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Investigating the impact of endometrial compaction on clinical pregnancy rate in artificial frozen-thawed embryo transfer cycles

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ABSTRACT

Objective: The aim of our study was to evaluate sonographic endometrial thickness succeeding the estrogen-only stage and on the day when embryo transfer (ET) occurred in artificial frozen embryo transfer (FET) cycles to delve into the effect of endometrial compaction (EC) on clinical pregnancy rate (CPR).

Patients and Methods: In the first group endometrial thickness diminished when ET occurred when compared to the end of the estrogen-only phase (n:37). Endometrial thickness increased/did not alter for the second group (n:70).

Demographic characteristics were recorded and the following were studied: in vitro fertilization (IVF) treatment indications, hormone levels, total antral follicle count, duration of infertility, embryo quality, embryo-fundus distance, endometrial thickness at the end of estrogen-only phase and on ET day, luteal support, CPR.

Results: No significant difference occurred in CPRs (n:107). ET, on day 5 was higher in the first group ($p<0.05$). Regression analysis revealed EC was 8.000 times higher in those with ET day 5 than those with 3.

Conclusion: Endometrial compaction is non-relevant to the rate of clinical pregnancy. The day of ET affected the presence of EC.

Keywords: Endometrial compaction, Artificial frozen embryo transfer cycles, Clinical pregnancy rate, Day of embryo transfer

1. INTRODUCTION

Endometrium changes its surface epithelium, vascular network as well as expressing certain glycoproteins, integrins, receptors, along with chemokines to prepare endometrial environment for embryo implantation. Endometrial receptivity is common during the implantation window which occurred on days 20-24 in a 28-day cycle [1]. Recent research has revealed the findings pertaining to that endometrial thickness and pattern carry a pivotal role for embryo transfer (ET) outcomes at the end of the proliferative phase [2,3]. When the endometrial thickness was measured less than 7-8 mm or greater than 13 mm, the clinical pregnancy rate (CPR) and live birth rate lower both for fresh and frozen embryo transfer (FET) cycles [4,5]. Whilst, the assessment of endometrial thickness on the human chorionic gonadotropin (hCG) trigger day in fresh cycles or subsequent to the estrogen-only phase in FET cycles is a key factor to decide the ET, evaluating endometrial thickness on the day of ET is also deemed critical [6].

The decrease in endometrial thickness, boost in density and hyperechoic appearance on ultrasound by progesterone initiation between the closing of the estrogen-only phase and the time of ET is entitled endometrial compaction (EC). The relation between EC and the rate of pregnancy of clinical sort is controversial, although, some studies unveiled a relation between CPR and EC, some actually did not [7-9].

In this direction, we intended to evaluate sonographic endometrial thickness in the wake of the estrogen-only phase

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and on the day when ET occurred in artificial FET cycles with a view to scrutinizing the effect of EC on CPR.

2. PATIENTS and METHODS

This retrospective research was conducted with 107 women in the in-vitro fertilization (IVF) clinic of Etlik Zübeyde Hanim Women's Health Training and Research Hospital, Ankara, Turkey. The study protocol was approved by the said hospital's Ethics Committee (Clinical study 06.07.2022/2022/94). The present research had two groups and in the first one there were women whose endometrial thickness was spotted to diminish at the time of ET when compared to that of the end of the estrogen-only phase (n:37). The second group involved women whose endometrial thickness increased or did not alter (n:70).

Solely patients with artificial FET cycles and single ET were included in the study. History of chronic diseases, the patients who received mild or natural cycle protocols, the ones with fresh cycles, with more than one embryo transfer, the use of preimplantation genetic diagnosis, oocyte and embryo recipients were all excluded in this regard.

Characteristics that are pertinent to demographic information of the participants maternal age, body mass index (BMI), gravidity, abortion, and living child were documented. IVF treatment indications e.g., male factor, diminished ovarian reserve and others, day 3 (D3) estradiol (E2), levels belonging to follicle stimulating hormone (FSH), luteinizing hormone (LH) and anti-Müllerian hormone (AMH), total antral follicle count, duration of infertility, transferred embryo quality [10], embryo-fundus distance, E2 level on ET, progesterone level on ET, day of ET, endometrial thickness following the estrogen-only phase and on the very day when ET took place, luteal support, CPR were calculated. Clinical pregnancy was considered as the determination of gestational sac via ultrasound.

All the patients received oral E2 pill (Estrofem 2 mg pill, Novo Nordisk Pharma, Denmark) twice daily, on day 2–3 of the menstrual cycle, and ultrasound evaluation of endometrial thickness and pattern was executed 7 days after the initiation of E2. All ultrasound evaluations were performed by the same clinician in the IVF clinic by LOQIC A5 ultrasonography. On the condition that endometrial thickness was located as < 7 mm, the dose was elevated three times per day (6 mg E2). The endometrium was re-assessed on the 10-12 day after starting E2, and provided it was measured as >7-8 mm through a trilaminar pattern, the progesterone was initiated, if it was still < 7 mm, estrogen administration was prolonged for up to 28 days with maximum 6 mg E2 dosage per day [11].

Intramuscular progesteron (100 mg daily, Progestan, Koçak Pharma, Türkiye) and oral dydrogesteron (10 mg 3 times a day, Duphaston, Abbott Pharma, USA) or intramuscular progesteron (100 mg daily) and vaginal progesterone (90 mg 2 times a day, Crinone gel, Merck Pharma, Germany) were used and the endometrial thickness were measured on the day of embryo ET. Embryo freezing was performed using the vitrification method (RapidVit Omni, Vitrolife, Sweeden) on days 3 or 5. Embriyos were loaded onto straw (Kitazato Cryotop, Spain) for freezing. The thawing procedure (RapidWarm Omni, Vitrolife) was applied for thawed embryos. The embryos were transferred by using soft ET catheter (ET catheter, Laboratoire CCD, France) to the uterus via transabdominal ultrasound guidance [10]. Blastocyst stage embryo was transferred on the 6th day of progesterone administration, the cleavage stage embryo was transferred on the 4th day of progesterone administration.

Statistical Analysis

Statistical work of the data was implemented using the Statistical Package for Social Sciences (SPSS) software v.24 (SPSS Inc., Chicago, IL, USA). To be able to examine variables of continuous nature, the data coming from the two independent groups were contrasted resorting to the Independent Samples T-Test for normal distribution and the Mann-Whitney U test was referred to for non-normal distribution. "Pearson-χ2 crosstabs" were used to examine the relationships between two qualitative variables. A multiple linear regression analysis was utilized so as to observe the relationship between day of embryo transfer and EC group. Parameter estimates, alongside 95% confidence intervals were noted. A two-sided p-value < 0.05 was found out statistically significant for all the analyses realized.

3. RESULTS

A total of 107 women participated in this study. We found no significant difference in demographic and obstetric characteristics, D3 FSH level, D3 LH level, D3 E2 level, AMH level, total antral follicle count, duration of infertility, transferred embryo quality, embryo-fundus distance, E2 level on ET, progesterone level on ET between the groups (p>0.05) (Table I).

No difference of significant sort was figured out either in male factor, tubal factor, diminished ovarian reserve, unexplained infertility, luteal support, and CPR between the two groups (p>0.05). The day 5 of ET was significantly higher for the first group (p<0.05) (Table II).

As a result of the backward endeavor and the LR logistic regression analysis according to the existence of EC, all insignificant parameters were removed and ET day was determined as the only significant parameter in the model; the optimal model was given in Table III.

In the current model it was discerned that the day of ET was a crucial factor affecting the presence of EC (p<0.05). The existence of EC was 8,000 times more in those with ET day 5 than those with 3.

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***Table I**. Comparison of demographic, laboratory, and cycle characteristics*

Variables	Study group (n=37)		Control group (n=70)		Statistical analysis* P value
	X̄ ±S.S.	Median [Min-Max]	X̄ ±S.S.	Median [Min-Max]	
Age (years)	29.33±3.19	29.0 [23.0-36.0]	2.32±3.45	28.5 [2.0-34.0]	Z=-1.305 p=0.192
BMI (kg/m²)	26.01±5.39	23.9 [16.7-37.2]	25.29±4.34	24.7 [18.6-36.0]	Z=-0.362 p=0.717
Gravida	0.53±0.85	0.0 [0.0-4.0]	0.59±0.91	0.0 [0.0-4.0]	Z=-0.077 p=0.939
Living child	0.08±0.28	0.0 [0.0-1.0]	0.06±0.29	0.0 [0.0-2.0]	Z=-0.789 p=0.430
Abortion	0.44±0.84	0.0 [0.0-4.0]	0.31±0.61	0.0 [0.0-2.0]	Z=-0.759 p=0.448
AMH (ng/mL)	3.68±3.31	3.0 [0.2-10.4]	4.77±4.71	3.7 [0.2-23.7]	Z=-1.058 p=0.290
D3 FSH (mIU/mL)	6.53±2.26	6.2 [2.2-11.0]	6.83±2.86	6.3 [1.5-22.0]	Z=-0.103 p=0.918
D3 LH(mIU/mL)	6.19±4.56	5.4 [0.4-23.1]	5.24±2.51	5.0 [0.2-15.2]	Z=-0.540 p=0.589
D3 E2(pg/mL)	46.50±25.83	39.8 [13.0-161.0]	43.82±20.23	42.2 [5.0-118.5]	Z=-0.033 p=0.973
Total antral follicul count	17.41±8.54	17.0 [3.0-30.0]	18.07±9.12	17.5 [0.0-30.0]	Z=-0.304 p=0.761
Duration of infertility (month)	63.24±36.13	60.0 [12.0-180.0]	70.35±42.71	60.0 [12.0-192.0]	Z=-0.606 p=0.545
Transferred embryo quality	1.50±0.63	1.0 [1.0-3.0]	1.48±0.64	1.0 [1.0-3.0]	Z=-0.181 p=0.856
Embryo – fundus distance (mm)	9.64±3.67	10.0 [1.6-19.0]	9.77±3.38	9.9 [0.5-16.7]	t=-0.174 p=0.862
ET Progesteron (ng/mL)	11.60±11.34	8.7 [0.5-60.0]	8.55±5.96	8.9 [0.1-33.6]	Z=-0.776 p=0.438
ET E2 (pg/mL)	377.21±468.29	265.0 [31.4-2810.0]	300.30±229.34	244.5 [27.9-1458.7]	Z=-0.762 p=0.446

*BMI: body mass index, AMH: anti-mullerian hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone, E2: estradiol, ET: embryo transfer. S.D: standard deviation, Independent Sample-t test (t-table value), Mann-Whitney U test (Z-table value) statistics. *P-value of less than 0.05 was considered to be statistically significant*

***Table II.** Comparison of IVF parameters*

Variables	Study group (n=37)		Control group (n=70)		Statistical analysis* P value
	n	%	n	%	
Male factor					
Yes	14	37.8	30	42.9	χ^2=0.252 p=0.616
Tubal factor					
Yes	1	2.7	4	5.7	χ^2=0.493 p=0.483
Unexplained infertility					
Yes	16	43.2	25	35.7	χ^2=0.581 p=0.446
Diminished ovarian reserve					
Yes	5	17.9	9	15.3	χ^2=0.095 p=0.758
Luteal support					
Crinone gel	25	67.6	51	72.9	χ^2=0.329
Duphaston pill	12	32.4	19	27.1	p=0.566
Clinical pregnancy					
Yes	15	40.5	26	37.1	χ^2=0.118 p=0.731
Day of embryo transfer					
day 3	1	3.4	14	22.2	χ^2=5.129
day 5	28	96.6	49	77.8	**p=0.024**

*Pearson χ2 crosstabs. *P-value of less than 0.05 was considered to be statistically significant*

Table III. *The logistic regression model according to the presence of endometrial compaction*

Variables	B	S.E.	Wald	df	p	OR	95% Odds Ratio (OR)	
							Min	Max
Day of embryo transfer*	2.079	1.062	3.835	1	**0.049**	8.000	1.124	22.143
Constant	-2.639	1.035	6.500	1	0.011	0.071		

**Reference category: day of 3. B: beta coefficient, S.E: standard error, df: degrees of freedom*

4. DISCUSSION

It is noteworthy to highlight here that we did not find any significant difference between EC and CPR in artificial FET cycles. Though, in the literature, there were conflicting results about the impact of EC on CPR [7,12].

A review of the line of literature signals various results. To cite an example, in a study by Haas et al., the continuing pregnancy rate was significantly higher in EC group whereas Jin et al. reported that the CPR was higher in cycles that had no EC [7,13]. In contrast with Jin et al., Kaye showed that the CPR was higher in EC group [14]. In accordance with our study, Olgan determined that CPR did not differ between EC and non-compaction groups [15].

In the past, a fair number of studies concentrated upon the endometrial lining thickness rather than EC [16,17]. Recently, considering the endometrial pathophysiology, clinicians have begun to focus on whether EC may have an impact on pregnancy rate. Plentiful factors come into play in relation to the presence or absence of EC. In regular menstrual cycles, endometrial proliferation halts for 2–3 days posterior to ovulation and becomes denser by progesterone effect [18]. The continuation of endometrial proliferation during the luteal phase might be due to insufficient progesterone effect that cannot be observed by measuring serum progesterone levels. In the research of Usadi et al., it was announced that histological endometrial dating did not reflect circulating progesterone concentrations, the duration of progesterone exposure was more essential than serum progesterone concentrations on the quality of luteal function [19]. In addition to these, the continuation of endometrial proliferation during the luteal phase which manifested itself with absence of EC can emerge in the existence of progesterone receptor insufficiency or resistance in the endometrium. Several studies have underpinned that the activation of KRAS gene and the over-expression of Sirtuin 1 (SIRT1), BCL6 (B Cell Lymphoma 6) and escalated progesterone receptor (PGR) expression were associated with progesterone resistance [20, 21].

As a result of this study, we recognized that EC was more common in women undergoing day of 5 ET. As has been mentioned earlier, the duration of progesterone exposure on the endometrium was more influential than serum concentration. Blastocyst stage embryo was transferred on day 6 of progesterone initiation thereby, progesterone exposure on the endometrium was higher than the day of 3 ET.

In a nutshell, it would be fair to italicize that EC seems not to be linked to CPR, and the results of our study entails validation by prospective studies.

Compliance with Ethical Standards

Ethical Approval: The ethics committee of Etlik Zübeyde Hanim Women's Health Training and Research Hospital of Ankara, Turkey, approved the study on July 06, 2022, with decision number 2022/94.

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Conflict of Interest: The authors declare that there are no conflicts of interest.

Authors' Contributions: KE: visualization, investigation, methodology, supervision, writing-review and editing, NTS: investigation, conceptualization, writing – original draft, EUO: investigation, conceptualization, writing – original draft, SD: conceptualization, writing – original draft, IK: investigation, conceptualization, writing – original draft, YEU: investigation, conceptualization, writing – original draft. All authors approved the final version of the article.

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