hormone (LHRH) agonist ampoules were begun. Following confirmation of pituitary downregulation, 225 IU/day r FSH vials were provided. Doses were adjusted throughout the hyperstimulation follow-up phase depending on each woman's response.

When at least three dominant follicles (a size 18- 20 mm) were reached in every patient, the HCG 10000 IU was taken. The follicles were retrieved 35 hours following HCG administration. Dydrogesterone 30 mg daily was utilized to support the luteal phase. At the day of embryo transfer, 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 utilized to detect clinical pregnancy while the ongoing pregnancy was detected at the end of first trimester.

3D power Doppler technique

We utilized dedicated 3D transducers to obtain 3D US image. Firstly, determination of the volume box. Secondly, activation of the 3D probes 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 degree), we can evaluate the tissue vascularity. Three vascular parameters were utilized 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 vessles and the intensity of blood flow within the area of interest [13]. The "shell" function was utilized at different thickness around the predetermined endometrium.

Ethical considerations:

The study was approved by the Ethics Board of Al-Azhar University.All patients were informed about the surgery and the auto transplantation technique, value and possible complications and informed written consent was taken from every patient. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

IBM SPSS version 22.0 was utilized to analyse computer-generated data. To express quantitative data, percentages and numbers were employed. We subdivided subjects to those who completed pregnancy till live birth and those who did not. Before utilizing the median in nonparametric analysis or the interquartile range in parametric analysis, it was required to perform Kolmogorov-Smirnov test to ensure that the data were normal. We utilized the 0.05 significance threshold to establish the significance of the findings. The Chi-Square test is utilized to compare two or more groups. The Monte Carlo test may be utilized to adjust for any number of cells with a count less than 5. Fischer Chi-Square adjustment was applied to 2 tables when at least a quarter of cells had a count of less than 5.

RESULTS

There was no significant difference between the two groups concerning basal characteristics (Table 1).

Table (1): Patients basal characteristics

	Pregnant (N=39)	Non-Pregnant (N=61)	P-Value
Maternal Age (years)	29.6 ± 4.26	27.59 ± 6.7	0.0984
Paternal Age (years)	35.68 ± 3.4	36.1 ± 3.3	0.54
BMI	29.43 ± 5.3	28.8 ± 6.7	0.62
Duration of infertility	5.43 ± 1.66	5.65 ± 1.87	0.55
Factors of infertility			
Male	13 (33.33%)	22 (36.07%)	0.78
Ovulatory	5 (12.82%)	9 (14.75%)	0.79
Tubal	7 (17.95%)	8 (13.11%)	0.5
Uterine	2 (5.13%)	3 (4.92%)	0.96
Mixed	8 (20.51%)	11 (18.03%)	0.76
Unexplained	4 (10.26%)	8 (13.11%)	0.67

P> 0.05 non-significant

There was no significant difference between the two groups concerning hormonal data of included subjects (Table 2).

Table (2): Hormonal data of included subjects

	Pregnant (N=39)	Non-Pregnant N=61)	P-Value
Baseline FSH (IU/L)	6.24 ± 1.3	6.1 ± 1.5	0.63
Baseline LH (IU/L)	3.5 ± 2.3	3.24 ± 2.43	0.595
Baseline PRL (nmol/L)	20.35 ± 12.1	21.65 ± 13.2	0.62
Baseline estradiol (pg/mL)	38.2 ± 13.26	39.4 ± 12.2	0.64
Baseline T (nmol/L)	0.82 ± 3.3	0.88 ± 3.4	0.93

P> 0.05 non-significant

There was no significant difference between the two groups concerning ICSI data of included subjects (Table 3).

Table (3): ICSI data of included subjects

	Pregnant (N=39)	Non-Pregnant (N=61)	P-Value
No. of HMG amp	31.24 ± 3.32	31.7 ± 3.75	0.53
Duration of induction (Day)	13.94 ± 1.66	13.32 ± 1.85	0.092
No. of follicles retrieved	16.6 ± 4.75	15.67 ± 5.15	0.366
No. of Metaphase II oocytes	10.48 ± 2.9	9.59 ± 2.87	0.13
No. of transferred blastocyst	3.2 ± 0.82	2.92 ± 0.84	0.1

P> 0.05 non-significant

There was significant increase in endometrial VI, FI, VFI and thickness in injection day in cases became pregnant compared to those who did not fulfill pregnancy. Plasticity Index and Resistance Index were significantly decreased in pregnant group. No significant difference between pregnant and non-pregnant groups concerning endometrial volume (Table 4).

Table (4): Endometrial parameters in the two groups

	Pregnant (N=39)	Non-Pregnant (N=61)	P-Value
Endometrial VI	4.62 ± 0.91	4.21 ± 1.25	0.026
Endometrial FI	20.4 ± 1.42	20.14 ± 1.32	0.0036
Endometrial VFI	1.14 ± 0.21	0.87 ± 0.14	0.007
Endometrial Volume	5.86 ± 1.89	5.28 ± 1.23	0.066
PI	1.35 ± 0.13	1.58 ± 0.21	<0.001
RI	0.82 ± 0.07	0.85 ± 0.06	0.003
Endometrial thickness injection day (mm)	11.38 ± 0.41	10.83 ± 0.39	<0.001

P< 0.05 significant, PI: Plasticity Index | RI: Resistance Index

Concerning EFI, with cut off value of 18.74, sensitivity reached 94.9% and specificity reached 98.4% with significance of 0.296. Concerning EVFI, with cut off value of 0.88, sensitivity reached 97.4% and specificity reached 47.5% with significance of < 0.0001. Concerning EV, with cut off value of 3.54, sensitivity reached 97.4% and specificity reached 96.7% with significance of 0.001. Concerning PI, with cut off value of 1.33, sensitivity reached 66.7% and specificity reached 98.4% with significance of <0.0001. Concerning RI, with cut off value of 0.775, sensitivity reached 79.5% and specificity reached 98.4% with significance of 0.001. Concerning endometrial thickness, with cut off value of 10.37 sensitivity reached 97.4% and specificity reached 98.4% with significance of <0.0001 (Table 5 & figure 1)).

Table (5): Validity of different parameters in prediction of success of ICSI and pregnancy occurrence

Parameter	Cut off Value	Area	Sensitivity	Specificity	Asymptotic 95% Confidence Interval		P-Value
					Lower Bound	Upper Bound	
EVI	3.76	0.572	94.9%	77%	0.461	0.683	0.224
EFI	18.74	0.562	94.9%	98.4%	0.442	0.682	0.296
EVFI	0.88	0.904	97.4%	47.5%	0.848	0.961	<0.0001
EV	3.54	0.697	97.4%	96.7%	0.580	0.813	0.001
PI	1.33	0.115	66.7%	98.4%	0.053	0.176	<0.0001
RI	0.775	0.298	79.5%	98.4%	0.188	0.409	0.001
Thickness	10.37	0.841	97.4%	98.4%	0.745	0.937	<0.0001

P < 0.05 significant

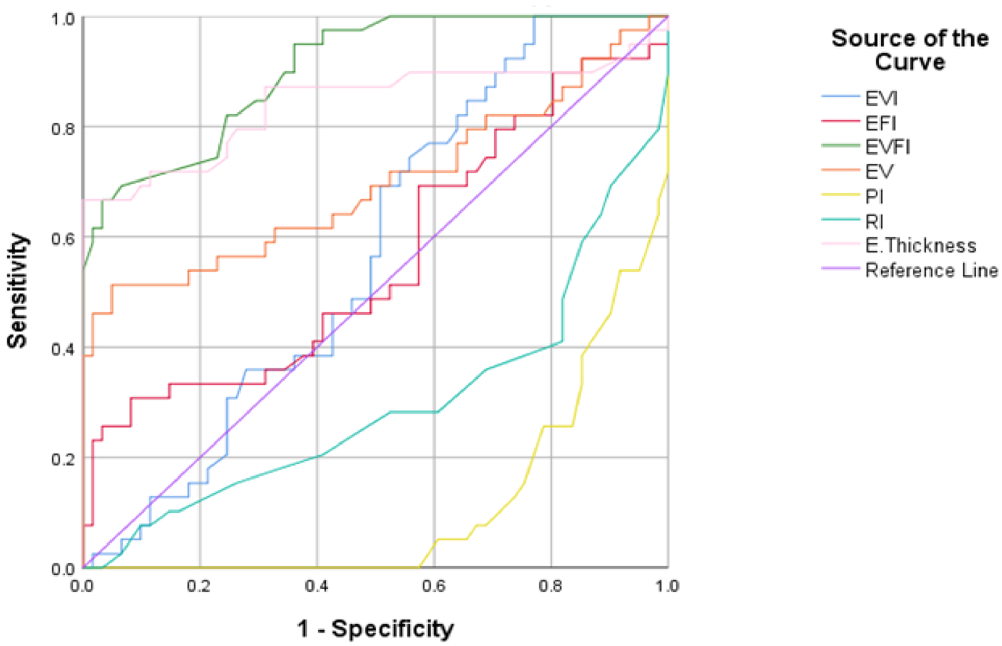

Figure (1): Roc curve analysis of different parameters in prediction of success of ICSI and pregnancy occurrence.

There was significant increase in endometrial thickness in cases became pregnant with live birth compared to cases aborted or became with ectopic pregnancy (Table 6).

Table (6): Different endometrial thicknesses according to pregnancy follow up outcomes

	Mean	SD	P value
Pregnant live birth (n=26)	11.62	0.071	P1 < 0.0001 P2 0.46 P3 < 0.0001
Pregnant miscarriage (n=8)	11.16	0.104	
Ectopic pregnancy (n=5)	10.595	0.352	

P1: Pregnant live birth & Ectopic pregnancy | P2: Pregnant miscarriage & Ectopic pregnancy | P3: Pregnant live birth & Ectopic pregnancy, P< 0.05 significant

DISCUSSION

The 3D PD is the most important diagnostic tool to evaluate restricted tissue, by showing and calculating relevant parameters. The power Doppler ultrasound has extreme sensitivity to slight blood flow to detect overlapping vessels. The restricted tissue like endometrium is important for uterine receptivity [(14)]. Because sufficient blood supply is necessary for endometrial receptivity, the endometrial neomicrovascularization increases significantly in the follicular and early luteal phase and is affected by different factors like age, medication and hormones [(15)]**.**

The endometrial neomicrovascularization can be assessed by power Doppler combined with 3D US [(16)].

Our study, similar to **Schild *et al.*** [(17)], found a positive correlation with pregnancy concerning endometrial vascular indices. In spite, the assessment of vascularization was questioned in different reports [(18)]. The clinical value of 3D-PD has been intensively studied. **Jinno *et al.*** [(19)] stated that the endometrial blood flow during second half of the cycle could predict the outcome in IVF cycles. **Ng *et al.*** [(14)] found a positive correlation between flow of blood in endometrial and subendometrial regions and pregnancy outcome. Also, along with our results on the day following HCG therapy, **Mercé *et al.*** [(20)] discovered a statistically significant increase in endometrial indices of vascularization, flow, and vascularization flow in the pregnant group.

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. 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 [(21)] while another research showed no pregnancy with volume less than 1 ml [(22)].

Concerning endometrial thickness, with cut off value of 10.37, sensitivity reached 97.4% and specificity reached 98.4% with significance of <0.0001. We found that there was significant increase in endometrial thickness in cases became pregnant with live birth compared to cases aborted or became with ectopic pregnancy. A recent study by **Souidan & Salama,** [15] found no relation between the endometrial volume together with the endometrial thickness and pregnancy. Our findings are consistent with those of a previous meta-analysis by **Kasius *et al*.,** [23] who found that an EMT of 7 mm or less is linked with a considerably lower likelihood of pregnancy after IVF–ICSI and embryo transfer therapy. The conception rate in women with an EMT of 7 mm or less was 23.3% in that meta-analysis, substantially lower than 48.1% in those with an EMT more than 7 mm. Our findings are remarkably comparable to those of **Yuan *et al*.** [24] who reported that women with EMTs less than 8 mm (lower 5th centile) had a conception rate of 23.0% (120/521), which rose dramatically to 41.4% (4252/10266) for women with EMTs of 8 mm or above. So far, published research seems to have produced good evidence of a link between a thin endometrium (8 mm) and a lower conception rate. A thick endometrium is a source of contention. A thick endometrium (>16, or 17 mm) has been linked to an increased likelihood of pregnancy in earlier studies [25].

3D power & endometrial volume, according to **Abuelghar *et al*.** [26] Doppler angiography indices were not predictive of clinical pregnancy after the current ICSI studies.

Yuan *et al.* [24] found that EMT reliably predicted clinical outcomes for intrauterine pregnancy, ectopic pregnancy, spontaneous abortion, and live delivery, similar to our findings. Patients with a thin endometrium should be given the option of freezing all embryos and transferring embryos in a frozen–thawed cycle if a thicker endometrium is possible, taking into account all of the negative consequences.

CONCLUSION

3D power Doppler is a useful noninvasive predictor for predicting the viability of the endometrium to receive embryos for ICSI patients.

Declarations:

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