Senses Sci (Educ Sci Tech) 2023: 10 (1) :17-36
doi: 10.14616/sands-2023-1-1736

Article

Impact of endometrial compaction on pregnancy outcome in patients undergoing frozen-thawed embryo transfer

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Abstract. *Background:* For a successful pregnancy to occur, two major components play an important role; a receptive endometrial environment and a good-quality embryo. *Objective:* This work aimed to evaluate the impact of endometrial compaction following progesterone administration on pregnancy outcomes in patients undergoing frozen-thawed embryo transfer. *Methods:* Prospective observational cohort study at a single IVF Centre, including 307 patients undergoing good-quality vitrified–thawed blastocyst transfer in a hormone replacement therapy (HRT) cycle. The change in endometrial thickness between the end of the estrogen-only phase and the day of embryo transfer, measured using sequential TVUS, was used to categorize endometrium as undergoing compaction (≥5% decrease), no change, or expansion (≥5% increase). The primary outcome measure was the ongoing pregnancy rate. *Results:* 25.73% of the cycles showed endometrial compaction, 33.87% showed no EMT change, and 40.39% showed endometrial expansion. The ongoing pregnancy rate was significantly higher in the compaction

group compared to the no change and expansion group (48.1% vs. 40.4% vs. 30.6%, respectively; $p < 0.039$). The clinical pregnancy rate, abortion rate, implantation rate, and chemical pregnancy rate were comparable between the groups. Results were evaluated according to the degree of compaction by dividing the patients into 5% compaction slices. Implantation and ongoing pregnancy rates were significantly higher at a 5-10% compaction level ($p = 0.039$ and 0.008, respectively). *Conclusion:* In patients undergoing HRT–FET, the change in endometrial thickness measured at the end of the estrogen phase and on ET day (endometrial compaction) plays a role in predicting cycle outcome.

Keywords: Endometrial receptivity, Endometrial compaction, Endometrial thickness, HRT, Ongoing pregnancy, Vitrified–thawed embryo transfer.

Introduction

The endometrium's receptiveness implies its ability to accept embryos during the implantation window, which in the natural menstrual cycle is around seven days after ovulation.(1)

Embryo transfer (ET) in patients undergoing in-vitro fertilization (IVF) is typically performed in the middle of the implantation window. Thus, it is reasonable to believe that the condition of the endometrium on the day of transfer is more indicative of endometrial receptivity than the day of human chorionic gonadotropin (hCG) trigger or progesterone administration (both precede ET by at least 3–5 days).(2, 3)

The importance of measuring endometrial thickness and its relationship to endometrial receptivity and implantation potential in assisted reproduction remains debatable; some authors suggest a significant relationship between endometrial thickness and pregnancy outcomes (4, 5), while others concluded that this relationship was absent.(6, 7)

Assessment of endometrial thickness has become part of standard monitoring during fertility treatment. Early studies suggested that transvaginal sonography serves as an alternative method to invasive biopsy-based techniques in predicting a favorable endometrium.(1)

To date, the focus of sonographic evaluation of the endometrium during an IVF cycle is on the endometrial pattern and thickness before triggering the final stage of oocyte maturation or at the end of the estrogen phase in frozen-thawed cycles (FET) (4, 8-12), while endometrial assessment in the luteal phase at the time of embryo transfer following progesterone exposure has been less commonly investigated.(13)

Recently, researchers suggested that the change in endometrial thickness between the end of the estrogen phase and the time of embryo transfer may be more critical in predicting the pregnancy outcome than the absolute measure of endometrial thickness at the time of ET (14-18) as the condition of the endometrium is known to be changeable in the natural menstrual cycle and also in IVF treatment cycles, but the results have been inconclusive.

One of the typical ultrasound findings during IVF cycles is that the endometrial pattern changes from a triple-line pattern (pattern A)/intermediate isoechogenic pattern (pattern B) to a homogenous, hyperechogenic (pattern C).(19) However, little is known about how the endometrial thickness changes after hCG or progesterone exposure.

These observations reflect the underlying physiology of endometrial development, which is distinct and differs between the follicular and luteal phases. During the follicular phase, the endometrium is exposed to estrogen, which increases endometrial thickness and accelerates the linear growth of endometrial glands and blood vessels, resulting in the typical trilaminar appearance on two-dimensional ultrasound. The endometrial proliferation ceases 2–3 days after ovulation. However, the continuous growth of glands and vessels under the influence of progesterone within the constrained endometrium results in tortuosity of the glands and vessels. (20) There is an accumulation of glycogen in the gland lumens and increased proliferation of T cells, macrophages, and lymphoid nodules.(21) Together, these changes result in increased endometrial density that appears on two-dimensional ultrasound as a homogeneous bright pattern.(22)

From these findings, it is hypothesized that the endometrial thickness should decrease (endometrial compaction) in a natural or artificial luteal phase as the endometrium becomes denser (hyperechoic on ultrasound) as a result of the secretory changes that are induced by progesterone.(14, 22, 23)

Endometrial compaction is the change in endometrial thickness between the end of the estrogen-only phase and the day of embryo transfer.(24) In concept, the compaction of the endometrium after progesterone initiation indicates that the endometrium is responsive to progesterone and could therefore be used as a proxy for endometrial receptivity predictability of FET cycle outcome.

Objective

The objective of the present study is to record the dynamic changes in the endometrial thickness using two-dimensional transvaginal ultrasound (2D TVUS) at the end of the estrogen phase and on the day of embryo transfer following progesterone administration in hormonally prepared FET cycles. And if endometrial compaction (decreased thickness) -after the administration of progesterone- affects

pregnancy outcomes compared to the endometrium, which expands or remains unchanged.

Methods

Study design, setting, and participants:

The present study was an observational prospective cohort study performed from august 2021 to March 2022 in an IVF center in Alexandria, Egypt. Our final data analysis included a total of 307 HRT–FET cycles.

The Institutional ethical review board approved the study protocol (approval number 0201493, dated 15 April 2021), and full written informed consent was obtained from all participants after discussing the nature of the study and explaining all the steps of the research methodology.

The Inclusion criteria were artificial endometrial preparation in IVF/ICSI patients undergoing frozen (vitrified) thawed embryo transfer, age below 40 years, Body mass index (BMI) <30, embryos undergoing vitrification on day 5 using the open system (cryotop) and transfer of ≤2 thawed good quality blastocyst(s).

Cases showing Stage 3 or 4 endometriosis, intrauterine adhesions or major uterine anomalies, previous uterine surgery, untreated endocrinopathies, and cycles of patients with persistent endometrial thickness <7mm during treatment protocol were excluded from this study.

Sample size calculation:

At least a minimum total sample size of 155 cases is needed to achieve 90% power to detect an effect size (W) of 0.3 in pregnancy outcome between increasing, decreasing, or no change in endometrial thickness, using a 2 degree of freedom Chi-Square Test with a significance level (alpha) of 0.05, with 10% follow up rate.

Endometrial preparation and embryo transfer:

Embryo transfer was performed in hormone replacement (HRT) cycles using exogenous estrogen (E2) in the form of oral estradiol valerate daily (cycloprogynova; Bayer, Germany) on day 2–3 of a natural cycle. Patients were given oral 4 mg micronized E2 twice daily (total dose of 8mg/day).

Transvaginal ultrasound measurement (TVUS) of the endometrial thickness (EMT) using a 2D 6.5MHz probe was performed ten days after starting E2 to measure endometrial thickness and pattern. EMT was defined by the maximal distance from one endometrial myometrial interface to the other in the mid-sagittal plan.

The endometrium was considered adequate to start progesterone administration if it is ≥7 mm with a trilaminar pattern. If not adequate, estrogen administration was continued, and serial ultrasound assessment was undertaken until an adequate endometrium was observed.

Cycles with persistent endometrial thickness <7mm were canceled and excluded from the analysis.

When the endometrial thickness reached ≥7 mm, patients started vaginal progesterone in the form of (prontogest; Marcyrl, Egypt) 400 mg twice daily.

Embryos were thawed/warmed and transferred on day 6 of progesterone. All blastocysts were assessed before embryo transfer by an experienced embryologist using the grading system proposed by Gardner (25) with the selection of high-quality blastocysts. The study included patients undergoing ≤ 2blastocyst(s) transfer.

On the day of embryo transfer under TVUS guidance, endometrial thickness was re-evaluated and measured, and images of the endometrium were recorded.

Serum Progesterone and estrogen were measured on day ten after priming endometrium with estradiol valerate, then re-assed in the early morning of the day of embryo transfer.

Luteal phase support:

On the day after FET, patients continued vaginal progesterone, 400mg twice daily, with added progesterone injections in oil (prontogest; Marcyrl, Egypt) 50 mg intramuscular daily. Both were continued until pregnancy was assessed by serum β-HCG 11 days after embryo transfer.

On positive pregnancy test, progesterone supplementation continued until approximately 12-14 weeks gestation.

Patients were divided into three groups based on the calculation of the percentage of endometrial compaction, defined as the difference in endometrial thickness at the end of the estrogen-only phase and the day of embryo transfer after five days of progesterone exposure, divided by the thickness at the end of the estrogen-only phase:

According to Riestenberg et al. (16), compaction was defined as a ≥5% decrease in EMT and expansion as a ≥5% increase. Cycles with less than 5% percentage change were classified as no-change cycles.

Cycles, where endometrial thickness is calculated to decrease by the time of embryo transfer compared with the thickness at the end of the estrogen-only phase, were further analyzed according to the degree of compaction, i.e., 5%, 10%, or 15% decrease in thickness.

Outcome measures:

Primary outcomes:

• Ongoing pregnancy rate, defined as the visualization of fetal cardiac activity on transvaginal ultrasound at 12 weeks gestation in each group.

• Whether endometrial compaction affects pregnancy outcome.

Secondary outcomes:

• Implantation rate, defined as the number of implanted embryos relative to the total number of embryos transferred in each group.

• Clinical pregnancy rate, determined by visualizing a viable embryo within the uterine cavity by ultrasound 3– 4 weeks after ET in each group.

• Biochemical pregnancy rate, detected by positive hCG test in the absence of pregnancy findings on TVU in each group.

Statistical analysis:

The data were evaluated statistically using IBM SPSS software, version 20.0. IBM Corporation, Armonk, New York. Numbers and percentages were used to describe qualitative data. The normality of the distribution was examined using the Kolmogorov-Smirnov test. The range (minimum and maximum), mean, standard deviation, median, and interquartile range were used to characterize quantitative data (IQR). $P< 0.05$ was regarded as significant for the analysis.

The chi-square test was employed for categorical variables and group comparisons. A Student t-test was used to compare two groups under study for quantitative variables with normally distributed distributions. Use the Mann-Whitney test to compare two groups under study with improperly distributed quantitative variables.

Results

A total of 315 FET cycles were monitored during the study period; 8 cycles were canceled before the day of ET and were not included in our study. These cycles were canceled due to persistent thin endometrium <7 mm (2 cases), presence of endometrial polyp during monitoring (2 cases), COVID-19 diagnosis (1 case), lack of post-thaw viable embryo (1 case), and social reasons (2 cases). Therefore, our final data analysis included a total of 307 HRT–FET cycles that showed an overall implantation rate of 53.38%, a clinical pregnancy rate of 47.55%, and an ongoing pregnancy rate of 38.43%

Using 2D TVUS, 25.73% of the cycles showed endometrial compaction, 33.87% showed no EMT change, and 40.39% showed endometrial expansion. Baseline patient characteristics showed no difference among groups.

(TABLE 1) represents the FET cycle variables among the three studied groups, including baseline demographic data, serum estradiol and progesterone levels at the end of the estrogen phase and on the day of ET, the quality of transferred embryos, and the number of embryos transferred in each group.

Endometrial thickness parameters among compaction, no change, and expansion groups are also shown in **Table 1**. A significantly higher mean endometrial growth rate at the end of the estrogen phase was found in the compaction group compared to the no change and expansion groups (8.58 ± 1.10 vs. 8.19 ± 1.25 vs. 7.51 ± 1.75, respectively; $p < 0.001$). Also, the mean EMT at the end of the estrogen phase was significantly higher in the compaction group compared to no change and expansion groups (12.44 ± 1.16 vs. 12.05 ± 1.27 vs. 11.40 ± 1.79, respectively; $p < 0.001$).

The mean EMT on the day of embryo transfer and EMT percentage change were 11.21 mm (9.84%), 12.23 mm (-1.63 %), and 12.70 mm (-12.25 %) in the compaction, no change, and expansion groups, respectively.

Table (1): Comparison between the two studied groups according to basic and different cycle parameters.

Parameter	Compaction* (n = 79)	No change** (n = 104)	Expansion*** (n = 124)	Test of Sig.	p
Age					
Median (Min. – Max.)	29.0(26.0 – 35.0)	30.0(27.0 – 34.50)	29.0 (26.0 – 33.0)	F=2.700	0.324
Male age (/years)					
(Min. – Max.)	37.0(31.0 – 39.50)	34.50(30.0 – 42.0)	33.50(30.0 – 40.0)	F=1.139	0.322
BMI (kg/m²)					
Median (Min. – Max.)	26.0(24.0 – 28.0)	26.0(24.0 – 27.0)	26.50(24.0 – 28.0)	F=0.776	0.461
Previous pregnancy					
Number/%	25(31%)	38(36.5%)	38(30.6%)	$\chi 2$ =0.966	0.617
Cause of infertility					
Unexplained	21(26.5%)	18(17.2%)	24(19.3%)		
Male	12(15.2%)	34(32.7%)	29(23.4%)	χ^2=	
Ovarian	31(39.2%)	28(26.9%)	39(31.5%)	11.694	0.432
Endometriosis	3(3.8%)	2(1.9%)	4(3.2%)		
Tubal factor	12(15.2%)	22(21.2%)	28(22.6%)		
Estradiol at the end of the estrogen phase (pg/ml)					
Mean ± SD.	276.6 ± 68.81	274.3 ± 71.44	282.5 ± 68.16	F=0.424	0.655

Parameter	Compaction* (n = 79)	No change** (n = 104)	Expansion*** (n = 124)	Test of Sig.	p
Estradiol at ET day (pg/ml)					
Mean ± SD.	315.45 ± 134.40	322.01 ± 149.31	311.37 ± 112.19	F=0.396	0.570
progesterone at the end of the estrogen phase (ng/ml)					
Mean ± SD.	0.19 ± 0.16	0.22 ± 0.19	0.25 ±0.09	F=0.232	0.978
Progesterone at ET day (n/ml)					
Mean ± SD.	10.21 ±3.07	11.19 ± 3.98	10.54 ± 4.11	F=0. 240	0.787
Embryo quality (number/%)					
Excellent	38(48.1%)	40(38.5%)	56(45.2%)	$\chi 2$= 1.890	0.389
Good	41(51.9%)	64(61.5%)	68(54.8%)		
Number of ET (number/%)					
1	34(43.0%)	50(48.1%)	58(46.8%)	$\chi 2$= 0.481	0.768
2	45(57.0%)	54(51.9%)	66(53.25)		
Baseline EMT					
Min. – Max	3.0 – 4.50	3.0 – 4.50	3.0 – 4.50	F= 0.124	0.883
Mean ± SD.	3.85 ± 0.56	3.86 ± 0.54	3.89 ± 0.55		
Median (Min. – Max.)	4.0 (3.54 – 4.52)	4.1(3.51 – 4.50)	4.0 (3.50 – 4.49)		
Endometrial growth					
Min. – Max	6.0 – 10.50	4.0 – 10.0	3.50 – 10.0	F= 0.124	0.883
Mean ± SD.	8.58 ± 1.10	8.19 ± 1.25	7.51 ± 1.75		
Median (Min. – Max.)	9.0 (7.50 – 9.50)	8.50 (7.50 – 9.0)	8.0 (6.50 – 9.0)		
Significance between groups			p1=0.168, p2<0.001*,p3=0.001*		
Endometrial thickness at the start of progesterone					
Min. – Max	10.2 – 14.50	8.51 – 14.0	8.32 – 14.10	F= 12.908*	<0.001*
Mean ± SD.	12.44 ± 1.16	12.05 ± 1.27	11.40 ± 1.79		
Median (Min. – Max.)	12.50(11.50–13.50)	12.25(11.0–13.0)	11.50(11.0–13.0)		
Significance between groups			p1=0.185,p2<0.001*,p3=0.003*		

Parameter	Compaction* (n = 79)	No change** (n = 104)	Expansion*** (n = 124)	Test of Sig.	p
The endometrial thickness on the day of ET					
Min. – Max	9.0 – 13.0	9.0 – 14.0	9.0 – 15.0	F= 30.660*	<0.001*
Mean ± SD.	11.21 ± 1.04	12.23 ± 1.21	12.70 ± 1.57		
Median (Min. – Max.)	11.0(10.50 – 12.0)	12.50(11.50–13.25)	13.0(12.0 – 14.0)		
Significance between groups	p1<0.001*, p2<0.001*,p3=0.022*				
% Change in EMT					
Mean ± SD.	7.14 – 15.38	-5.88 – 4.55	-28.57 – -7.14	H= 270.340*	<0.001*
Median (Min. – Max.)	9.84 ± 2.27	-1.63 ± 2.63	-12.25 ± 5.80		
Median (IQR)	9.09 (8.0 – 11.32)	0.0 (-4.17 – 0.0)	-9.09 (-15.0 – -8.0)		
Significance between groups	p1<0.001*,p2<0.001*,p3<0.001*				

SD: Standard deviation **t: Student t-test** **U: Mann Whitney test** **χ^2: Chi-square test**

IQR: Inter quartile range

p: p-value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$

F: F for One-way ANOVA test, Pairwise comparison bet. every two groups were done using Post Hoc Test (Tukey)

p: p-value for comparing the three studied groups

p1: p-value for comparing between Negative and No change

p2: p-value for comparing between Negative and Positive

p3: p-value for comparing between No change and Positive

*: Statistically significant at $p \leq 0.05$

*Cycles with ≥5% decrease in EMT between the end of the oestradiol-only phase and the day of embryo transfer.

** Cycles with <5% change in EMT between the end of the oestradiol-only phase and the day of embryo transfer.

***Cycles with ≥5% increase in EMT between the end of the oestradiol-only phase and the day of embryo transfer

The pregnancy outcomes between the groups are represented in **Table 2**. The ongoing pregnancy rate was significantly higher in the compaction group compared to the no change and expansion group (48.1% vs. 40.4% vs. 30.6%, respectively; $p < 0.039$).

The clinical pregnancy rate, abortion rate, implantation rate, and chemical pregnancy rate were comparable between the groups.

Results were evaluated according to the degree of compaction by dividing the patients into 5% compaction slices. Implantation and ongoing pregnancy rates were significantly higher at a 5-10% compaction level ($p = 0.039$ and 0.008, respectively) **(Table 3).**

Table (2): Comparison between the three studied groups according to pregnancy outcomes

parameter	Compaction (n = 79)	No change (n = 104)	Expansion (n = 124)	χ^2	p
Overall Pregnancy rate					
Not pregnant	35 (44.3%)	52 (50%)	74 (59.7%)	4.949	0.084
Pregnant	44 (55.7%)	52 (50%)	50 (40.3%)		
Abortion rate					
No abortion	40 (90.9%)	46 (88.5%)	43 (86.0%)	0.549	0.760
Abortion	4 (9.1%)	6 (11.5%)	7 (14.0%)		
Number of Sacs					
0	37 (46.8%)	56 (53.8%)	74 (59.7%)		
1	24 (30.4%)	32 (30.8%)	26 (21.0%)	5.367	0.252
2	18 (22.8%)	16 (15.4%)	24 (19.4%)		
Twin pregnancy rate	18 (22.8%)	16 (15.4%)	24 (19.4%)	1.634	0.442
Chemical pregnancy rate					
No chemical	77 (97.5%)	98 (94.5%)	119 (96.0%)	1.095	$^{MC}p=$ 0.558
Chemical	2 (2.5%)	6 (5.8%)	5 (4.0%)		
Ongoing pregnancy rate					
No	41 (51.9%)	62 (59.6%)	86 (69.4%)	6.466*	0.039*
Yes	38 (48.1%)	42 (40.4%)	38 (30.6%)		
Implantation rate#	60/124 (48.4%)	64/158 (40.5%)	74/190 (38.9%)	2.949	0.229

χ^2: **Chi-square test** MC: **Monte Carlo**

p: p-value for comparing between the three studied groups

*: Statistically significant at $p \leq 0.05$

#: Implantation Rate = total number of sacs/total number of embryos transferred *100

Table (3): Pregnancy outcome measures at different endometrial compaction levels

	5-10% (n = 41)		>10-15% (n = 26)		>15% (n = 12)		χ^2	p
	No.	**%**	**No.**	**%**	**No.**	**%**		
Clinical Pregnancy rate								
Not pregnant	14	34.1	15	57.7	6	50.0	3.761	0.153
Pregnant	**27**	**65.9**	**11**	**42.3**	**6**	**50.0**		
Abortion rate								
No abortion	27	100.0	9	81.8	4	66.7	7.816*	^{MC}p= 0.014*
Abortion	0	0.0	2	18.2	2	33.3		
Number of Sacs								
0	15	36.6	14	53.8	8	66.7	5.885	^{MC}p= 0.206
1	13	31.7	9	34.6	2	16.7		
2	13	31.7	3	11.5	2	16.7		
Chemical pregnancy rate								
No chemical	40	97.6	26	100.0	11	91.7	2.310	^{MC}p= 0.381
Chemical	1	2.4	0	0.0	1	8.3		
Ongoing pregnancy rate								
No	15	36.6	16	61.5	10	83.3	9.569*	0.008*
Yes	26	63.4	10	38.5	2	16.7		
Implantation rate#	39/66	59.1	15/41	36.6	6/17	35.3	6.481*	0.039*

χ^2: **Chi-square test** MC: **Monte Carlo**

p: p-value for comparing between the three studied subgroups

*: Statistically significant at $p \leq 0.05$

#: Implantation Rate = total number of sacs/total number of embryos transferred *100

Logistic regression analysis examined the independent effects of different variables on the ongoing pregnancy rate in the total study sample (**Table 4**). In HRT-FET cycles, the chance for ongoing pregnancy was significantly higher in cycles that showed endometrial compaction [OR: 1.715, 95% confidence interval (CI) 1.021 – 2.880, p = 0.041].

Table (4): Logistic regression analysis for parameters affecting ongoing pregnancy rate (n = 118 vs. 189) in the total sample

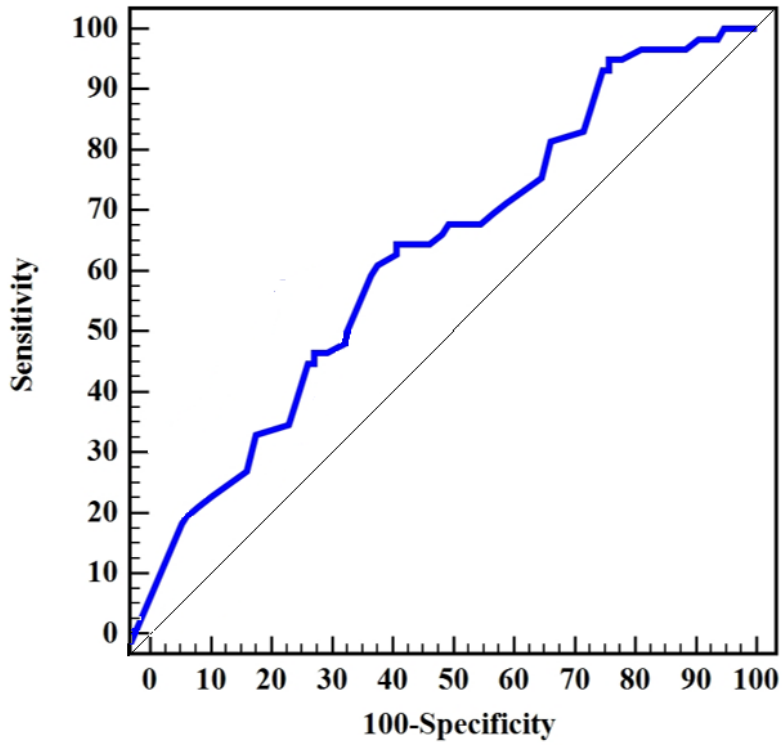
	Ongoing pregnancy rate			Univariate		Multivariate
	No® (n = 189)	Yes (n = 118)	p	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
Female age (/years)	29.56 ± 5.17	30.57 ± 4.94	0.092	1.040 (0.994 – 1.089)	0.205	1.031 (0.983 – 1.082)
Male age (/years)	35.19 ± 6.04	36.31 ± 7.75	0.161	1.025 (0.990 – 1.060)		
BMI (kg/m²)	25.87 ± 2.31	26.01 ± 2.48	0.626	1.024 (0.930 – 1.129)		
Baseline endometrial thickness	3.86 ± 0.55	3.88 ± 0.55	0.820	1.050 (0.690 – 1.597)		
Endometrial growth	7.79 ± 1.67	8.38 ± 1.10	0.001*	1.336 (1.124 – 1.589)		
EMT at the end of the estrogen phase	11.65 ± 1.73	12.26 ± 1.07	0.001*	1.330 (1.123 – 1.576)	0.081	1.457 (0.954 – 2.225)
EMT on the day of ET	12.06 ± 1.51	12.32 ± 1.34	0.128	1.133 (0.965 – 1.331)	0.605	0.886 (0.561 – 1.400)
Excellent Embryo quality	72 (38.1%)	62 (52.5%)	0.013*	1.799 (1.129 – 2.866)		
Number of embryos transferred						
1	92 (92)	50 (42.4%)	0.282	0.775 (0.488 – 1.232)		
2	97 (51.3%)	68 (57.6%)	0.282	1.290 (0.812 – 2.050)	0.083	1.543 (0.946 – 2.516)
Occurrence of compaction (negative change group)	41 (21.7%)	38 (32.2%)	0.041*	1.715 (1.021 – 2.880)	0.828	1.118 (0.407 – 3.071)

OR: Odd`s ratio ®: Reference group CI: Confidence interval LL: Lower limit
UL: Upper Limit *: Statistically significant at p ≤ 0.05 EMT:endometrial thickness

A receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic performance of TVUS-measured percentage change in endometrial thickness to ongoing pregnancy rate. The analysis showed a significant relationship between TVUS-measured EMT percentage change and ongoing pregnancy rate.

The sensitivity and specificity of TVUS calculated from the ROC curve were 78.41 and 59.26, respectively (AUC: 0.754, 95% CI 0.641 – 0.738; p = 0.002) (**Figure 1**)

Figure (1): ROC curve for evaluation of the predictive performance of TVUS-measured percentage change in endometrial thickness to ongoing pregnancy rate (AUC 0.754, 95% CI 0.641 – 0.738, P = 0.002)
AUC: Area Under a Curve; CI: Confidence Intervals; p-value: Probability value with Statistically significant at p ≤ 0.05 # Cutoff was chosen according to the Youden index



Discussion

Our notion of using endometrial ultrasound measurements at two distinct points during an embryo transfer cycle was based on the assumption that these measurements could be used as a marker of progesterone activity and endometrial receptivity. By analyzing the change in endometrial thickness from the end of the estrogen phase to the day of embryo transfer, follicular/luteal transition may be detected.

Based on known physiologic changes in the endometrium during the menstrual cycle, there is an observed decrease in endometrial thickness between 1.0-1.5 mm. (about 10–15%) around the 5th day after ovulation. (24) This occurrence appears to precede the presumed receptive phase immediately. Although the physiological effects of endometrial compaction in response to progesterone exposure are unknown, a sonographically detectable window of optimal endometrial receptivity may potentially be predicted.

The current study was performed to assess the impact of endometrial compaction on pregnancy outcomes in hormonally prepared FET cycles and to analyze cycle parameters related to compaction.

Compaction was defined as a ≥5% decrease in EMT, corresponding to a 0.5 mm or more reduction in endometrial thickness by the day of embryo transfer. Using 2D TVUS, 25.73% of the cycles showed endometrial compaction, 33.87% showed no EMT change, and 40.39% showed endometrial expansion

According to the results, FET cycles that showed endometrial compaction after progesterone administration had significantly higher ongoing pregnancy rates than cycles in which endometrium didn't change or expand (48.1% vs. 40.4% vs. 30.6%, respectively; $p < 0.039$). Results were then evaluated according to the degree of compaction by dividing the patients into 5% compaction slices. Implantation and ongoing pregnancy rates were significantly higher at a 5-10% compaction level. Also, it was associated with lower abortion rate ($p=0.014$).

It was also noted that endometria that expanded the most from baseline to progesterone start were the most likely to compact, suggesting that estradiol exposure and response during the follicular phase may be another aspect to consider.

Similar to our findings, Haas et al. (2019) (24) reviewed 274 FET cycles that also underwent hormonal preparation. Haas et al. concluded that endometrial compaction following progesterone exposure was associated with higher rates of ongoing pregnancy. In 2020, Zilberberg et al. (15) assessed 225 hormonally prepared FET cycles in which PGT-A was applied before ET with similar outcomes.

A 42.4% and 43.1% compaction rate were reported by Haas et al. and Zilberberg et al. (15, 24), respectively. These compaction rates are higher than our current study (25.73%); the disparity in the research results can be explained by the authors' use of AUS rather than TVUS to assess endometrial thickness on the ET day.

Other studies investigating endometrial compaction yielded different outcomes.

Bu et al. (2019) (26) conducted an observational study involving 3091 patients undergoing FET in either natural or hormonal cycles. Results showed that endometrial thickness on the day of embryo transfer increased or remained stable compared to the day of progesterone administration and that better pregnancy outcomes were associated with endometrium expansion following progesterone administration.

Olgan et al., 2022 (18); Riestenberg et al.(16), 2021; and Ye et al.(27), 2020 studies results yielded comparable pregnancy outcomes among cycles that showed compaction, expansion, or no change.

Ye et al. (2020)(27) concluded that regardless of whether endometrial thickness increased, decreased, or remained unchanged after progesterone exposure, there was no statistically significant difference between clinical pregnancy rate and live birth rates(LBR) across cycles. Riestenberg et al. (2021) (16) indicated that there was no difference in LBR with compaction (58.1%), no change (54.7%), and expansion (58.6%). Moreover, clinical pregnancy and spontaneous abortion rates were comparable among groups. In the study by Olgan et al. (2022) (18), 204 HRT-FET cycles were observed prospectively through sequential TVUS, (15.2%) showed compaction, (60.3%) expanded, and (24.5%) remained unaltered. Additionally, all groups' levels of estrogen, progesterone, and estrogen/progesterone on the day of embryo transfer were comparable.

Possible explanations of inadequate endometrial response to progesterone exposure include altered estrogen/progesterone ratio, suboptimal progesterone dosing, progesterone resistance, chronic endometritis, progesterone receptor gene mutations, or epigenetic changes affecting progesterone receptors.(24)

Usadi et al. (2008) (28) designed a study to investigate the effects of serum progesterone levels on endometrial changes. In this study,17 women undergoing HRT cycles were pretreated with a GnRH agonist and a standard physiological dose of transdermal estradiol before receiving a randomly assigned daily dose of 10 or 40 mg intramuscular progesterone. Although the study did not specifically assess alterations in endometrial thickness, it showed comparable progesterone concentrations among the groups that underwent compression, no change, and expansion.

Our study findings showed that mean estradiol and progesterone concentrations at the end of the estrogen phase and ET day didn't show statistically significant differences among the studied groups. These results suggest that compaction failure might be attributed to progesterone receptor deficiency or resistance rather than serum hormonal levels.

The key strengths of our study were its prospective nature, use of TVUS in endometrial assessment, and precise inclusion and exclusion criteria to avoid confounding factors. Also, the logistic regression analysis model was applied to examine the independent effects of different variables on the ongoing pregnancy rate in the total study sample. ROC curve analysis evaluated the predictive performance of TVUS-measured percentage change in endometrial thickness to ongoing pregnancy rate.

Limitations of the current study include its relatively moderate sample size and the unreported live birth rate.

The current study contributes to the emerging research on the clinical significance of endometrial compaction.

Conclusion

Measurement of the dynamic changes in the endometrial thickness using TVUS at the end of the estrogen phase and on the day of embryo transfer following progesterone administration in hormonally prepared FET cycles plays a role in improving pregnancy outcomes. Future research may be able to determine how to prevent continued endometrial expansion after progesterone exposure.

Whether the endometrium contracted or expanded is significant, but the real question is when it did. Alternately, sonographic examination of the timing of endometrial thickness changes may provide insight into the optimal timing for individualized embryo transfer. This would be useful because it is unknown whether cycles that did not show compaction within five days of progesterone exposure may have compacted shortly after that (delayed compaction) with altered or delayed receptivity.

Financial Disclosure and Funding

No financial support was gained from any organization and no one contributed to this work other than the authors

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

None to declare.

Data availability

The data are available upon request.

Conflict of interest

None

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