

# Effect of differential endometrial injury timing on frozen-thawed embryo transfer pregnancy outcomes

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## Summary

**Objective:** To explore whether differential endometrial injury (EI) timing prior to a frozen-thawed embryo transfer (FET) cycle yields similar improvements in pregnancy outcomes. **Materials and Methods:** A total of 688 women underwent consecutive FET cycles. Based on their desire to undergo differentially timed EI or not, patients were divided into four groups: on the 3<sup>rd</sup>–5<sup>th</sup> day of the menstrual phase of the FET cycle ( $n = 308$ ), on the 3<sup>rd</sup>–5<sup>th</sup> day of the menstrual phase preceding the FET cycle ( $n = 78$ ), during the luteal phase of the cycle preceding the FET cycle ( $n = 83$ ), and no intervention ( $n = 219$ ). **Results:** The pregnancy outcomes in the four groups were significantly different. The chemical pregnancy, clinical pregnancy, implantation, and live birth rates of patients who underwent EI on the 3<sup>rd</sup>–5<sup>th</sup> day of the menstrual phase preceding the FET cycle were the highest, followed by those who underwent EI on the 3<sup>rd</sup>–5<sup>th</sup> day of the menstrual phase of the FET cycle. The lowest rates were those during the luteal phase of the cycle preceding the FET cycle and patients who had no interventions, which were similar. **Conclusions:** Differential EI timing resulted in differential improvement of pregnancy outcomes for FET.

**Key words:** Endometrial biopsy; Endometrial injury; Frozen embryo transfer; Implantation; Pregnancy rate.

## Introduction

Embryo implantation is a rate-limiting step for a successful pregnancy in a patient undergoing in vitro fertilization and embryo transfer (IVF-ET) [1]. Although embryonic factors are important implantation determinants, inadequate endometrial receptivity remains a major reason for implantation failure [2]. Up to two-thirds of implantation failures may be secondary to inadequate uterine receptivity [3]. To date, some techniques, including endometrial injury (EI), have been reported to promote endometrial receptivity. However, the results have been inconsistent.

The relationship between EI and improved implantation was observed initially in animal models. In 1907, Loeb *et al.* first reported that EI in guinea pigs induced rapid endometrial decidualization and led to improved uterine receptivity [4]. This research suggested that the EI-induced decidual cell development was similar to that of the normal menstrual cycle. Subsequently, similar effects were observed in mouse models from 1968 to 1972 [5, 6]. Since 1993, clinical studies on the relationship between EI and successful implantation have been performed in women undergoing IVF [1, 7–10]. In these studies, Barash *et al.* first demonstrated the possible role of EI in implantation improvement. They selected 134 patients who failed to conceive during one or more cycles of IVF-ET. Of them, 45 patients received repeated endometrial biopsies using a dis-

posable endometrial biopsy instrument on days 8, 12, 21, and 26 of the menstrual cycle preceding the IVF-ET cycle. The results showed that EI preceding the IVF-ET cycle doubles the chances for implantation and a successful pregnancy, compared with IVF-ET without EI. The implantation, clinical pregnancy, and live birth rates in the EI group were 28%, 67%, and 49% compared to 14%, 30%, and 23% for IVF-ET without EI, respectively. Furthermore, a systematic review by Almog *et al.* [11] strongly supported performing EI prior to IVF-ET cycles in patients with previous repeated IVF failures to increase implantations, clinical pregnancies, and live birth rates. However, they raised questions that remain unanswered about the impact of differential EI timing on IVF-ET outcomes. In addition, another meta-analysis by El-Toukhy *et al.* [12] systematically summarized all existing trials that examined EI impact on IVF outcomes. In their analysis, 901 participants in eight studies were divided into two groups, those patients from the two randomized studies ( $n = 193$ ) and those patients from the six non-randomized controlled studies ( $n = 708$ ). They demonstrated that EI prior to IVF significantly increased clinical pregnancy rates in both randomized (relative risk [RR], 2.63; 95% confidence interval [CI], 1.39–4.96;  $p = 0.003$ ) and non-randomized studies (RR, 1.95; 95% CI, 1.61–2.35;  $p < 0.00001$ ).

To the present authors' knowledge, most research has mainly focused on EI-mediated IVF-ET improvement. Al-

though EI has improved clinical pregnancy rates, reports on the relationship between EI and frozen–thawed embryo transfer (FET) are few. The present authors have found only one article researching the impact of EI preceding FET to date. In a study by Dunne *et al.* [13], 40 patients underwent EI during the luteal phase of the cycle preceding their FET cycle, and the primary chemical and clinical pregnancy rates were compared to those of the 40 patients who did not undergo EI. They found that luteal phase EI did not improve pregnancy rates.

There has not been any research comparing the effectiveness of differential EI timing on FET. Therefore, the present study aimed to explore whether differential EI timing prior to a FET cycle yields similar improvements in pregnancy outcomes.

## Materials and Methods

The study was approved by the institutional ethics committee of Shanxi Women & Children's Hospital. Written informed consent was obtained from all participants.

This interventional clinical trial was performed at the Human Assisted Reproduction Center at Shanxi Women & Children's Hospital of China from January 2013 to May 2015. A total of 688 women who were undergoing consecutive FET cycles were enrolled in this study. All patients had undergone at least one or more prior IVF-ET cycle(s) in which they failed to become pregnant. Exclusion criteria were as follows: 1) age < 24 or  $\geq$  40 years, 2) body mass index (BMI)  $>30$  kg/m<sup>2</sup>, 3) congenital or acquired uterine anomaly, 4) active vaginal or cervical infection, and 5) hydrosalpinx.

Subjects in the experimental group were those who volunteered to participate in one of the three endometrial scratching groups, whereas the control group subjects were those who declined endometrial biopsy in contemporaneous FET cycles. Therefore, based on their desire to undergo differentially timed EI or not, patients were divided into four groups. The distribution of 688 women were as follows: 308 patients underwent EI on the third to fifth day of the menstrual phase of the FET cycle ( $n = 308$ ), 78 patients underwent EI on the third to fifth day of the menstrual phase preceding the FET cycle ( $n = 78$ ), 83 patients underwent EI during the luteal phase of the cycle preceding the FET cycle ( $n = 83$ ), and 219 patients underwent no intervention before FET ( $n = 219$ ). Details of the EI protocol have previously been described [14]. An experienced clinical doctor “injured” the endometrium with a no. 5 Kevorkian-Younger biopsy catheter under the guidance of B-ultrasound in sterile conditions. The doctor scraped around the whole endometrium twice in a clockwise direction, and it was important that the procedure be gentle.

In order to avoid bias, all patients underwent the artificial endometrial preparation program for the FET cycle, and the program was similar for each group. All patients took oral estradiol valerate tablets (1 mg) 2 mg daily from the third day of the menstrual phase for five days. Then, estradiol doses were increased according to endometrial thickness. Transvaginal ultrasonography was performed on the 12<sup>th</sup> or 13<sup>th</sup> day of the cycle, and endometrial thickness was measured at its thickest portion in the longitudinal axis of the uterus. When the endometrial thickness was  $\geq 7.0$  mm with a triple-line appearance, patients were administered daily in-

tramuscular progesterone injections (20 mg).

FET was performed on the third day after endometrial transformation using the CCD catheter under ultrasound guidance. Transferred embryos were graded on day 3, using a score of 1 to 4 with 1 being the best, based on cell symmetry, fragmentation, and blastomere number [15]. Chemical pregnancies were confirmed by measuring increased serum  $\beta$ -hCG concentrations, which were tested 14 days after FET. Clinical pregnancy was defined as the presence of an intrauterine gestational sac using transvaginal ultrasonography examination 30–35 days after FET.

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 18.0. Continuous data were expressed as mean  $\pm$  standard deviation (SD) and enumeration data were expressed as percentages. Statistically significant differences were assessed using the Fisher exact test, ANOVA, or chi-square tests, as required.  $P < 0.05$  was considered statistically significant.

## Results

A total of 688 patients underwent FET, and all patients received at least one embryo. Table 1 presents the baseline patient characteristics for the four groups. Baseline characteristics of the four groups including age, duration of infertility, BMI, percentage of primary infertility, number of prior failed cycles, and the mode of fertilization, were comparable ( $p = 0.11, 0.79, 0.33, 0.59, 0.13,$  and  $0.28$ , respectively). Regardless of EI treatment, the mean endometrial thickness on the first day of progesterone administration was similar in the four groups ( $p = 0.57$ ). In addition, there were no differences in baseline characteristics after stratification by number and quality of the transferred embryos or by etiology of infertility. The proportions of cycles with one, two, or three embryos transferred as well as the proportions of cycles with none, one, two, or three top quality embryos transferred were also similar in the four groups ( $p = 0.30$  and  $0.24$ , respectively). Additionally, the proportions of cycles with endometriosis, anovulation, tubal factor, male factor, and unexplained, mixed factor were similar in the four groups ( $p = 0.39$ ).

Clinical outcomes following FET are shown for each group in Table 2. The chemical pregnancy, clinical pregnancy, implantation, and live birth rates in the four groups were significantly different ( $p = 0.001, 0.001, 0.04,$  and  $0.001$ , respectively). The chemical pregnancy, clinical pregnancy, implantation, and live birth rates of patients who underwent EI on the third to fifth day of the menstrual phase preceding the FET cycle were the highest (70.5%, 62.8%, 27.7%, and 52.6%), followed by those who underwent EI on the third to fifth day of the menstrual phase of the FET cycle (53.2%, 45.5%, 24.4%, and 35.1%). The lowest rates were those of patients who underwent EI during the luteal phase of the cycle preceding the FET cycle and patients who had no interventions before FET, which were similar (39.8%, 36.1%, 22.3%, and 28.9% vs. 42.5%, 37.4%, 19.3%, and 27.9%, respectively). Regardless of whether

Table 1. — Baseline characteristics of the FET for each group.

EI timing	Menstrual phase of the FET cycle	Menstrual phase preceding the FET cycle	Luteal phase preceding the FET cycle	No interventions before FET	<i>p</i>
Cycles	n = 308	n = 78	n = 83	n = 219	
Age (years)	30.20 ± 4.05	30.12 ± 3.95	31.06 ± 3.80	30.90 ± 4.27	0.11
Duration of infertility (years)	4.79 ± 2.85	4.79 ± 2.48	4.43 ± 3.23	4.79 ± 3.21	0.79
BMI (kg/m <sup>2</sup> )	23.43 ± 3.43	23.20 ± 3.46	23.07 ± 2.58	22.89 ± 3.32	0.33
Primary infertility, <i>n</i> (%)	174 (56.5%)	49 (62.8%)	44 (53.0%)	120 (54.8%)	0.59
Endometrial thickness (mm)	9.78 ± 1.20	9.85 ± 1.30	9.94 ± 1.60	9.72 ± 1.26	0.57
Number of previous failed cycles	1.90 ± 1.30	1.67 ± 0.99	2.11 ± 1.02	1.84 ± 1.25	0.13
Mode of fertilization (ICSI), <i>n</i> (%)	65 (21.1%)	19 (24.4%)	26 (31.3%)	51 (23.3%)	0.28
Number of embryos transferred, <i>n</i> (%)					0.30
One embryo	7 (2.3%)	1 (1.3%)	2 (2.4%)	7 (3.2%)	
Two embryos	116 (37.7%)	21 (26.9%)	33 (39.8%)	66 (30.1%)	
Three embryos	185 (60.1%)	56 (71.8%)	48 (57.8%)	146 (66.7%)	
Proportions of quality embryos, <i>n</i> (%)					0.24
No top quality embryos	20 (6.5%)	4 (5.1%)	5 (6.0%)	6 (2.7%)	
One top quality embryos	39 (12.7%)	6 (7.7%)	15 (18.1%)	37 (16.9%)	
Two top quality embryos	134 (43.5%)	39 (50.0%)	36 (43.4%)	108 (49.3%)	
Three top quality embryos	115 (37.3%)	29 (37.2%)	27 (32.5%)	68 (31.1%)	
Etiology of infertility, <i>n</i> (%)					0.39
Endometriosis	16 (5.2%)	4 (5.1%)	5 (6.0%)	8 (3.7%)	
Anovulation	26 (8.4%)	9 (11.5%)	7 (8.4%)	28 (12.8%)	
Tubal factor	187 (60.7%)	47 (60.3%)	49 (59.0%)	123 (56.2%)	
Male factor	45 (14.6%)	15 (19.2%)	16 (19.3%)	46 (21.0%)	
Unexplained	4(1.3%)	1(1.3%)	2 (2.4%)	1 (0.5%)	
Mixed factor	30(9.7%)	2(2.6%)	4 (4.8%)	13 (5.9%)	

Table 2. — Clinical outcome following FET for each group.

EI timing	Menstrual phase of the FET cycle	Menstrual phase preceding the FET cycle	Luteal phase preceding the FET cycle	No interventions before FET	<i>P</i>
Cycles	n = 308	n = 78	n = 83	n = 219	
Chemical pregnancy rate, <i>n</i> (%)	164/308 (53.2%)	55/78 (70.5%)	33/83 (39.8%)	93/219 (42.5%)	0.001
Clinic pregnancy rate, <i>n</i> (%)	140/308 (45.5%)	49/78 (62.8%)	30/83 (36.1%)	82/219 (37.4%)	0.001
Implantation rate, <i>n</i> (%)	193/791 (24.4%)	61/220 (27.7%)	45/202 (22.3%)	112/581 (19.3%)	0.04
Ectopic pregnancy	3/140 (2.1%)	1/49 (2.0%)	1/30 (3.3%)	6/82 (7.3%)	0.22
Early abortion rate <12 gestational weeks, <i>n</i> (%)	14/140 (10.0%)	4/49 (8.2%)	3/30 (10.0%)	12/82 (14.6%)	0.64
Late abortion rate <12 gestational weeks, <i>n</i> (%)	15/140 (10.7%)	3/49 (6.1%)	2/30 (6.7%)	3/82 (3.7%)	0.27
Live birth rate, <i>n</i> (%)	108/308 (35.1%)	41/78 (52.6%)	24/83 (28.9%)	61/219 (27.9%)	0.001

the patient underwent EI, early and late abortion rates were not different among the four groups.

## Discussion

FET is a significant progress in IVF/ICSI treatment, as it increases the cumulative pregnancy rate after ovum retrieval [16]. Endometrial receptivity is a main factor affecting FET outcomes [17]. Considering that EI increases the likelihood of endometrial receptivity and clinical pregnancy, the present authors evaluated the effects of differential EI timing on pregnancy rates following FET cycles for the first time.

In the present study, the authors found that differential EI timing in FET cycles has differential effects on pregnancy rate improvement. First, they found that patient baseline

characteristics were comparable for the four groups. In particular, there were no differences in clinical pregnancy and live birth rates after stratification by number of embryos transferred, proportions of quality embryos, and etiology of infertility. This indicates that the basic data on the number and quality of transferred embryos and infertility diagnoses were at equilibrium and did not influence the pregnancy and live birth rates. In other words, endometrial injury is beneficial for the patient regardless of the number of top quality embryos transferred, proportions of quality embryos, and etiology of infertility. The present authors found that although endometrial thickness appeared unaffected by EI, chemical pregnancy, clinical pregnancy, implantation, and live birth rates were significantly different in the four groups. The most significant improvement in chemical pregnancy, clinical pregnancy, implantation, and

live birth rates were observed for patients who underwent EI on the third to fifth day of the menstrual phase preceding the FET cycle (70.5%, 62.8%, 27.7%, and 52.6%, respectively), followed by those who underwent EI on the third to fifth day of the menstrual phase of the FET cycle (53.2%, 45.5%, 24.4%, and 35.1%, respectively). The slightest improvements were observed for patients who underwent EI during the luteal phase of the cycle preceding the FET cycle and patients who had no interventions before FET, which had similar clinical pregnancy, implantation, and live birth rates at 39.8%, 36.1%, 22.3%, and 28.9% vs. 42.5%, 37.4%, 19.5%, and 27.9%, respectively. However, contrary to the present findings, in a systematic review and meta-analysis, Potdar *et al.* [18] reported that EI in the preceding ovarian stimulation cycle strongly improved pregnancy outcomes in women with unexplained recurrent implantation failure. When they compared EI timing, there was no conclusive evidence to suggest an optimal time. In their review, EI timing included intervention during the early proliferative phase, during both the early proliferative and luteal phases, and only during the luteal phase.

To date, as an exogenous injury factor, the accurate mechanism by which EI is beneficial to IVF outcomes remains unclear. EI may induce endometrial decidualization and promote wound healing, which eventually benefits embryo implantation and improves pregnancy outcomes. During this process, EI might trigger a series of biological responses, including inducing the secretion of cytokines, adhesion molecules, and growth factors like leukemia inhibitory factor, heparin-binding endothelial growth factor-like growth factor, interleukin-11, and integrin b3 [19, 20]. Several studies have also reported increased EI-induced gene expression [21, 22]. In the latest study, Gnainsky *et al.* found that EI induced upregulation of the adhesive molecule osteopontin (OPN), its receptors ITGB3 and CD44, and implantation-associated genes, such as CHST2, CCL4, and GROA. They concluded that such an inflammatory milieu is not generated in recurrent implantation failure patients who do not undergo EI. This also suggests that EI improves endometrial receptivity through EI-induced inflammatory conditions [23]. However, why differential EI timing has differential effects on pregnancy rates in FET cycles remains unclear. Based on the results of the present study, EI in the menstrual phase preceding FET improves clinical pregnancy and live birth rates in women undergoing FET, which was also confirmed in the IVF-ET cycle by Potdar *et al.* [18]. In the present analysis, the mechanism by which EI preceding FET improves pregnancy outcomes could be due to the endometrium having enough time to proliferate in accordance with endometrial growth cycles. Li *et al.* reported that EI during a previous cycle delays endometrial maturation and results in enhanced synchronicity between the endometrium and the transferred embryo in the next IVF-ET cycle [9].

The present analysis also provides evidence that EI in the same cycle of FET positively impacts FET pregnancy outcomes. On the contrary, Karimzade *et al.* [24] performed EI on the day of oocyte retrieval and found that EI disrupts the receptive endometrium and negatively impacts both implantation and IVF outcomes. The present study was different, as the authors performed EI on the third to fifth day of the menstrual phase in the same FET cycle. Perhaps EI during the menstrual phase synchronizes with endometrial growth, allowing the endometrium enough time to proliferate and eventually improving clinical pregnancy outcomes. However, the effects of EI on the third to fifth day of the menstrual phase of the same FET cycle were inferior to EI on the third to fifth day of the cycle before the FET cycle. This may have provided a longer time for the endometrium to repair before FET and a further increase in pregnancy. Therefore, the present authors recommend FET be performed in the cycle immediately after EI.

Consistent with the work of Dunne *et al.* [13], the present results failed to demonstrate that EI during the luteal phase of the menstrual cycle preceding the FET cycle can improve clinical pregnancy after FET. However, this result was in contrast with other prior literature. Some authors have presented proof supporting luteal phase EI as an intervention to increase pregnancy [25–28]. They showed improvement in clinical pregnancy rates with EI in the luteal phase preceding the controlled ovarian hyperstimulation cycle (COH) or during the COH cycle. In 1969, Humphrey *et al.* [25] demonstrated that the uterine decidualization reaction was maximal after five days of progesterone exposure in ovariectomized mice, and they suggested that it was appropriate to perform EI in the luteal phase. Subsequently, Karimzade *et al.* [26] concluded that endometrial biopsy in the luteal phase of the cycle preceding IVF-ET could improve clinical pregnancy rates (27% in the EI group vs. 9% in the control group). Guven *et al.* [27] reported a similar result. Kumbak *et al.* [28] confirmed that hysteroscopy and concurrent EI performed on the day of GnRH agonist initiation (in the luteal phase) significantly improve implantation and IVF outcomes. Injury induced in the luteal phase was suggested to induce more decidualization. The present authors hypothesized that EI in the luteal phase in the COH cycle and FET cycle have different effects. This requires further research. In addition, based on the present participant selection of EI timing, the number of patients who underwent EI during the luteal phase was small, and therefore, a larger sample to study is required.

In the present study, the authors showed that the chemical pregnancy, clinical pregnancy, implantation, and live birth rates among four groups were statistically different based on EI timing. However, the ectopic pregnancy, early abortion, and late abortion rates among the four groups were similar. A pilot survey also showed that clinical pregnancy, ongoing pregnancy, and live birth rates were significantly higher in the EI group than the control group of

pregnant women with a history of repeated embryo implantation failure [10]. There were also no significant differences in the ectopic pregnancy or miscarriage incidences.

In conclusion, in the present study, the authors demonstrated that differential EI timing resulted in differential improvements in embryo implantation and clinical pregnancy rates for FET. Finally, they would like to point out the limitations of this study. All references cited were of reports of patients who underwent IVF-ET except one report by Dunne *et al.* [13], and further prospective randomized controlled trials are needed to demonstrate the present conclusions. Another limitation was that the study was non-randomized because, due to ethical considerations, patient preference for EI and EI timing was followed. Therefore, the number of patients who underwent EI during the luteal phase of the cycle preceding the FET cycle was less, and further studies are required.

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