RELATIONSHIP BETWEEN ENDOMETRIAL THICKNESS AND PREGNANCY OUTCOMES IN ASSISTED REPRODUCTIVE TECHNOLOGY CYCLES

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ABSTRACT

OBJECTIVE: To explore the relations of different ultrasonic endometrial thickness (EMT)values on hCG trigger day and the pregnancy rate (PR) after fresh embryo transfer (ET) in controlled ovarian stimulation (COS) cycles.

BACKGROUND: Successful implantation and delivery require both the functional embryo and receptive endometrium in assisted reproductive technology (ART) cycles which is an expensive procedure with low implantation and pregnancy rate (PR). It is estimated that embryos account for one-third, and suboptimal endometrial receptivity for the remaining two-thirds of implantation failures. There is still an ongoing debate regarding the predictive ability of ultrasonic endometrial evaluation on the day of human chorionic gonadotrophin (hCG) trigger during controlled ovarian stimulation (COS) on the outcomes of pregnancies after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI).

METHOD: A retrospective review of data from medical records of all patients who underwent COS, oocyte retrieval, IVF/ICSI, and fresh ET between March 2021and July 2022 at Centre for Fertility and Reproductive Medicine (CFRM), St Paul Millennium medical College (SPHMMC) Addis Ababa, Ethiopia. Patients were categorized based on their ET outcome (as pregnant or non-pregnant) and EMT values on the day hCG trigger (groups A <8mm, B 8-12mm, and C>12 in mm) to study and analyze if any relation between endometrial thickness and pregnancy rate existed.

RESULTS: A total of 548 records were analyzed. PR was 40.9%. The odds of pregnancy were higher among patients with EMT group B (82.8% vs 74.6%, p=0.05) and was shown to be significant after controlling for the effects of multiple confounding factors. Although receiver operator curve (ROC) analysis indicated that EMT has a limited value to be used as an indicator of the pregnancy rate as evidenced by the area under the curve (AUC) of 0.59 (95% CI= 0.53, 0.63), it was not possible to determine a cutoff of the endometrial thickness value with an acceptable trade-off between sensitivity and specificity

CONCLUSION: There is a positive relationship between the EMT measured on the day of hCG injection and PR and that EMT is an independent factor. Further prospective study is needed to explore the issue in more detail in our setup.

KEY WORDS: assisted reproductive technology, controlled ovarian stimulation, in vitro fertilization, intracytoplasmic sperm injection, endometrial thickness, embryo transfer

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INTRODUCTION

It is estimated that embryos account for one-third, and suboptimal endometrial receptivity for the remaining two-thirds of implantation failures in Assisted reproductive treatment (ART) cycle which is an expensive procedure with low implantation and pregnancy rate. Successful implantation and delivery require both the functional embryo and receptive endometrium in assisted reproductive technology (ART) cycles.

A 2D grayscale ultrasound EMT measurement during monitoring in ovarian stimulation in IVF cycles can be an indirect marker of endometrial receptivity (ER) at low resource settings as in our setup[1,2].

Ultrasonographic endometrial thickness ranges from 1 to 4mm in the menstrual phase, 4 to 8mm in the mid-proliferative phase, 8 to 14mm in the late follicular phase, and 7 to 14mm in the secretory phase.

Studies on the potential relationship between ultrasonic EMT on the day of hCG administration and IVF/ICSI ET pregnancy outcome came up with mixed results. While several studies have suggested a positive correlation[2,3], other multiple studies have refuted the correlation, Shakerian and suggest that neither individual nor combined analysis of EMT and pattern had predicting effects on live birth following IVF treatments, and embryo quality might be the one that really has effects[4,5].

While some studies demonstrated a higher pregnancy rate at certain endometrial thickness 11,50. no conclusive cut-off value of endometrial thickness has been established in order to help ART providers in counseling the couple about the outcome.

The aim of this study is to examine the relationship between endometrial thickness measured on the day of administration of human Chorionic Gonadotrophin (hCG) on pregnancy rate and if possible, to identify a cut off value at which pregnancy rate is too low.

METHOD

Study setting, design, and period

The study was a retrospective cross-sectional study in which clinical data of all fresh IVF/ICSI cycles performed between March, 2021 to July 2022 at CFRM - SPHMMC, Addis Ababa, Ethiopia was reviewed. The study included all first fresh ETs cycles in women aged 18–45 years. Exclusion criteria used were incomplete record (missing values), frozen embryo transfer cycles, abnormal uterine cavity as demonstrated by HSG, SHG or hysteroscopy, and previous failed IVF/ICSI ET cycle. Our center is rendering comprehensive ART services except donor gametes, perinatal genetic diagnosis, and surrogacy. Three major stimulation protocol used in our center are the conventional long agonist, antagonist, and minimal protocols. The choice of COS protocol, the starting dose of gonadotropin and monitoring frequency were based on the institution's standard protocol. Endometrial thickness was measured in the midsagittal plane of the uterus as the maximum distance between the 2 interfaces of endometrial–myometrial junction. Patients were assigned on hCG administration day into either of three groups depending on the endometrial thickness; groups A: <8mm; B: 8-12mm. C: >12mm.ovulation was triggered using a 5,000 -10,000 IU SC urinary HCG or decapeptyl when indicated. Thirty-six hours later ultrasound guided oocyte retrieval procedure using a single lumen 17G, 35cm long aspiration needle under light anesthesia will be performed. Partners' semen will also be collected the same day for subsequent IVF/ICSI use. Luteal support was initiated on the same day after oocyte retrieval procedure with for all and continued in the event of positive serum hCG until 12th week. After IVF/ICSI- procedures were carried out as per indication the derived embryos were classified according to the Istanbul consensus 11. A fresh maximum of 2–3 cleavage-stage embryos (day 3) or 1-2 day 5 embryos were transferred accordingly. Serum hCG levels were assessed two weeks after oocyte retrieval and ultrasound scan confirmation of all pregnancies was performed on all patients between five to six weeks estimated gestational age based on ET day.

Data Compilation and Statistical Analysis

Data were compiled and entered initially using excel 2022 and shipped to Stata 11 software for coding, cleaning, and analysis. All tests were two tailed, and $p < 0.05$ was considered statistically significant. Continuous variables were presented as mean and SD and were tested by student's t-test. Comparisons of proportions were made by the chi squared test. The effect of endometrial thickness on the pregnancy outcome was studied using multivariate analysis, where all other factors affecting the pregnancy outcome were controlled for. To determine the independent relation of endometrial thickness and pregnancy rate a stepwise logistic regression analysis was performed using aforementioned confounding factors in the Stata software. The Receiver operating characteristic (ROC) analysis was used to evaluate if an endometrial thickness can predict pregnancy outcome.

RESULTS

Out of the total 1286 embryo transfers performed during the 15 months of the study period, only 548 cycles were eligible for inclusion in the study. Most of the exclusions were due to incomplete and missing data. Total, biochemical, and clinical pregnancy rates were 40.9%, 36.2% and 4.7% respectively. Spontaneous abortion rate was 1 %. Endometrial thickness measured on the day of hCG administration ranged from 5 to 14 mm.

Almost four fifth of the women were aged younger than 35 and had more than five AFCs at the start of the stimulation. Majority of the patients had no adnexal or uterine pathology (89% and 93.7% respectively), had normal semen analysis result (85%), or had a history of previous pregnancy by the male partner (84.2%), had grade B (77.9%) and trilaminar endometrium (99.1%) on the day of hCG administration, oocyte retrieval of more than five (76.9%) and their embryo transfers were performed by REI subspecialists (88.5%). ICSI was performed more often (53.4%) than IVF. Minimal stimulation protocol (52.8%) was the most often used method (Table 1).

Table 1: Characteristics of women who underwent IVF/ICSI fresh ET procedures in the study

Characteristics	No.	%
Age of the woman		
<35 y	298.0	78.6
>=35 y	81.0	21.4
AFC		
>=5	435.0	80.6
<5	105.0	19.4
Duration of infertility		
<5 y	256.0	48.3
≥5 y	274.0	51.7
Adnexal pathology		
Absent	487.0	89.0
Present	60.0	11.0
Endometrial grading		
A	96.0	18.3
B	408.0	77.9
C	20.0	3.8
Cause of infertility		
Both Male & Female	21.0	3.8
Female	308.0	56.3
Male	48.0	8.8
Unexplained	170.0	31.1
Level of physician		
Second-year fellow	63.0	11.5
Subspecialist	484.0	88.5
Semen analysis		
Abnormal	81.0	14.8
Normal	466.0	85.2
Protocol		
Antagonist	102.0	18.6
Long Agonist	156.0	28.5
Minimal stimulation	289.0	52.8
Uterine abnormality		
Absent	118.0	93.7
Present	8.0	6.3
Type of fertilization		
ICSI	292.0	53.4
IVF	255.0	46.6
Endometrial Morphology		
Non-trilaminar	5.0	0.9
Trilaminar	542.0	99.1
Previous pregnancy by the male		
None	176.0	84.2
One or more	33.0	15.8
Oocytes retrieved		
>5	406.0	76.9
<5	122.0	23.1
Pregnancy status		
Abortion	5	0.91
Biochemical Pregnancy	198	36.20
Clinical Pregnancy	21	3.84
Negative	323	59.05

Endometrial thickness measured on the day of hCG administration ranged from 5 to 14mm and pregnancy was achieved at each endometrial thickness value beyond 5mm(Table 2).

Table 2: Pregnancy rates at different endometrial thickness values

Endom Thickness	Pregnancy status		Pregnancy Outcome		
	Negative	Positive	BCP	CP	Ab
5	3	0	0	0	0
6	20	9	9	0	0
7	48	16	14	2	0
8	70	34	29	4	1
9	45	36	31	5	0
10	60	59	56	5	1
11	31	23	21	1	1
12	30	21	19	1	1
13	9	11	10	1	0
=>14	7	15	9	2	0
	323	224	198	21	5

BCP = biochemical pregnancy, CP= Clinical Pregnancy, Ab= Abortion

There was no statistical difference between those who could and couldn't achieve pregnancy in terms of the diagnosis and the duration of infertility, presence of uterine pathology, semen analysis abnormality, previous pregnancy by the male partner, endometrial morphology, type of fertilization, or level of physicians who performed the embryo transfer (Tables 3 and 4).

Compared to non-pregnant group according to bivariate analysis, the odd of pregnancy tends to be higher with age < 35y (84.4% vs 15.6%, p=0.04), AFC > 5 (p<0.001), a long agonist stimulation protocol (39.3% vs 21.1%, p<0.001), oocyte retrieval of >5, higher number of follicles on the day of hCG administration, day 3 and grade 1 embryos transfers (Tables 4 and 5). All except for the endometrial grading and day of embryo transfer have lost their significance when subjected to multivariate logistic regression analysis (Table 5).

Receiver operator curve (ROC) analysis

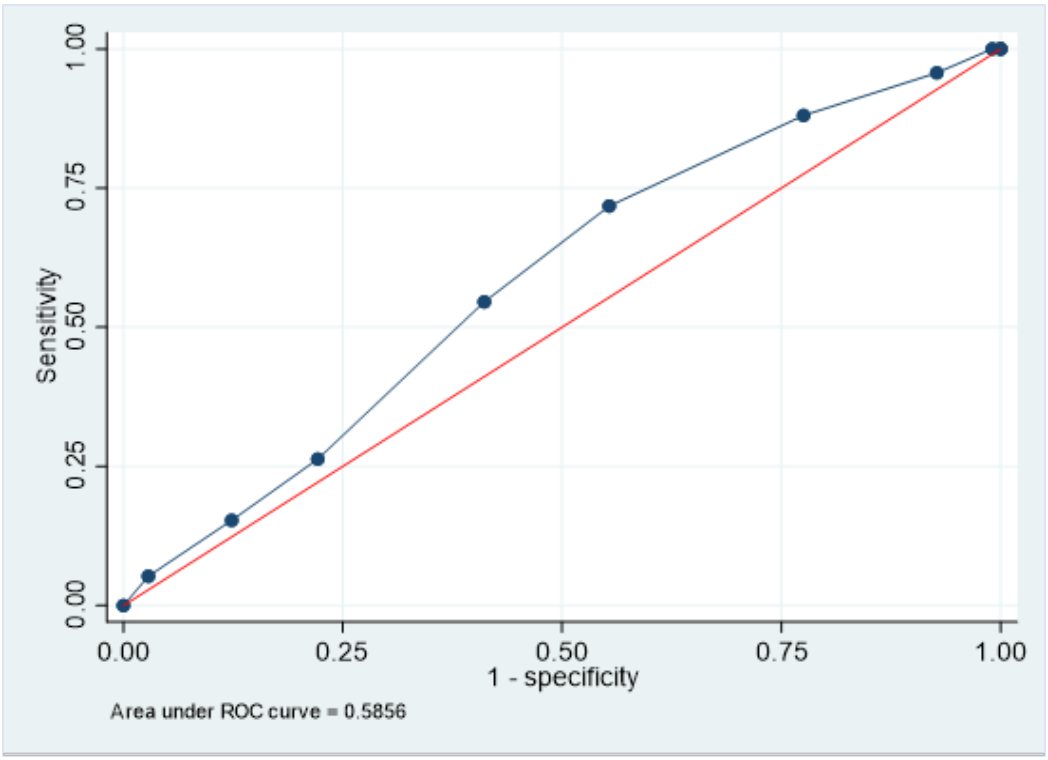

Table 3: Bivariate analysis of factors associated with pregnancy rate

Factor	Level	Negative (323)	Positive (224)	p-value
Age of the woman	<35y	286 (89.7%)	215 (96.0%)	0.007
	≥35y	33 (10.3%)	9 (4.0%)	
AFC	≥5	242 (75.9%)	193 (87.3%)	<0.001
	<5	77 (24.1%)	28 (12.7%)	
Duration of infertility(y)	<5	140 (45.0%)	116 (53.0%)	0.071
	≥5	171 (55.0%)	103 (47.0%)	
Adnexal pathology	Absent	287 (88.9%)	200 (89.3%)	0.87
	Present	36 (11.1%)	24 (10.7%)	
Endometrial grading	A	71 (22.5%)	25 (12.0%)	0.005
	B	235 (74.6%)	173 (82.8%)	
	C	9 (2.9%)	11 (5.3%)	
Cause of infertility	Both male & female	12 (3.7%)	9 (4.0%)	0.80
	Female	187 (57.9%)	121 (54.0%)	
	Male	26 (8.0%)	22 (9.8%)	
	Unexplained	98 (30.3%)	72 (32.1%)	
Level of physician	2nd year fellow	44 (13.6%)	19 (8.5%)	0.064
	Subspecialist	279 (86.4%)	205 (91.5%)	
Semen analysis	Abnormal	40 (12.4%)	41 (18.3%)	0.055
	Normal	283 (87.6%)	183 (81.7%)	
Type of protocol	Antagonist	66 (20.4%)	36 (16.1%)	<0.001
	Long Agonist	68 (21.1%)	88 (39.3%)	
	Minimal stimulation	189 (58.5%)	100 (44.6%)	
Uterine abnormality	Absent	70 (95%)	48 (92%)	0.60
	Present	4 (5%)	4 (8%)	
Type of fertilization	ICSI	182 (56.3%)	110 (49.1%)	0.095
	IVF	141 (43.7%)	114 (50.9%)	
Endometrial morphology	Non trilaminar	3 (0.9%)	2 (0.9%)	0.97
	Trilaminar	320 (99.1%)	222 (99.1%)	
Previous pregnancy by the male	None	105 (86.1%)	71 (81.6%)	0.38
	One or more	17 (13.9%)	16 (18.4%)	
Oocytes retrieved	>5	221 (70.4%)	185 (86.4%)	<0.001
	<5	93 (29.6%)	29 (13.6%)	
Day of ET	3	199 (79.9%)	117 (60.6%)	<0.001
	5	50 (20.1%)	76 (39.4%)	

Table 4. Bivariate analysis Comparisons of oocyte and embryo aspects between pregnant and nonpregnant women following a fresh embryo transfer (Bivariate analysis)

Factor	Negative	Positive	p-value
N	323	224	
Number of follicles on trigger, median (IQR)	6.0 (4.0, 10.0)	9.0 (5.0, 15.0)	<0.001
Eggs Retrieved, median (IQR)	5.0 (3.0, 11.0)	9.0 (5.0, 16.0)	<0.001
MII, median (IQR)	3.0 (2.0, 6.0)	6.0 (3.0, 12.0)	<0.001
Number of Embryo Transferred, median (IQR)	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	<0.001
EmbGr1, median (IQR)	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)	<0.001
EmbGr2, median (IQR)	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.030
EmbGr3, median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.23

Table 5: Multivariate logistic regression analysis of factors associated with a pregnancy rate

Factor	Level	Pregnancy test		AOR	p-value	95%	CI
		Negative (n=323)	Positive (n= 224)				
	<35y	286 (89.7%)	215 (96.0%)	1.00			
	≥35y	33 (10.3%)	9 (4.0%)	0.48	0.14	0.18	1.29
AFC	≥5	242 (75.9%)	193 (87.3%)	1.00			
	<5	77 (24.1%)	28 (12.7%)	0.77	0.38	0.43	1.38
Endometrial grading	A	71 (22.5%)	25 (12.0%)	1.00			
	B	235 (74.6%)	173 (82.8%)	1.91	0.03	1.07	3.43
	C	9 (2.9%)	11 (5.3%)	2.61	0.11	0.81	8.40
Level of physician	2nd yr. fellow	44 (13.6%)	19 (8.5%)	1.00			
	Subspecialist	279 (86.4%)	205 (91.5%)	1.53	0.21	0.79	2.95
Protocol	Antagonist	66 (20.4%)	36 (16.1%)	1.00			
	Long Agonist	68 (21.1%)	88 (39.3%)	1.63	0.14	0.85	3.13
	Minimal stimulation	189 (58.5%)	100 (44.6%)	1.40	0.27	0.77	2.56
Type of fertilization	ICSI	182 (56.3%)	110 (49.1%)	1.00			
	IVF	141 (43.7%)	114 (50.9%)	1.48	0.07	0.96	2.27
Endometrial morphology	Non trilaminar	3 (0.9%)	2 (0.9%)				
	Trilaminar	320 (99.1%)	222 (99.1%)	0.38	0.37	0.04	3.20
#of Embryo Transferred, (Median, IQR)		2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	2.88	0.00	1.56	5.30
Day of embryo transfer	Day 3	199 (79.9%)	117 (60.6%)	1.00			
	Day 5	50 (20.1%)	76 (39.4%)	2.55	0.01	1.17	3.29

DISCUSSION

This study is the first of its kind in terms of addressing the issues of relation of endometrial thickness and pregnancy rate after fresh ET. The endometrial thickness at which most of the pregnancies in this study occurred falls in grade B group that ranged from 8 to 12 mm (82.8% vs 74.6%, p=0.05) and after controlling for the effects of multiple confounding factors using multivariate logistic regression analysis (p=0.02) it became evident that endometrial thickness has an independent relationship with pregnancy rate in this study.

Non-parametric Receiver-Operating Characteristic (ROC) analysis was carried out to identify the predictive ability of endometrial thickness on the pregnancy rate. Although the analysis indicated that endometrial thickness has a limited predictive ability of the pregnancy as evidenced by the areas under the curve (AUC) of 0.59 (95% CI= 0.53, 0.63) it was not possible to determine a cutoff of the endometrial thickness value with an acceptable trade-off between sensitivity and specificity.

Our findings were akin to the finding from other studies[6-10] including Richter et al, who indicated that EMT was greater in cycles resulting in pregnancy than in cycles not resulting in pregnancy and that clinical pregnancy and live-birth or ongoing pregnancy rates increase significantly with increasing endometrial thickness, independent of the effects of patient age and embryo quality.

Al-Ghamdi et al in their retrospective cohort study of 2464 cycles concluded that there is a positive linear relationship between the endometrial thickness measured on the day of hCG injection and PR and that endometrial thickness is independent of other variables[4].

Yuan indicated in a retrospective study, of 10,787 fresh IVF–ICSI treatment cycles that EMT is a significant and independent predictor of intrauterine pregnancy, ectopic pregnancy, spontaneous abortion and live birth after IVF–ICSI treatment[5].

Yang et al Combined analysis revealed those with endometrial thickness > 8mm and triple-line endometrial pattern had significant higher clinical pregnancy rates[6]. In a Canadian study of >22,000 fresh IVF-embryo transfer cycles, clinical pregnancy and livebirth rates were progressively lower with decreasing endometrial thickness. In fresh IVF-embryo transfer cycles, the livebirth rate decreased progressively per millimeter below 8mm[14].

On the other hand, studies have suggested that only the extremes of endometrial thickness values less than 8mm or greater than 14mm[15,16] negatively impact pregnancy rates. Many studies showed endometrial thickness of <6–7mm or >10–14 mm on hCG trigger day, has been reported to adversely affect implantation rate[11-13]. Our study has less to comment on the pregnancy outcome related with extremes of endometrial thickness values less than 8mm or greater than 14mm as their number is very small.

Regarding pregnancy outcomes when ET is above 14mm, results of studies are conflicting and more controversial. While some studies claim improved conception rate[9,14,15] others have reported a detrimental effect of a >14mm thick endometrium on conception rate[8]. Still other studies found no reduction in pregnancy rates with very thick linings[9]. A case report is widely cited describing a successful twin pregnancy in a woman with an endometrial stripe measuring 20mm[10].

According to some other studies if an endometrial thickness of at least 7mm cannot be attained, patients should be counselled for either continuing, or cancelling and subsequent frozen cycle while others recommend completion of all IVF cycles regardless of the thickness of the preovulatory endometrium. Accordingly a meta-analysis including 22 studies with a total of 10724 IVF–ICSI treatment cycles suggested that EMT cut-off of 7 mm has a limited capacity to identify pregnancy rates after IVF–ICSI and its use as a tool to decide on cycle cancellation, freezing of all embryos or refraining from further IVF treatment reported not to be justified[11].

On the other hand multiple studies have refuted the correlation between endometrial thickness and

pregnancy, and further went to suggest that neither individual nor combined analysis of EMT and pattern had predicting effects on live birth following IVF treatments, and embryo quality might be the one that really has effects[3].

Surprisingly, confounding effects of female age and number of oocytes retrieved according to regression were not associated with pregnancy prospects. This 'ecological fallacy' can be explained by the fact that our infertile women do not know their exact age and by inadequacy of our data.

DECLARATIONS

Limitations of the study

The study is retrospective, lacks adequate number of cases to comment on the pregnancy outcome of extremes of endometrial thickness values. Besides, as the data sources suffer from missing values our conclusions too were compromised.

Strength

This is the first attempt to review not only the relation of EMT in IVF in the country but also the role of possible confounders.

Conclusion and Recommendation

Current study indicates that EMT has a limited capacity to identify women who have a low chance to conceive after IVF. The frequently reported cut-off of 7mm is occurring infrequently. The use of EMT as a tool to decide on cycle cancellation, freezing of all embryos or refraining from further IVF treatment seems not to be justified based on EMT. Further research is needed to investigate the real independent significance of EMT in IVF in our setup.

Competing Interests

The author declares that he has no competing interests.

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