Endometrial sonographic parameters in prediction of intracytoplasmic sperm injection outcome following fresh embryo transfer in normal responders: a cohort study

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ABSTRACT

Objective. To find the relation between the endometrial sonographic parameters and the success of ICSI in normal responders.

Material and Methods. A prospective cohort study was performed from September 2020 to March 2022 including 262 women normal responder women undergoing an ICSI cycle. Endometrial thickness (ET), endometrial pattern, and sub-endometrial blood flow were measured on the day of HCG. According to ET, the patients were classified into 3 groups: < 8 mm, 8-12 mm, and > 12 mm, according to endometrial pattern into a triple and non-triple line, as well as according to endo-sub endometrial blood flow into the zone I, zone II and zone III. Pregnancy rates were compared between all groups.

Results. The overall pregnancy rate among all groups was 43.12%. The clinical pregnancy rate was significantly lower with ET below 7 mm, but increased in the group with ET 8-12 mm 86/113 (76.1%), lower in the group with ET > 12 mm 25/113 (22.1%), and lowest when ET < 8 mm 2/113 (1.8%). The pregnancy rate in the triple endometrial pattern 70/113 (61.9%) is higher than in the non-triple pattern 43/113 (38.1%). However, the endo-sub endometrial blood flow did not affect the pregnancy rate significantly (P-value = 0.435).

Conclusions. Endometrial thickness exhibits a curvilinear relationship with pregnancy outcomes in fresh embryo transfer cycles. A triple ET 8 mm thickness or more, could be a reliable predictor for successful pregnancy outcomes in fresh ICSI cycles. Yet, ET (≤ 7 mm) and no triple-line endometrial pattern coexist in an ICSI candidate, cryopreservation should be recommended.

INTRODUCTION

Over the past three decades, assisted reproductive technology has been widely used in infertility treatment. Both endometrial receptivity and the quality of the embryo remain important predictors of ICSI success [1]. Endometrial receptivity is a key stage in embryo implantation, and ultrasound is considered a simple and appreciated technique in the evaluation of endometrium before embryo transfer [2]. The implantation success depends on harmony between the blastocyst and the endometrium [3]. Previous studies have explained that a good endometrium thickness on the day of embryo transfer resulted in a better pregnancy outcome, while other studies reported contradictory results. There is growing evidence regarding the role of sub-endometrial blood flow in embryo implantation; thus,

the evaluation of sub-endometrial blood flow is of immense importance in patients prepared for IVF [4]. Endometrial and sub-endometrial blood flows are better indicators than uterine artery Doppler which does not reflect the actual endometrial blood flow. However, their role in the prediction of pregnancy in IVF treatment is still contradictory due to a lack of large-scale systemic studies [5, 6]. Sonographic parameters, such as endometrial thickness (ET), endometrial pattern, endometrial volume, and endometrial or sub-endometrial blood flow are used to identify endometrial receptivity. The measurement of endometrial blood flow as a physiologic dimension in addition to the anatomic parameters gained by the ultrasound had played a significant role in the expectation of pregnancy outcomes in ICSI cycles [3, 6]. Although there have been numerous studies investigating the relationship between ET and pregnancy outcomes, there is still no consensus. The inconsistency of the results may attribute to many potential confounders such as maternal age, stimulation protocol used, number of oocytes retrieved, and embryos transferred [7]. Considering the promising role of ultrasound in ET daily practice, moderate evidence supports the beneficial effect of transvaginal ultrasound-guided embryo transfer in terms of the percentage of pregnancies per transfer, both in the general population and in the reference population, compared with transfers performed under transabdominal ultrasound guidance. Transvaginal ultrasound facilitates the performance of difficult transfers, even with easy transfers it facilitates non-traumatic approaches and, achieves outcomes of precise embryo deposition [8]. This study aimed to evaluate the role of the endometrial thickness, morphology, and endo-sub endometrial blood flows assessment by 2D power Doppler ultrasound in the prediction of pregnancy in normal responders undergoing fresh ICSI cycles.

PATIENTS AND METHODS

Study design and setting

This a prospective cohort study following the guideline highlighted in the Observational studies STROBE (https://www.equator-network.org/reporting-guidelines/strobe/). Our study was conducted at a private fertility and IVF centre in Zagazig, Egypt, during the period From September 2020 to March 2022. Assuming the difference in pregnancy rate is 10.1% and 23.92 % based on two different endometrial thickness groups, the sample size was 262 patients using open Epi at confidence 95% and power 80% [2].

Ethical consideration

This study has been approved by Institutional Review Board (IRB) committee number IRB-Zu-#:6370-26-8-2020. All enrolled women signed informed consent before participation in the study. We included all infertile women ages 20-39 years old, who were planning to undergo ICSI for male factor or tubal factor, uterine and pelvic causes, or unexplained infertility. We included and analysed all cases of normal responses, fresh embryo transfer, and blastocyst stage of the high or good-quality embryo We excluded from the study all Women who have the potential for either high response (*e.g.*, women with polycystic ovarian syndrome (PCOS)) or poor response (*e.g.*, age above 39 years old, reduced ovarian reserve, ovarian endometriosis, and previous poor response). We exclude all women below the age of 20 who were unable to give written consent.

Ovarian stimulation

Our cohort participants were initially assessed for their ovarian reserve: through transvaginal ultrasound, antral follicle count, anti-mullerian hormone, and FSH. All eligible normal responder participants received long agonist protocol: mid-luteal phase down-regulation using GnRH-a (triptorelene acetate 0.1 IU, Decapeptyl®, Ferring Pharmaceuticals) in a daily subcutaneous dose from day 21 of the preceding cycle till the day of hCG trigger. Women were down regulated when the serum FSH was suppressed to < 5 mIU/mL, LH to < 5 mIU/mL, and estradiol to < 50 pg/mL, and an ultrasound evaluation was performed to validate an endometrial thickness < 5 mm and a diameter of the largest bilateral ovarian follicle < 10 mm. Controlled ovarian stimulation (COS) was conducted using daily intramuscular injection of human menopausal gonadotropin (hMG) (Menogon® 75 IU, Ferring Pharmaceuticals) from day 2 of menstruation, the initial dose was determined by the patient's age, ovarian reserve tests, and prior ovarian response. The dose was either maintained or readjusted according to the serum estradiol level and sonographic folliculometry conducted 6 days after COS. When at least

3 dominant follicles reach a size above 18 mm in average dimension, 10,000 IU of hCG (Choriomon®, IBSA Pharmaceuticals) was given intramuscularly to trigger final oocyte maturation.

Ultrasound measurement

The fertility specialist physician evaluated all participants on the day of hCG triggering using a 2D transvaginal ultrasound machine (SonoScape S20 Pro, SonoScape Medical Corp., Guangdong, China;) with 7.5-9 MHz-convex array transducer as follows:

1. The grayscale function of the ultrasound machine is to measure the endometrial thickness as the thickest part of the endometrium between the highly reflective echogenic lines in the true longitudinal scan of the uterus.
2. The morphological pattern of the endometrial line was classified as a triple line or a non-triple line (**Figure 1**).
3. The Doppler function of the ultrasound machine was activated to evaluate the endo-sub endometrial blood flow or vascularization and is either, zone I in which the blood flow reached only the sub-endometrial region, zone II in which the blood flow reached the outer hyper-echoic region or zone III in which the blood flow reached the inner hypo-echoic zone (**Figure 2A-C**).
4. Finally, the pulsed Dopplers were activated to measure the Doppler indices of the endometrial vasculature. We applied the Doppler gate over the appropriate colour area and then tried to have five or more consecutive waveforms for the study to be satisfactory (each wave represented the maximum Doppler shift). Then we measure the resistive index = *Peak systolic velocities - Peak diastolic velocities/Peak systolic velocities*, and the standard of deviation ratio (S/D ratio) were calculated on three consecutive uniform waveforms (**Figure 2D**).

Oocyte retrieval was conducted at 34.5-37 hours after hCG injection. Only the oocyte that reached the MII phase was injected. All participants underwent fresh embryo transfer at the blastocyst stage. Included women received luteal phase support in the form of vaginal progesterone (Prontogest® sup., IBSA 400 mg) twice per day till the day of quantitative serum hCG assay. Women with unexpectedly low responses (3 or fewer retrieved oocytes), high responses (more than 18 retrieved oocytes), and those who had no blastocyst-stage embryo transfer were excluded from the analysis.

Study outcomes

They included positive biochemical pregnancy (defined as positive serum hCG level above 25 IU/L 14 days after embryo transfer), positive clinical pregnancy (defined as sonographic detection of the viable gestational sac(s)), and positive ongoing clinical pregnancy (defined as sonographic detection of the viable gestational sac(s) beyond 12 weeks of gestation).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS Inc, Chicago) version 24 for Microsoft Windows. Data were described in terms of mean ± SEM (standard error of
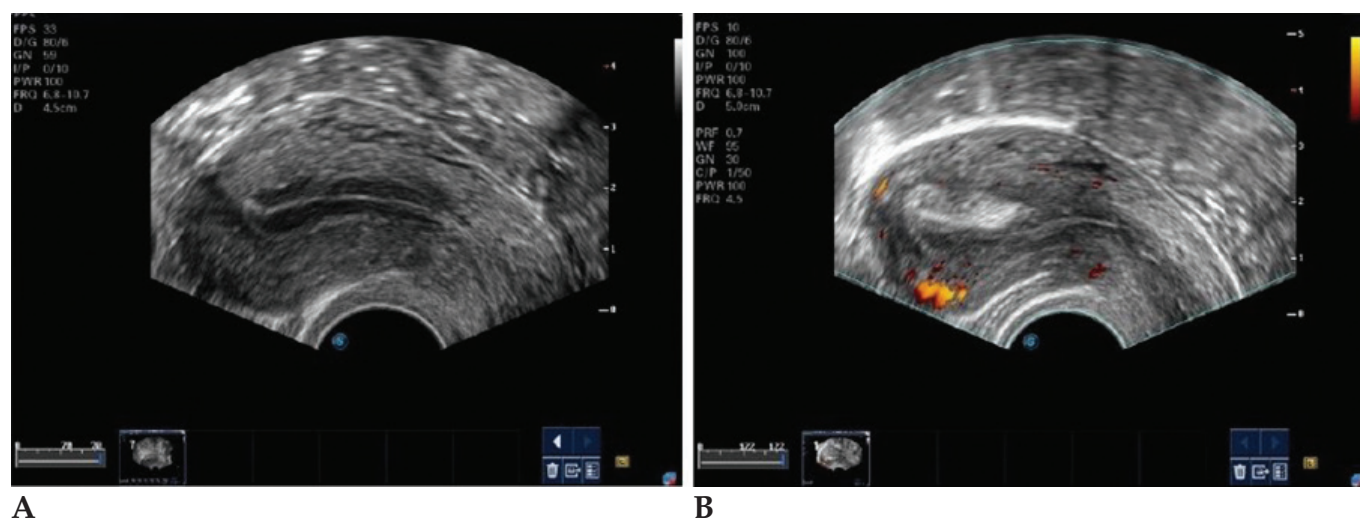

A   **B**

Figure 1. *Longitudinal ultrasound images demonstrate the endometrial pattern.*
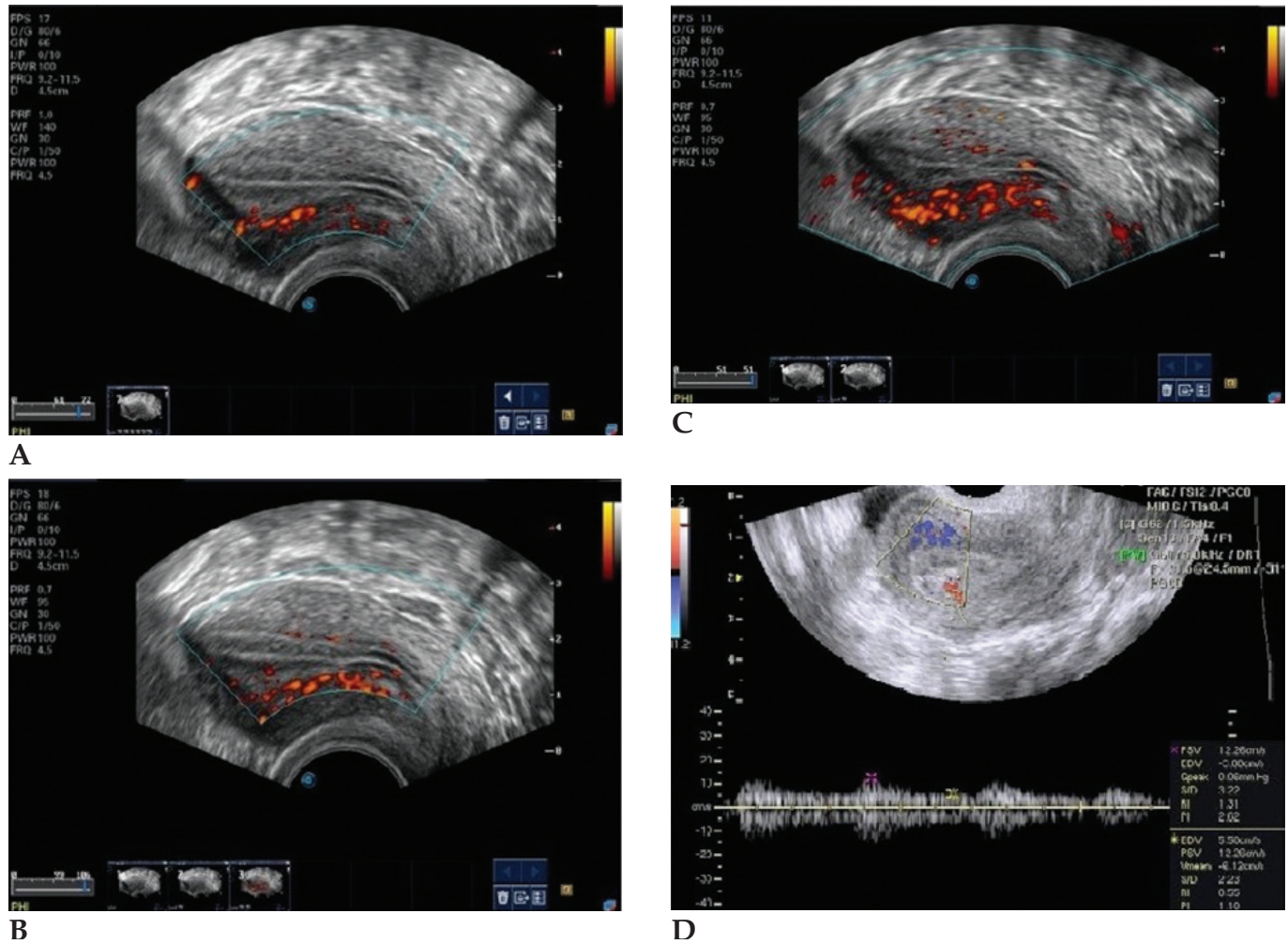
Figure 2. *Endo-sub endometrial blood flow zones and Doppler study.*

the mean) for continuous variables and frequencies (number of cases) and percentages for categorical data. Independent Student's t-test was used to compare quantitative variables and the chi-square was used to compare categorical data. A P-value < 0.05% was considered significant. The receptor operating characteristic (ROC) curve analysis was performed to determine the best predictive values.

RESULTS

Baseline cycle characteristics

A total number of 281 women were recruited; of them, 19 (6.76%) were excluded (7 had unexpected hypo response, 2 had cancelled embryo transfer due to non-fertilization, 7 underwent day-3
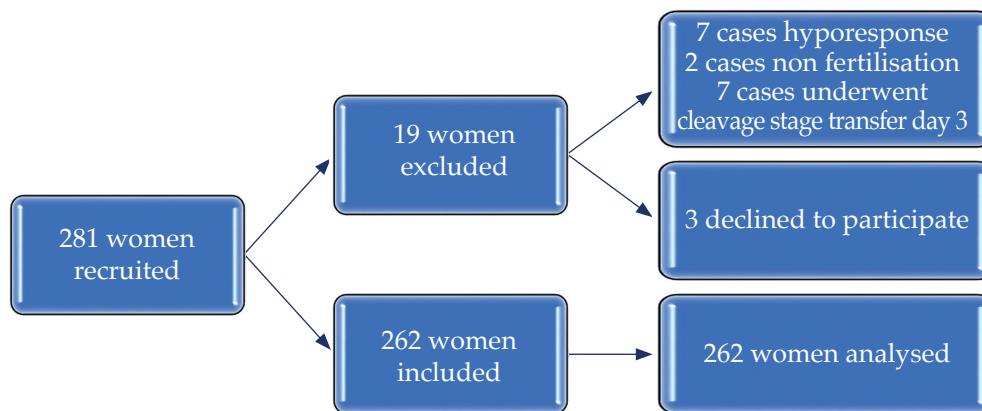

Figure 3. *Flow chart of the study.*

(cleavage-stage) embryo transfer, and 3 refuse to participate in the study). Therefore, 262 women were included finally (**Figure 3**).

A total of 262 women aged 20-39 with fresh embryo transfer were included in the analysis. The endometrial thickness on the hCG day ranged from 5 mm to 18.7 mm. The overall pregnancy rate was 43.12%. The clinical pregnancy rate was significantly lower in cases with endometrial thickness below 7 mm.

The demographic characteristics of the groups are shown in **Table 1**. Age, BMI, infertility duration, baseline FSH, and total gonadotrophin dose were similar among both groups. The effect of BMI on pregnancy outcome showed in Box blot (**Figure 4**). According to the cause of infertility (male, pelvic and uterine, tubal, and unexplained), there were no significant differences among both groups (**Table 2**).

The clinical pregnancy rate increased in the group with ET 8-12 mm 86/113 (76.1%), lower in the group with ET > 12 mm 25/113 (22.1%) and lowest in the group with ET < 8 mm 2/113 (1.8%) as shown in **Table 3**. There is an increased pregnancy rate in triple endometrial pattern 70/113 (61.9%) than in non-triple endometrial pattern 43/113 (38.1%). There is no significant difference between the groups concerning the endo-sub endometrial blood flow (P-value = 0.435). As regards the Doppler indices for endometrial sub-endometrial blood flow, there was no sig-
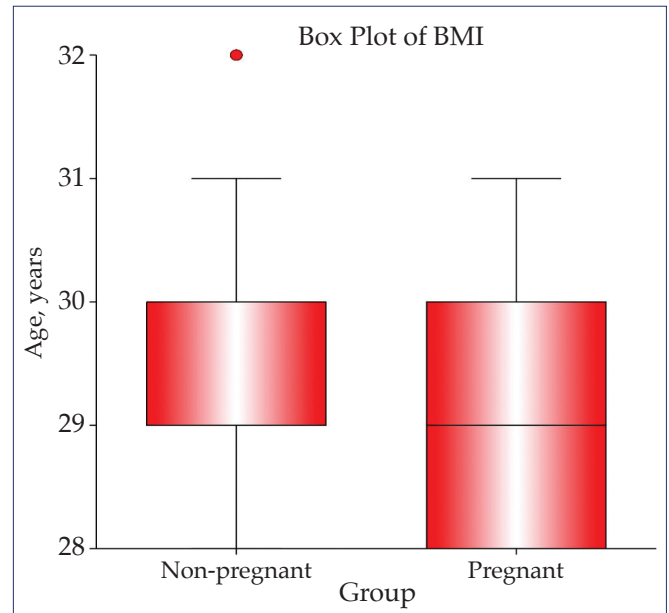

Figure 4.   *Box-plot diagram represents the effect of BMI in the studied groups.*

nificant difference in the Doppler indices in the Pregnant and Non-pregnant groups. P-values for all impedance indices are as follow: PI, RI, and S/D ratio was 0.72, 0.23, and 0.58, respectively with no significant difference (**Table 4**). The ROC curves of endometrial thickness were constructed to analyse the effect of endometrial thickness on the day of hCG triggering and its predictive values for clinical pregnancy (**Figure 5**). Endometrial thickness for clinical pregnancy had a cut-off of 7 mm (sensitivity of 98.23% and

Table 1.   *Demographic characteristics and infertility-related data in both groups.*

	Non-pregnant n = 149	Pregnant n = 113	Total n = 262	MW test	P-value	Confidence interval
	Median (Range)	Median (Range)	Median (Range)			
Age	30 (23-37)	29 (22-39)	29 (22-39)	-0.6	0.537	0.477-0.596
BMI	30 (28-32)	29.6 (28-31)	30 (28-32)	-2.7	0.078	0.0513-0.117
Infertility duration	6 (2-12)	4 (3-10)	6 (2-12)	-0.8	0.402	0.344-0.462
Baseline FSH	5.2 (2.8-9.5)	6.5 (3.3-10)	6.2 (2.8-10.0)	-0.2	0.875	0.829-0.91
Total Gn dose	3,900 (2,200-5,100)	3,917 (2,200-5,100)	3,917 (2,200-5,100)	-1.2	0.245	0.197-0.301

Table 2.   *Causes of infertility in both groups.*

		Non-pregnant n = 149	Pregnant n = 113	Total n = 262	χ^2 test	P-value	Confidence interval
		n (%)	n (%)	n (%)			
Cause of infertility	Male	38 (25.5%)	26 (23.0%)	64 (24.4%)	0.7	0.885	0.841-0.918
	Pelvic and uterine	18 (12.1%)	15 (13.3%)	33 (12.6%)			
	Tubal	65 (43.6%)	47 (41.6%)	113 (42.7%)			
	Unexplained	28 (18.8%)	25 (22.1%)	53 (20.2%)			

Table 3. *Ultrasound endometrial parameters in both groups.*

		Non-pregnant n = 149	Pregnant n = 113	Total n = 262	χ^2 test	P-value	Confidence interval
		n (%)	n (%)	n (%)			
Endometrial Thickness	< 8mm	16 (10.7%)	2 (1.8%)	18 (6.9%)			0.0069-0.041
	> 12 mm	28 (18.8%)	25 (22.1%)	53 (20.2%)	8.2	0.017	
	8 to 12 mm	105 (70.5%)	86 (76.1%)	191 (72.9%)			
Endometrial pattern	A	113 (75.8%)	70 (61.9%)	183 (69.8%)	5.8	0.015	0.0058-0.0382
	B	36 (24.2%)	43 (38.1%)	79 (30.2%)			
ET Zone	I	45 (30.2%)	40 (35.7%)	85 (32.6%)			0.376- 0.496
	II	61 (40.9%)	47 (42.0%)	108 (41.4%)	1.5	0.435	
	III	43 (28.9%)	25 (22.3%)	68 (26.1%)			

Table 4. *Doppler indices in both groups.*

	Non-pregnant n = 149	Pregnant n = 113	Total n = 262	MW Test	P-value	Confidence interval
	Median (Range)	Median (Range)	Median (Range)			
RI	0.84 (0.70-0.98)	0.84 (0.70-0.98)	0.84 (0.70-0.98)	-0.4	0.72	0.663-0.771
PI	1.03 (0.70-1.35)	1.03 (0.70-1.35)	1.03 (0.70-1.35)	-1.2	0.23	0.183-0.285
S\D ratio	16.3 (11.1-20.2)	16.3 (11.1-20.2)	16.3 (11.1-20.2)	-0.6	0.58	0.520-0.638

Table 5. *The receiver operating characteristic (ROC) curve analysis of endometrial thickness in mm to predict pregnancy.*

Cut-off	Sensitivity % 95%CI	Specificity % 95%CI	PPV 95%CI	NPV 95%CI	AUC 95%CI	P-value
> 7	98.23	10.74	45.5	88.9	0.55	0.17
	93.8 - 99.8	6.3 - 16.9	44.0 - 47.0	65.2 - 97.2	0.486 to 0.610	

AUC: area under the ROC curve; 95%CI: 95% confidence interval; PPV: positive predictive value; NPV: negative predictive value.

specificity of 10.74%, PPV 45.5%, NPV 88.9%), but the areas under the curve were 0.550 (95%CI 0.486-0.610) with P-value 0.17 (**Table 5** and **Figure 5**).
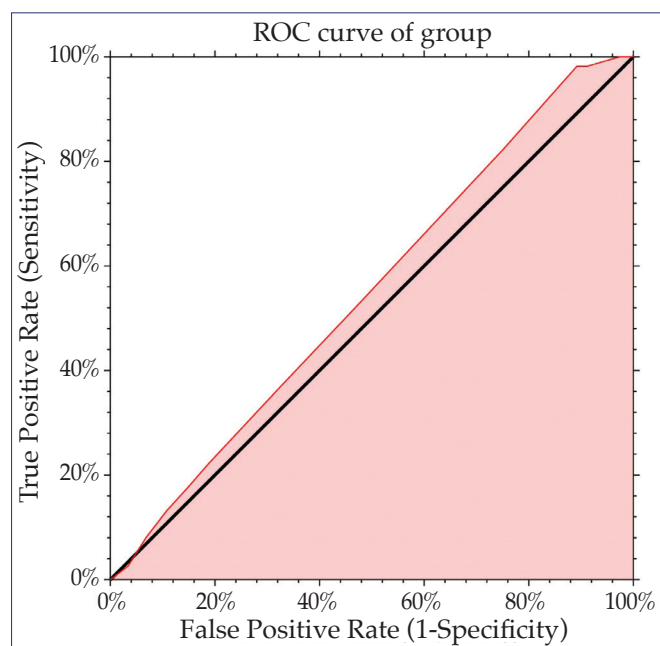

Figure 5. *ROC curve analysis of endometrial thickness in mm to predict pregnancy.*

DISCUSSION

Endometrial receptivity determines the success of ICSI cycles and improves the pregnancy outcome [9]. Recently, there has been a growing interest to focus on the assessment of endometrial receptivity by ultrasound scan as a non-invasive and reliable method. Many studies tried to evaluate endometrial receptivity using sonographic parameters, such as endometrial thickness, pattern, and or sub-endometrial blood flow, however, the evidence is still lacking regarding the best ultrasonographic parameter for endometrial receptivity [10]. We studied the fresh ICSI cycle of 262 patients and determined the effect of ultrasound endometrial parameters on the day of final triggering on pregnancy outcome. Our results showed that there is a significant correlation between endometrial thickness and pregnancy rate in all groups (< 8 mm, 8-12 mm, and > 12 mm) with the highest pregnancy rate

being in endometrial thickness 8-12 mm. Similarly, several studies have confirmed the association between a thin endometrium and a low clinical pregnancy rate. Nevertheless, the endometrium cutoff point for IVF-ET pregnancy outcome has not been identified yet. Some studies showed that the clinical pregnancy rate and ongoing pregnancy rate are significantly reduced when endometrium was less than 7 mm on the hCG day [11, 12]. This was in line with our study where the cutoff point here in our study was 7 mm with sensitivity and specificity was 98.23% and 10.74% respectively. In terms of endometrial thickness with fresh embryo transfer the results of the literature are conflicting: some studies reported that the spontaneous abortion rate is significantly increased when endometrial thickness > 14 mm [13], whereas another study proposes there is no adverse effect on pregnancy outcome when endometrial thickness > 14 mm [11]. In our study, we observed that the pregnancy rate increased in the group with endometrial thickness from 8 mm to 12 mm (76.1%), decreased in women with endometrial thickness > 12 mm (22.1%), and lowest when endometrial thickness < 8 mm (1.8%).

According to Bu *et al.* who studied patients undergoing IVF with different ovarian responses to get a more accurate relationship between endometrial thickness and IVF outcome, a thin endometrium on the day of hCG triggering was associated with a lower pregnancy rate [14]. Some studies found that thick endometrium of more than 17 mm has a positive impact on the pregnancy rate, while other studies found thick endometrium has a poor pregnancy rate outcome [15, 16]. Yuan *et al.*, in their study, found a consistently positive correlation between endometrial thickness and conception rate, with patients having an endometrial thickness greater than 15 mm achieving the highest conception rate of 53.3% [17]. This could be explained in fresh cycles that increased endometrial thickness was associated with significantly higher mean numbers of oocytes retrieved, mean peak oestradiol levels, and mean numbers of usable embryos. This raises the possibility that the improvement in outcomes with thicker endometrial linings could simply reflect confounding by patients with a better ovarian reserve and, therefore, a better prognosis for pregnancy [18, 23]. Conversely, our results concluded that increased endometrial thickness > 12 mm has a determinable effect on the pregnancy rate 53 (20.2%) in correlation to other groups. This finding could reflect the presence of underlying en-

dometrial pathology that mitigates hysteroscopic evaluation.

Vânia Costa Ribera and coworker have done their retrospective cohort study on 3350 IVF single-centre cohorts to find a relationship between endometrial thickness and the success of fresh embryo transfer. In the multivariate regression analysis, live birth was non-linearly associated with endometrium, the results showed the lowest live birth rates when the endometrial thickness was less than 7.0 mm (21.6%; p < 0.001) and then between 7.0 and 9.0 mm (30.2%; p = 0.008), also there was a decrease in neonatal birth weight z-scores with endometrial thickness less than 7.0 mm. This study concluded that endometrial thickness can be used as a prognostic indicator for neonatal birth weight and live birth rates [19].

Gingold *et al.* studied endometrial patterns on the day of hCG triggering and its influence on implantation [20]. Grunfeld *et al.* [21] classified the pattern of the endometrium into 3 categories: 1) late proliferative (in this category < 50% of the endometrium is hyperechoic, with hyperechoic basalis and hypoechoic functional), 2) early secretory (hyperechoic basalis and > 50% of the endometrium is functional), and 3) mid-late secretory (homogeneous hyperechoic functionalize extending from the basalis to the lumen). The presence of endometrial pattern type 3 on the day of hCG triggering means a prematurely closed window of implantation [20]. Mohammady and coworker studied the combination between endometrial pattern and thickness on the intracytoplasmic sperm injection (ICSI) cycles success, this study found that the presence of trilaminar endometrium together with endometrial thickness of 10-12.9 mm was accompanied by higher ICSI cycles success [18]. According to our study, endometrial thickness and pattern of studied groups showed significant differences between both Pregnant and Non-pregnant. Mahutte *et al.* [23], with fresh embryo transfers, reported that the positive pregnancy outcome and live birth rates increased significantly as the endometrium thickened until an endometrial thickness of 10-12 mm. In contrast, with frozen embryo transfer cycles, positive outcomes correlated significantly as the endometrium thickened until an endometrial thickness of 7-10 mm.

Herein, the Doppler study of the endo-sub endometrial blood flow or vascularization was classified into the zone I in which the blood flow reached only the sub-endometrial region, zone II in which the blood flow reached the outer hyper-echoic re-

gion or zone III in which the blood flow reached the inner hypo-echoic zone. There is also no significant difference between the groups as regards the zones of endometrial blood flow (P-value = 0.435). According to the Doppler indices of endometrial vasculature in our study, there was no significant difference between the Pregnant and Non-pregnant group, P-value for PI, RI, and S/D ratio was 0.72, 0.23, and 0.58, respectively with no significant difference. A meta-analysis of studies using endometrial/sub-endometrial 3-dimensional ultrasound and power Doppler angiography was performed to examine the vascularization index (VI), flow index (FI), and vascularization-flow index (VFI) in pregnant and non-pregnant women. Ten articles were analysed, including 895 pregnant women and 882 non-pregnant women which concluded that sub-endometrial FI on the hCG day and endometrial VI, FI, and VFI on the ET day are potentially associated with pregnancy occurrence during IVF-ET. The endometrial VI, FI, and VFI could help identify appropriate timing for embryo transfer. However, the accuracy of these indices in predicting pregnancy occurrence must be further evaluated in additional large-scale studies [22].

Implantation of this study to the research

Based on our results we reported a higher pregnancy rate with a triple endometrium line of thickness 8-12 mm on the day of hCG triggering, while poor pregnancy out with a non-triple endometrium of thickness less than 7 mm. Accordingly, we can conclude that in the presence of non-favourable ultrasound parameters of endometrium it is advisable to proceed with a freezing strategy and transfer in a later cycle.

Strength and limitation

The strength of this study is that we evaluated endometrial receptivity which is a key stage in IVF/ICSI success in a holistic perspective involving endometrial thickness, patterns, and vascularity in a combined analytic approach. We acknowledge there are also some limitations in this piece of work; although morphological good-quality of blastocysts that were used in our study, we were still limited by the unknown genetic composition of embryos. Long-term follows up until live birth was deficient in our study and finally small sample size in a single centre. However, we believe that these findings were of interest as previous similar studies revealed conflicting conclusions. A well-designed and powered randomized clinical trial will be needed for further research.

CONCLUSIONS

A no triple-line endometrial pattern seems to be a prognostic sign of a less favourable outcome, while a triple-line pattern appears to be associated with conception. When a thinner endometrium (≤ 7 mm) and no triple-line endometrial pattern coexist in an ICSI candidate, cryopreservation should be recommended. If a thinner endometrium with a good texture (triple-line) is present, other prognostic factors, such as embryo quality, should be taken into consideration. Combined analysis of endometrial thickness and pattern on the day of hCG administration could be more valuable than the separate analyses.

COMPLIANCE WITH ETHICAL STANDARDS

Informed consent

Patients who fulfilled the selection criteria were counselled and informed about the trial protocol and a written consent according to the declaration of Helsinki was signed.

Data sharing

Data are available under reasonable request to the corresponding author.

ACKNOWLEDGMENTS

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