

CLINICAL TRIAL STUDY

Comparison of the Effectiveness of Endometrial Scratching in Follicular and Luteal Phases in Pregnancy Rate of Frozen Embryo Transfer Candidate Women

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Abstract: Background: Endometrial scratching (ES) has been reported as a strategy to improve the outcome of IVF. Considering that the follicular phase and luteal phase have their specific characteristics and hormonal secretions, we investigated whether scratching in different phases affects a woman's chances of becoming pregnant following frozen embryo transfer.

Methods: A total of 300 frozen embryo transfer candidate women with normal cavities and good embryo quality were randomly divided into two groups: group A with ES in the follicular phase and group B with ES in the luteal phase. In both groups, endometrial scratching was performed before IVF. The rate of pregnancy and baseline characteristics, such as age, education, and embryo quality, were compared between the two groups.

Results: Our results showed no significant differences in baseline characteristics between the groups. Furthermore, no significant differences were observed between the women who underwent ES in the follicular phase and those in the luteal phase for the outcome of IVF and chemical or clinical pregnancies.

Conclusion: ES in different phases of the cycle preceding frozen embryo transfer did not affect the outcome of pregnancy.

Keywords: Endometrial injury, follicular phase, luteal phase, pregnancy rate, *in vitro* fertilization (IVF), endometrial scratching.

1. INTRODUCTION

In vitro fertilization (IVF) is a very important strategy for many couples who are infertile. There have been many advances in the outcome of IVF. However, the failure rate of this procedure is still very high, and even in the most successful fertility and infertility centers, many patients undergo repeated implantation failure [1].

According to the European Society of Human Reproduction and Embryology (ESHRE), only 32.4% to 33% of IVF cases result in a clinical pregnancy [2]. Interaction between the embryo and the endometrium is a major factor influencing embryo implantation [3], and successful implantation is determined by two main factors, namely embryo quality and

endometrial receptivity [4]. Despite numerous strategies to improve embryonic factors, including enriched diets, culture medium optimization, and predicting embryo viability, embryo implantation still fails [5-7].

Recent studies have focused on uterine factors, such as endometrial thickness and low endometrial receptivity, as causes of these failures [8, 9]. Mechanical damage to the endometrium prior to IVF has been suggested as a procedure that increases the implantation rate by improving the endometrial receptivity [10]. Endometrial scratching (ES) is one of the mechanical damages that has been reported that improves the IVF outcome by inflammatory mechanisms [11] and increases the release of growth factors [12]. Several studies have shown that ES prior to IVF has increased the rate of clinical pregnancy [13-15].

It has been reported that the time of embryo transfer affects the endometrial receptivity [16]. Therefore, we investi-

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gated whether ES follicular phase or luteal phase impacts the outcome of pregnancy in frozen embryo transfer candidate women.

2. MATERIALS AND METHODS

The present block randomized clinical trial was registered at the Iranian Registry of Clinical Trials (IRCT20191031045292N1) and approved by the Ethics Committee of the Hamadan University of Medical Sciences (IR.UMSHA.REC.1398.615).

All trial was performed in Endometrium and Endometriosis Research Centre, Hamadan, Iran, between July 2019 and January 2021, and all patients received comprehensive information about the study and gave their informed written consent.

A total of 300 patients who were 43 years of age or younger and had at least two normal embryos with a normal uterine cavity were enrolled in this study. The exclusion criteria consisted of patients over 43 years old and low-quality embryos.

Patients who met the inclusion criteria were divided into two treatment groups A and B, using the block randomization method.

In group A (Follicular group), the local endometrial scratches were made in the four directions using the standard pip

ette endometrial sampling method at the beginning of the follicular phase [17].

Group B (Luteal group) underwent local endometrial scratches in the mid-luteal phase.

Some patients of both groups had received GnRH agonist as suppression in the previous cycle. Half an hour before the procedure, the patients received 100 mg of rectal diclofenac. A daily dose of 6 mg of estradiol continued until the transfer.

Endometrial thickness was assessed before embryo transfer, and the dose of estradiol was increased if the thickness was low.

Then, the pregnancy rate, duration of medication, and the amount of estradiol consumed were assessed in both groups. The rate of biological or clinical pregnancy was evaluated two weeks or five weeks following embryo transfer, using β HCG and ultrasonography, respectively.

2.1. Statistical Analysis

Continuous variables were presented as the mean and standard deviation (SD), and categorical variables were reported as frequency and percentage. A T-test was used to compare the continuous variables between groups. The chi-square test was used to compare the categorical variables. The logistic regression model was used to assess the association between potential factors with chemical and clinical pregnancy and adjust the potential confounders. The significant level was considered as 0.05. The Stata 14.2 (Stata Corp, TX, US) was used for data analysis.

3. RESULTS

All 300 patients who met inclusion criteria and were enrolled in this study continued their participation, and therefore, there was no decrease in the sample size. As mentioned above, the patients were subclassified into two groups: follicular and mid-luteal phases groups. Their baseline characteristics have been summarized in Table 1. The mean age was 33.16 ± 6.29 in the follicular group and 32.79 ± 5.82 in the luteal group. There were no significant differences between the two groups regarding age. The percentage of highly educated participants was more in the follicular phase when compared to the luteal group ($p < 0.05$).

Analysis of the results showed no significant difference in the number of transfers between the two study groups (Table 2). Furthermore, the percent of cycle type of freeze transmission was almost the same not only in the subgroup with suppression but also in the patients without suppression of both follicular and luteal phases groups.

T-test analysis revealed that endometrial thickness was higher in the follicular phase than in the luteal phase ($p < 0.001$, Table 3). Although the duration of estrogen intake in the luteal phase group was longer than in the follicular group, there was no significance. At the beginning of the cycle, the estradiol dose was similar in both groups. Still, it significantly increased the transfer time in the luteal group related to the follicular group ($p < 0.001$).

There were no significant differences in the rate of pregnancy between the groups. As shown in Tables 4 and 5, thirty (20%) and thirty-two (21%) biochemical pregnancies were reported in follicular and luteal phases, respectively. Although the frequency of clinical pregnancy was more in the follicular group than in the luteal group, there was no significant difference.

Table 1. Characteristics of participants.

Variable	Follicular Phase (n=150)	Luteal Phase (n=150)	p-value
Age mean (SD)	33.16 ± 6.29	32.79 ± 5.82	0.59
Education	Frequency (percent)	Frequency (percent)	0.032
Under diploma	103 (68.67)	85(56.67)	
Upper diploma	47(31.13)	65(43.33)	

Table 2. Comparison of the quality of transplanted embryos.

Categorical Variables	Follicular Phase (n=150)		Luteal Phase (n=150)		p-value
	Frequency	(%)	Frequency	(%)	
Number of Transfers					
1	60	40.00	78	52.00	0.04
2	65	43.33	59	39.33	
3+	25	16.67	13	8.67	
Cycle Type of Freeze Transmission					
With suppression	63	42.00	68	45.33	0.56
No suppression	87	58.00	82	54.67	
Quality of Transplanted Embryos					
A	71	47.33	56	37.33	0.021
AB	61	40.67	84	56.00	
B	18	12.00	10	6.67	
Number of Embryos Transferred					
1	21	14.00	15	10.00	0.204
2	75	50.00	90	60.00	
3+	54	36.00	45	30.00	
Type of Estrogen Intake					
Set-up	70	46.67	73	48.67	0.73
High-dose	80	53.33	77	51.33	
Continuous variables	Mean	SD	Mean	SD	-
Endometrial thickness	8.72	1.26	8.36	0.81	<0.001
Duration of estrogen intake	10.81	2.51	11.12	3.61	0.25
Estradiol dose in Start the cycle	5.51	0.87	5.51	1.06	1.00
Estradiol dose in Transfer time	5.01	1.22	6.05	1.58	<0.001

Table 3. Results of biochemical and clinical pregnancy in both groups.

Variable	Follicular Phase (n=150)		Luteal Phase (n=150)		p-value
	Frequency	(%)	Frequency	(%)	
Pregnancy in Biochemical Pregnancy					
Yes	30	20.00	32	21.33	0.78
No	120	80.00	118	71.67	
Pregnancy in Clinical Pregnancy					
Yes	28	18.67	24	16.00	0.54
No	122	81.33	126	84.00	

4. DISCUSSION

In this study, we aimed to evaluate whether there is a difference between follicular and luteal phases of endometrial scratching on pregnancy and live birth rate following embryo transfer. We found no phase-specific endometrial injury effects on the clinical outcome of IVF.

Endometrial scratching is one of the strategies that has been postulated to enhance the success rate of IVF by inflammatory mechanisms [11]. It has been reported that the expression of the pro-inflammatory $TNF\alpha$ in the endometrium causes the secretion of cytokines from the endometrial stromal cells and the differentiation of monocytes into dendritic cells, resulting in the expression of adhesion-related molecules [11]. There is some clinical evidence that reported

the effectiveness of ES on the pregnancy outcome [14, 15]. For example, a randomized controlled trial study showed that endometrial scratching improved the rate of clinical pregnancy in patients with previous failed intrauterine insemination cycles. They recruited one hundred sixty-eight infertile women into intervention and control groups (Eighty-four in each group). They reported that the clinical pregnancy rate in the endometrial injury group was 22.2% in comparison with 9.8% in the control group [18].

Moreover, endometrial scratch improved the pregnancy rate. It resulted in a reduction in the mean time achieve pregnancy in the scratch group (49.5 days) in comparison to the group (102 days) in patients with unexplained infertility [13]. They concluded that the endometrial scratch procedure could promote the recruitment of endometrial natural killer

Table 4. The univariate analysis of associated factors with chemical and clinical pregnancy in both follicular and luteal phases.

Chemical Pregnancy						
Variables	Follicular Phase			Luteal Phase		
	OR	p-value	95%CI	OR	p-value	95%CI
Age	0.99	0.953	0.94, 1.06	0.96	0.271	0.90, 1.03
Number of transfer	1.49	0.035	1.03, 2.15	1.00	0.997	0.59, 1.71
Cycle Type of Freeze Transmission						
With suppression	1	-	-	1	-	-
No suppression	0.79	0.563	0.35, 1.76	1.28	0.547	0.58, 2.82
Quality of Transplanted Embryos						
A	1	-	-	1	-	-
AB	0.93	0.866	0.41, 2.13	0.24	0.001	0.10, 0.57
B	0.20	0.134	0.02, 1.64	0.45	0.341	0.09, 2.33
Number of embryos transferred	2.19	0.017	1.15, 4.18	1.34	0.389	0.69, 2.58
Type of Estrogen Intake						
Low dose	1	-	-	1	-	-
High dose	2.00	0.105	0.86, 4.63	0.80	0.570	0.36, 1.74
Endometrial thickness	1.26	0.124	0.94, 1.69	0.75	0.263	0.45, 1.25
Duration of estrogen intake	0.93	0.362	0.79, 1.09	1.08	0.356	0.91, 1.29
Estradiol dose in start the cycle	1.35	0.261	0.80, 2.27	1.14	0.478	0.79, 1.64
Estradiol dose in transfer time	1.43	0.026	1.04, 1.97	0.95	0.346	0.68, 1.33
Clinical Pregnancy						
Age	0.98	0.605	0.62, 1.05	0.98	0.595	0.91, 1.06
Number of transfer	1.20	0.343	0.82, 1.76	1.07	0.817	0.60, 1.92
Cycle Type of Freeze Transmission						
With suppression	1	-	-	1	-	-
No suppression	0.80	0.99	0.35, 1.83	0.80	0.617	0.33, 1.92
Quality of Transplanted Embryos						
A	1	-	-	1	-	-
AB	1.10	0.821	0.47, 2.57	0.29	0.009	0.11, 0.73
B	0.24	0.182	0.03, 1.96	0.30	0.277	0.04, 2.60
Number of embryos transferred	1.94	0.045	1.02, 3.68	1.36	0.415	0.65, 2.82
Type of Estrogen Intake						
Low dose	1	-	-	1	-	-
High dose	1.74	0.201	0.74, 4.08	0.94	0.887	0.39, 2.25
Endometrial thickness	1.29	0.096	0.96, 1.74	0.74	0.311	0.42, 1.32
Duration of estrogen intake	0.95	0.582	0.81, 1.13	1.18	0.113	0.96, 1.45
Estradiol dose in start the cycle	1.28	0.357	0.76, 2.16	1.08	0.698	0.72, 1.62
Estradiol dose in transfer time	1.38	0.049	1.01, 1.91	0.82	0.310	0.56, 1.20

cells that are considered to participate in implantation and maintenance of pregnancy by regulating the depth of invasion of placental trophoblast and releasing angiogenic and immune factors [19]. Although the effectiveness of ES on pregnancy in women who underwent ART has been supported by many studies, some pieces of evidence have reported that ES did not promote the rate of pregnancy and live births when compared to the no-intervention control group [20]. A previous study by our lab showed no significant increase in both clinical and clinical pregnancy rates following ES in intrauterine insemination women [17]. So, we designed a study with a large sample size to evaluate this intervention

and supposed that scratching in the luteal phase seems to be associated with better outcomes.

In this study, 300 patients were enrolled into two follicular and mid-luteal groups and underwent ES procedures before IVF. We found no differences in the pregnancy rate following ES between the two groups. Consistent with us, Liu *et al.* reported that local endometrial injury in the cycle preceding IVF of subfertile women did not significantly promote implantation and clinical pregnancy rates. Moreover, they found no significant difference in clinical outcomes and live birth rates in ES in the luteal phase when compared to the follicular phase [21].

Table 5. The adjusted analysis of associated factors with chemical pregnancy in both follicular and luteal phases.

Chemical Pregnancy				
Phase	Variables	OR	p-value	95% CI
Follicular	Number of embryos transferred	2.09	0.04	1.04, 4.18
	Endometrial thickness	1.43	0.03	1.04, 1.98
	Number of transfer	1.45	0.07	0.97, 2.18
	Estradiol dose in transfer time	1.51	0.02	1.06, 2.13
Luteal	Number of embryos transferred	1.62	0.17	0.81, 3.23
	Quality of transplanted embryos	0.33	0.00	0.16, 0.70
Clinical pregnancy				
Follicular	Endometrial thickness	1.39	0.040	1.01, 1.90
	Estradiol dose in transfer time	1.49	0.024	1.05, 2.12
	Number of embryos transferred	1.88	0.069	0.95, 3.68
Luteal	Quality of transplanted embryos	0.36	0.020	0.15, 0.84
	Duration of estrogen intake	1.18	0.130	0.95, 1.46
	Estradiol dose in transfer time	0.76	0.179	0.52, 1.13

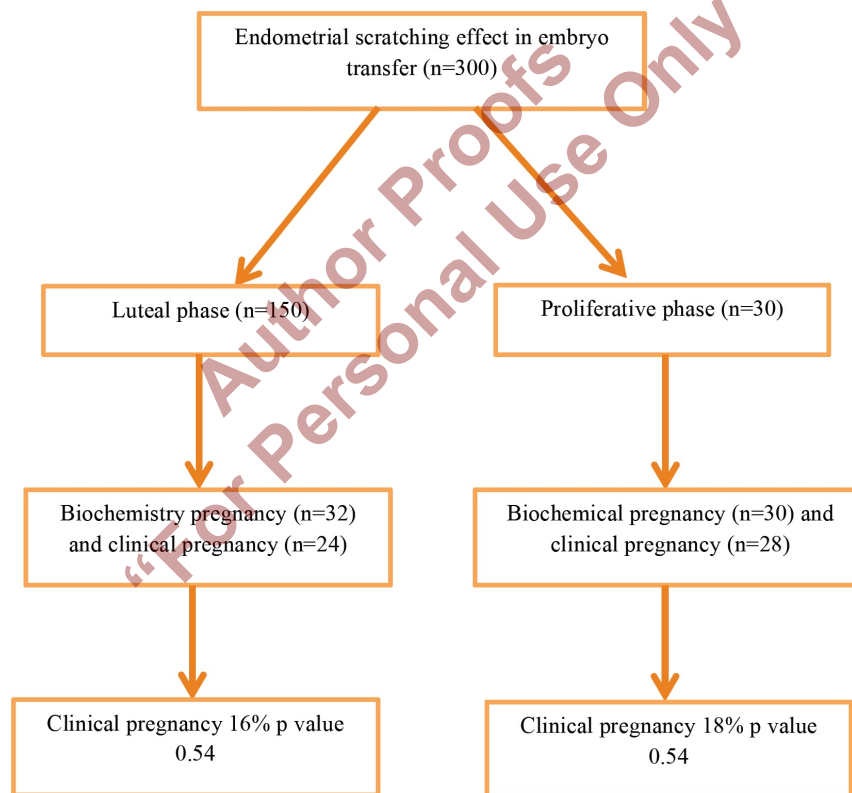


Fig. (1). Comparison of the effectiveness of endometrial injury in follicular and luteal phases in pregnancy rate of frozen embryo transfer candidate women.

A study by Hoogenhuijze *et al.* documented that the scratch in the mid-luteal phase prior to the start of stimulation for IVF/ICSI had no significant effect on the pregnancy rate [22]. Furthermore, the endometrial scratch procedure prior to first-time IVF caused no significant differences in the live birth rate in the women who underwent intervention

compared to treatment as usual. In total, 1048 participants were allocated to the study and received the procedure in the mid-luteal phase of the menstrual cycle. They recommend that although endometrial scratching is a safe method, it did not increase the live birth rate when performed in the mid-luteal phase [23] and suggested that ES is not undertaken in

this population. In contrast with the mentioned studies, Barash *et al.* documented that repeated endometrial biopsies during both follicular and luteal phases enhanced the clinical pregnancy and live birth rates [24]. Furthermore, it has been reported that local endometrial injury in the luteal phase prior to IVF/ICSI was an important prognostic factor for IVF success and enhanced the implantation and pregnancy rates [25]. The human menstrual cycle consists of four phases, including menstruation, the follicular phase, ovulation, and the luteal phase, each with its characteristics and different hormonal secretion (Fig. 1) [26].

Due to the secretion of growth factors and cytokines in the luteal phase, we hypothesized that ES in different phases may affect the outcome of IVF. However, our results showed no significant differences in the pregnancy rate between the two groups who underwent ES in the follicular or luteal phases.

CONCLUSION

We found that the endometrial scratching in the different menstrual phases didn't impact the IVF outcome. The results of this study are limited by the lack of a control group in different phases with no intervention and the small sample size that could be considered in future studies. Our results have limitations because the study sample was obtained from one center, and the results are not able to be generalized.

LIST OF ABBREVIATIONS

ES = Endometrial Scratching

ESHRE = European Society of Human Reproduction and Embryology

IVF = *In Vitro* Fertilization

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of the Hamadan University of Medical Sciences (IR.UMSHA.REC.1398.615).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

All patients received comprehensive information about the study and gave their informed written consent.

STANDARDS OF REPORTING

CONSORT guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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