

# Factors affecting the ongoing pregnancy rate in women with repeated implantation failure undergoing an endometrial receptivity array

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**Objective:** In this retrospective study, we analyzed factors influencing the ongoing pregnancy rate (PR) in women with repeated implantation failure (RIF) undergoing embryo transfer with endometrial receptivity array (ERA).

**Methods:** Eighty-three consecutive personalized embryo transfers (pETs) with ERA, from 54 women with RIF, were selected from June 2020 to April 2022. Vitrified blastocyst transfer was timed based on ERA results.

**Results:** The ongoing PR per pET was 33.7%. Using ERA, the endometrium was identified as pre-receptive in 26 cycles, early receptive in 25 cycles, receptive in 31 cycles, and late receptive in one cycle. With cycles categorized into three receptivity phases (pre-receptive, early receptive, or receptive), no significant differences were found in the clinical PR (27.3%, 55.6%, and 40%, respectively) or ongoing PR (9.1%, 55.6%, and 40%, respectively) after a single blastocyst transfer. Similarly, no significant differences were observed in the clinical PR or ongoing PR after the transfer of two or more blastocysts. Among women with ongoing pregnancy relative to those without, age at first pET was significantly lower (35 years vs. 39 years,  $p=0.001$ ), while blastocyst score (23 vs. 18,  $p=0.012$ ) and the proportion of blastocyst scores  $>18$  (71.4% vs. 38.9%,  $p=0.005$ ) were significantly higher. In multiple logistic regression analysis, the woman's age (odds ratio [OR], 0.814; 95% confidence interval [CI], 0.706 to 0.940;  $p=0.005$ ) and blastocyst score  $>18$  (OR, 3.052; 95% CI, 1.075 to 8.665;  $p=0.036$ ) were identified as significant factors influencing ongoing pregnancy.

**Conclusion:** In pET with ERA, ongoing pregnancy was closely associated with woman's age and blastocyst quality.

**Keywords:** Blastocyst; Embryo transfer; Endometrium; Pregnancy; Receptivity

## Introduction

Repeated implantation failure (RIF) is typically defined as the inability to become pregnant after three or more embryo transfer (ET) cycles, despite the use of good-quality embryos. A receptive endometrium is crucial for successful implantation, and cross-communication between the endometrium and the embryo is also required.

However, even euploid and morphologically good-quality blastocysts fail to implant in approximately one-third of transfer cases [1]. The endometrium must be in a receptive or acceptable state at the time of embryo implantation, a period known as the window of implantation (WOI), which typically occurs during the mid-luteal phase. If transfer is not conducted during the WOI, RIF may arise due to inadequate communication between the endometrium and the embryo.

Consequently, endeavors have been made to determine the timing of the receptive phase of the endometrium. A variety of "omics" techniques have been established to evaluate markers for DNA (genomics), messenger RNA (transcriptomics), and protein (proteomics) in the human endometrium during the WOI [2].

A previous study established the transcriptomic profiling of the endometrium throughout the menstrual cycle, including the WOI [3].

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The findings from these profiling analyses led to the development and patenting of the endometrial receptivity array (ERA) by Igenomix (Spain) in 2009. The ERA involves the analysis of 236 implantation-related DNA markers using next-generation sequencing techniques. A prediction program, based on the analysis of accumulated data, then indicates the appropriate timing for ET.

In artificial cycles supplemented with estradiol and progesterone treatment (EPT), an endometrial sample is obtained on day Progesterone (P)+5, at which point an ERA test is requested. Then, blastocysts are harvested and subsequently cryopreserved. These cryopreserved blastocysts are later transferred under the guidance of EPT, with the timing of this transfer determined based on the ERA results.

The ERA provides information on endometrial receptivity, allowing the endometrium to be categorized as receptive, non-receptive, early receptive, late receptive, pre-receptive, or post-receptive. The term "receptive" indicates that the endometrium is within the WOI at P+5 days, suitable for blastocyst transfer. "Early receptive" or "pre-receptive" signifies that the endometrium has not yet reached the WOI, suggesting that blastocyst transfer should occur slightly later than P+5 days. In contrast, "late receptive" or "post-receptive" indicates that the endometrium has passed the WOI, and the blastocyst transfer should thus take place slightly earlier than P+5 days.

The ERA offers insights into the optimal timing for blastocyst transfer for individual patients. Consequently, ET that is guided by the results of the ERA test is often referred to as personalized embryo transfer (pET).

In 2020, a multicenter randomized controlled trial examining the utility of pET using ERA was published [4]. The study involved women aged 37 years or younger, who were randomly assigned to three groups: pET (80 women), frozen ET (82 women), and fresh ET (94 women). Following the first ET, the clinical pregnancy rates (PRs) were 72.5%, 54.3% ( $p=0.01$ ), and 58.5% ( $p=0.057$ ), respectively. The live birth rates (LBRs) were 56.2%, 42.4% ( $p=0.09$ ), and 45.7% ( $p=0.17$ ), respectively. The cumulative LBRs within a 12-month period were 71.2%, 55.4% ( $p=0.04$ ), and 48.9% ( $p=0.003$ ), respectively, indicating a significant improvement in the pET group. However, if the LBR from the first ET is considered the most crucial evidence of efficacy, pET with ERA could be deemed ineffective.

A retrospective study published in 2021 enrolled women who were undergoing their first ET with a euploid embryo. The LBR demonstrated no significant difference, with a rate of 56.5% recorded in 147 pET cycles compared to 56.6% in 81 standard frozen ET cycles [5]. Another retrospective study from 2021 revealed no significant difference in LBR (49.6% in 133 pET cycles vs. 54.9% in 353 control cycles) [6].

A recent randomized clinical trial indicated that the ERA did not improve the ongoing PR from single euploid ET in an unselected

population [7]. In that report, the clinical PR and LBR were 68.8% and 58.5%, respectively, in the pET group ( $n=381$ ) and 72.8% and 61.9%, respectively, in the control group ( $n=386$ ,  $p>0.05$  for all). The studies mentioned above were not specifically targeted at patients with RIF. To date, very few studies have examined the efficacy of pET among such patients.

In patients with RIF, a multicenter retrospective study published in 2020 demonstrated no significant benefit of pET with ERA [8]. In that study, clinical *in vitro* fertilization (IVF) outcomes were compared among groups treated with preimplantation genetic testing for aneuploidy (PGT-A), ERA, PGT-A+ERA, and standard frozen ET (i.e., neither test). Among 2,110 patients with moderate RIF, defined as implantation failure after the transfer of three embryos, only the PGT-A group exhibited a significantly improved implantation rate and ongoing PR relative to the standard ET group. In 488 patients with severe RIF (defined as implantation failure after the transfer of five embryos), neither PGT-A nor ERA had a meaningful impact. In a subsequent study involving 255 patients with a single previous failed transfer, pET with ERA did not improve pregnancy outcomes when compared with non-pET controls, which included both fresh ET and frozen ET groups [9].

Similarly, another study demonstrated no significant improvement in clinical outcomes associated with pET using ERA [10]. That research indicated that neither the combination of PGT-A and ERA nor ERA alone improved the clinical PR compared to standard frozen ET in women with RIF. Treatment with PGT-A alone was associated with a statistically higher likelihood of achieving clinical pregnancy than frozen ET.

However, a separate retrospective study carried out in China demonstrated that pET with ERA yielded a significantly higher ongoing PR and implantation rate than standard frozen ET ( $p<0.01$ ) among 281 patients with RIF [11]. Therefore, the utility of pET with ERA requires further clarification for both non-RIF and RIF populations. In a systematic review encompassing eight studies, Arian et al. [12] reported that the ongoing PR and LBR in the ERA group were comparable to those in the non-ERA group. This observation applied to groups with two prior unsuccessful ET attempts as well as those with more than two such attempts [12].

Conversely, it remains unclear which factors affect the establishment of ongoing pregnancy in patients with RIF receiving pET using ERA. The objective of this study was to identify and analyze the factors that impact ongoing pregnancy in this patient population.

## Methods

An ERA test under EPT was performed at a single center (the iORA clinic). This study involved 54 women with RIF, defined as three or

more previous failed ETs. Based on the ERA results, 83 consecutive pETs were performed. All vitrified blastocyst transfer cycles took place between June 2020 and April 2022. The study received approval from the Institutional Review Board (IRB) at Seoul National University Bundang Hospital (IRB No. B-2301-802-101). Written informed consent by the patients was waived due to the retrospective nature of our study.

The mean number of previous failed ETs, despite the use of good-quality embryos, was seven cycles (range, 3 to 16). The mean age of the women at the time of the first pET was 37.7 years (range, 28 to 46). Any woman with a thin endometrium, measuring less than 7 mm, was excluded from the study.

In the cycle for endometrial biopsies, all women received artificial EPT. This involved the daily administration of 6 to 8 mg of estradiol valerate (Progynova; Bayer), which was initiated on the third or fourth day of the menstrual cycle. Once an endometrial thickness of more than 7 mm was achieved, a daily intramuscular injection of 100 mg progesterone (Sugest; Watson Laboratories Inc. or Taiyu P; Jaytech Biogen) was introduced. Following EPT, endometrial biopsies were conducted at P+5 days using a 5-mm silastic catheter, and the samples were subsequently stored at  $-4^{\circ}\text{C}$ . These samples were then sent to Igenomix-Korea for ERA testing, and the results were obtained after 2 to 3 weeks.

For blastocyst formation, ovarian stimulation was performed using recombinant follicle-stimulating hormone (FSH) (Gonal-F; Merck-Serono), recombinant FSH with recombinant luteinizing hormone (Pergoveris; Merck-Serono), or purified human menopausal gonadotropin (Menopur; Ferring). Depending on the situation, pituitary suppression was achieved using either a flexible gonadotropin-releasing hormone (GnRH) antagonist protocol or a luteal long GnRH agonist protocol. Once ultrasound monitoring revealed the presence of two or more follicles  $\geq 18$  mm in diameter, 250  $\mu\text{g}$  of recombinant human chorionic gonadotropin (hCG) (Ovidrel; Merck-Serono) was administered. Oocyte retrieval was performed 36 to 38 hours after hCG injection. Mature oocytes were fertilized using the conventional method, split insemination, or intracytoplasmic sperm injection, as indicated.

The blastocysts were obtained through sequential culture up to day 7; ultimately, 88 blastocysts were obtained on day 5, 51 on day 6, and three on day 7.

For blastocyst vitrification, sequential equilibrium solution (ES) and vitrification solution (VS) were used with a Cryo-Top device (Kitazato). Initially, the blastocysts were suspended in the ES, which contained 7.5% ethylene glycol (EG; Sigma-Aldrich) and 7.5% dimethyl sulfoxide (DMSO; Sigma-Aldrich) in basic medium (Global for Fertilization; Life Global). This suspension was maintained for 5 minutes at room temperature (RT). Subsequently, the blastocysts were transferred to the VS, which contained 15% EG, 15% DMSO, and 0.5 mol/L sucrose (Sigma-Aldrich) in a basic medium. This step was carried out for 45 to 60 seconds at RT. Following this, the blastocysts were loaded into the Cryo-Top and immediately submerged in liquid nitrogen for storage.

For blastocyst warming, the Cryo-Top was directly immersed in a warming solution at  $37^{\circ}\text{C}$ , which contained 1.0 mol/L sucrose in basic medium, for 1 minute. The blastocysts were then immediately transferred to dilution solutions, which contained 0.5 and 0.25 mol/L sucrose in basic medium. These were serially incubated at RT for 3 minutes each, then washed twice with the basic medium. The warmed blastocysts were transferred to the culture medium (Sydney IVF Medium; Cook Medical), cultured until transfer at  $37^{\circ}\text{C}$ , and kept in a humidified air environment with 5%  $\text{CO}_2$ .

For vitrified-warmed blastocyst transfer, all women received the same artificial EPT as that administered for endometrial biopsies. The endometrial thickness was consistently above 7 mm. Blastocysts were transferred based on the timing suggested by the ERA test results (Table 1). All blastocysts were warmed for 4 to 16 hours prior to transfer.

At the time of transfer, blastocysts were graded based on the developmental stage, quality of the inner cell mass, and quality of the trophectoderm [13]. We utilized a straightforward formula, developed at our center, to calculate the blastocyst score: (development score)  $\times$  (inner cell mass or trophectoderm score). The development score was assigned as follows: early expanded blastocyst=1; middle expanded blastocyst=2; expanded blastocyst=3.5; hatching blasto-

**Table 1.** Timing of blastocyst transfer based on ERA results

Results of ERA	The time of blastocyst transfer	No. of cycles	The average no. of blastocyst transferred	Days of blastocyst-forming		
				Day 5	Day 6	Day 7
Pre-receptive	P+6 days	26	1.6 $\pm$ 0.6	31	11	-
Early receptive	P+133 hours	25	1.8 $\pm$ 0.7	24	19	1
Receptive	P+117 to P+123 hours	31	1.7 $\pm$ 0.6	31	21	2
Late receptive	P+110 hours	1	2	2	-	-

Values are presented as mean  $\pm$  standard deviation. ERA, endometrial receptivity array; P, progesterone.

cyst=5; and hatched blastocyst=6. The scores for the inner cell mass or trophectoderm were separately assigned based on a 4-grade scale, as follows: A=4; B=3; C=2; and D=1. For example, an expanded blastocyst with partial hatching and a grade B inner cell mass or trophectoderm received a score of 15. If two or more blastocysts were present, the total blastocyst score was calculated as the sum of the individual scores. Top-quality blastocysts were those that were expanded, hatching, or hatched, with assigned grades of A or B.

Serum hCG levels were measured at P+14 days. Pregnancy outcomes were categorized as clinical pregnancy, miscarriage, or ectopic pregnancy. A clinical pregnancy was defined by the identification of at least one gestational sac exhibiting a fetal heartbeat. Miscarriage was defined as the termination of a clinical pregnancy prior to the 12th week of gestation, and an ongoing pregnancy was defined as a clinical pregnancy that continued past 12 gestational weeks. The implantation rate was determined by dividing the number of gestational sacs by the number of transferred embryos.

Statistical analysis was performed using SPSS version 25 (IBM Corp.). All data were presented as the median and interquartile range. The Mann-Whitney *U* test was employed to compare numerical data between two groups. For comparisons among three groups, the Kruskal-Wallis test was utilized. The chi-square test or Fisher exact test was used to compare proportions between two groups. Multiple logistic regression analyses were performed to identify parameters influencing clinical or ongoing pregnancy. Receiver operating characteristic (ROC) curve analysis was conducted to determine cutoff values for specific parameters. A *p*<0.05 was considered to indicate statistical significance.

## Results

According to the ERA results for the 54 patients, 22 were categorized as receptive, 15 as pre-receptive, 16 as early receptive, and one as late receptive. As such, 59.3% of women with RIF exhibited a displaced WOI. None of the women were classified as post-receptive.

Among the 54 women studied, a total of 83 consecutive pETs were performed, with a range of 1 to 6 procedures per individual. The mean number of pETs performed per woman was 1.6±1.0. In the analysis of IVF cycle characteristics and pregnancy outcomes, each pET cycle was treated as an independent event.

The overall clinical PR per pET was found to be 44.6% (37 of 83). Nine miscarriages occurred; therefore, the miscarriage rate per clinical pregnancy was 24.3% (nine of 37). Overall, 28 ongoing pregnancies were confirmed, yielding an ongoing PR per pET of 33.7% (28 of 83).

For the 83 pET cycles examined, Table 1 details the receptivity phase, the timing of blastocyst transfer, the average number of blastocysts transferred, and the number of days required for blastocyst formation. A total of 142 vitrified-warmed blastocysts were transferred across these cycles: in 30 cycles, one blastocyst was transferred; in 48 cycles, two were transferred; in four cycles, three were transferred; and in one cycle, four were transferred. Table 2 presents the clinical PR and ongoing PR, by receptivity phase, for cycles in which a single blastocyst was transferred. No significant differences were observed in the cycle characteristics or the clinical outcomes of IVF. Table 3 presents the clinical PR, ongoing PR, and implantation rate by receptivity phase for cycles in which at least two blastocysts were transferred. Similarly, no significant differences were noted in

**Table 2.** Pregnancy outcomes in 30 pET cycles in which one blastocyst was transferred

Variable	Pre-receptive (11 cycles)	Early receptive (9 cycles)	Receptive (10 cycles)	<i>p</i> -value
Woman's age at the time of first pET (yr)	41 (32-42)	34 (32.5-38)	37 (34-41)	0.262
No. of previous failed cycles	7 (5-8)	6 (4.5-7.5)	7 (5.8-8.5)	0.425
Days of blastocyst-forming				0.897
Day 5	9	7	7	
Day 6	2	2	3	
Day 7	0	0	0	
Blastocyst score at transfer	15 (7-18)	18 (6.8-18)	14 (9.3-21)	0.714
Interval from endometrial biopsy to pET (day)	52 (48-244)	54 (28-64)	49 (22-94)	0.353
Clinical pregnancy	3	5	4	
Miscarriage	2	0	0	
Ectopic pregnancy	1	0	0	
Clinical pregnancy rate per pET (%)	27.3	55.6	40	0.539
Ongoing pregnancy rate per pET (%)	9.1	55.6	40	0.129

Values are presented as median (interquartile range). pET, personalized embryo transfer.

**Table 3.** Pregnancy outcomes in 52 pET cycles in which two or more blastocysts were transferred (excluding one cycle with late receptivity)

Variable	Pre-receptive (15 cycles)	Early receptive (16 cycles)	Receptive (21 cycles)	p-value
Woman's age at the time of first pET (yr)	41 (34–42)	37 (35–40.3)	37 (35–41)	0.544
No. of previous failed cycles	8 (6–10)	6 (4.3–8)	7 (4.5–8.5)	0.066
Days of blastocyst-forming				0.604
Day 5	22	17	24	
Day 6	9	17	18	
Day 7	0	1	2	
No. of blastocyst transferred	2 (2–2)	2 (2–2)	2 (2–2)	0.927
Total blastocyst score at transfer	22 (10.5–40)	23.8 (17.3–40.5)	24 (14.5–31.5)	0.337
Interval from endometrial biopsy to pET (day)	83 (51–237)	83 (27–161)	60 (27–149)	0.364
Clinical pregnancy	9	7	10	
Miscarriage	3	2	3	
Ectopic pregnancy	0	0	0	
Clinical pregnancy rate per pET (%)	60	43.8	52.4	0.505
Ongoing pregnancy rate per pET (%)	40	31.3	33.3	0.706
Implantation rate per embryo (%)	29	20	25	0.344

Values are presented as median (interquartile range).  
pET, personalized embryo transfer.

the cycle characteristics or clinical IVF outcomes.

Among the 83 pET cycles, the total blastocyst score ranged from 3.5 to 48. [Table 4](#) presents a comparison of seven parameters between those with and without clinical pregnancy, as well as between those with and without ongoing pregnancy. These parameters include the woman's age at first pET, the number of previous failed cycles, the proportion of cycles considered receptive, the number of blastocysts transferred, the total blastocyst score at the time of transfer, the proportion of total blastocyst scores at transfer that exceeded 18.0, and the interval from the endometrial biopsy to pET.

For clinical pregnancy, two factors—the total blastocyst score at transfer and the proportion of total blastocyst scores at transfer exceeding 18.0—exhibited significant differences between the two groups. Regarding ongoing pregnancy, three factors—the woman's age at first pET, total blastocyst score at transfer, and proportion of the total blastocyst scores at transfer surpassing 18.0—differed significantly between the groups.

As demonstrated in [Table 5](#), multivariate logistic regression analysis indicated that a total blastocyst score greater than 18.0 at the time of transfer was the only factor significantly predicting clinical pregnancy. Furthermore, two factors—the woman's age at the time of the initial pET and a total blastocyst score exceeding 18.0 at transfer—were identified as significant factors for predicting ongoing pregnancy.

As shown in [Table 6](#), the ongoing PR was significantly higher in the group for which the woman's age at first pET was under 34.5 years and the total blastocyst score at transfer exceeded 18.0, compared to the other three groups.

## Discussion

In the present study, we found that 59.3% (32/54) of women with RIF exhibited a displaced (that is, non-receptive) WOI. This incidence is relatively high when compared to other studies. In previous research, the incidence of displaced WOI among women with RIF has been reported as 25.9% [14], 27.5% [15], 24% [16], 17.7% [17], 41.1% [18], and 47.4% [19]. The higher incidence in our study could reflect the fact that the RIF group examined had a relatively high number of previous failed cycles (mean, 7.0). Similarly, Jia et al. [11] reported a higher incidence of displaced WOI (65%), comparable to our study, in a group with a mean of 5.8 previous failed cycles.

Bellver et al. [20] found that WOI displacement was much more common among women with obesity than among non-obese women (25.3% vs. 9.7%). This suggests that the displacement of the WOI may be dependent on the body mass index. Ota et al. [21] additionally proposed that chronic endometritis could potentially influence WOI displacement.

In the present study, involving women with relatively high-order RIF, the overall ongoing PR per pET was 33.7%. The clinical and ongoing PR, as well as the implantation rates, were similar regardless of whether one blastocyst or two or more blastocysts were transferred ([Tables 2 and 3](#)). This suggests that pET with ERA effectively informed the appropriate timing for ET.

Previous research has shown comparable clinical IVF outcomes between the receptive and non-receptive phases. For instance, a study by Mahajan [15] found that the ongoing PR was 42% (20 of 48) in women classified as receptive and 44.5% (eight of 18) in those classified as non-receptive, with the number of previous failed cycles



**Table 4.** Comparison of seven parameters based on clinical pregnancy and ongoing pregnancy statuses

Parameter	Clinical pregnancy (39 cycles)	No clinical pregnancy (44 cycles)	p-value	Ongoing pregnancy (28 cycles)	Not ongoing pregnancy (55 cycles)	p-value
Woman's age at the time of first pET (yr)	36 (34–40)	37.5 (35–41)	0.072	35 (33–38)	39 (36–41)	0.001
No. of previous failed cycles	6 (5–9)	7 (5–8.8)	0.8	6 (5–8)	7 (5–9)	0.455
Proportion of "receptive" cycle (%)	38.5	37.2	1	39.3	37	0.814
No. of blastocysts transferred	2 (1–2)	2 (1–2)	0.307	2 (1–2)	2 (1–2)	0.877
Total blastocyst score at transfer	22 (18–35)	16.3 (7–24)	0.001	23 (18–38.8)	18 (10–24)	0.012
Proportion of total blastocyst score at transfer > 18.0 (%)	69.2	32.6	0.001	71.4	38.9	0.005
Interval from endometrial biopsy to pET (day)	54	65	0.565	66	54	0.500

Values are presented as median (interquartile range).  
pET, personalized embryo transfer.

**Table 5.** Multiple logistic regression analysis of factors influencing clinical or ongoing pregnancy

Parameter	B	Standard error	Odd ratio	95% CI
<b>Clinical pregnancy</b>				
Total blastocyst score at transfer	0.33	0.032	1.033	0.971–1.100
Total blastocyst score at transfer > 18.0	1.573	0.474	4.821	1.902–12.220 <sup>a)</sup>
<b>Ongoing pregnancy</b>				
Woman's age at the time of first pET	–0.205	0.073	0.814	0.706–0.940 <sup>a)</sup>
Total blastocyst score at transfer	0.015	0.031	1.015	0.955–1.079
Total blastocyst score at transfer > 18.0	1.116	0.532	3.052	1.075–8.665 <sup>a)</sup>

CI, confidence interval; pET, personalized embryo transfer.

<sup>a)</sup>p<0.05.

**Table 6.** Clinical and ongoing pregnancy rates based on the cutoff values of two parameters

Group	Woman's age at the time of first pET (yr)	Total blastocyst score at transfer	Clinical pregnancy rate	Ongoing pregnancy rate
1	< 34.5	> 18.0	90.9 (10/11)	90.9 (10/11)
2	< 34.5	≤ 18.0	40.0 (4/10) <sup>a)</sup>	30.0 (3/10) <sup>a)</sup>
3	≥ 34.5	> 18.0	56.7 (17/30)	33.3 (10/30) <sup>a)</sup>
4	≥ 34.5	≤ 18.0	25.0 (8/32) <sup>a)</sup>	15.6 (5/32) <sup>a)</sup>

Values are presented as percentage (number).

pET, personalized embryo transfer.

<sup>a)</sup>p<0.05 when compared with Group 1.

ranging from 2 to 6. Similarly, a study by Hashimoto et al. [16] reported an LBR of 23.7% (14 of 59) in receptive patients and 16.7% (3 of 18) in the non-receptive group, with mean numbers of previous failed cycles of 7.1 and 7.8, respectively. In a study by Patel et al. [17], the ongoing PR was 32.4% (24 of 74) in the receptive and 63.6% (7 of 11) in the non-receptive group, with average numbers of previous failed cycles of 3.6 and 4.0, respectively. Two additional studies have also reported comparable clinical IVF outcomes between the receptive and non-receptive phases [18,19].

In the present study, the likelihood of ongoing pregnancy was negatively associated with the woman's age and positively associated with the quality of the frozen blastocyst. These two parameters are widely recognized as predictors of successful pregnancy in con-

ventional frozen ET cycles. Our team has also previously reported that a high-quality frozen blastocyst score at transfer (≥38.3) is a significant factor associated with clinical pregnancy [22]. Our current findings suggest that even in women with RIF undergoing pET using ERA, the probability of pregnancy remains associated with the quality of the frozen blastocyst.

Recently, ongoing debate has been held over the limitations of the ERA [23]. In their review article, Ben Rafael [24] described the ERA as an "unproven technology." Despite this, few reports have addressed the efficacy of the ERA in women with RIF [8–11]. This underscores the urgent need for additional research on this topic. Our findings suggest that the age of the woman and the quality of the blastocyst should be considered as potential confounding factors in any re-

search conducted on the efficacy of the ERA.

Furthermore, the combination of the ERA and endometrial immune profiling has been reported to potentially hold more clinical value than using either the ERA or immune profiling independently in women with RIF [25]. Therefore, this adjunctive strategy should also be considered when utilizing the ERA in women with RIF.

WOI displacement is an endometrial cause of embryo implantation failure, particularly in women with RIF. Consequently, a need exists for a more accurate tool to assess endometrial receptivity, beyond the conventional ERA. This tool would guide the optimal timing of ET with greater precision. Efforts to develop such a tool are ongoing. In a retrospective study conducted in Japan, a new endometrial receptivity test, known as ERPeakSM, was used in women with RIF. The findings indicated that the clinical PR (37.7% vs. 20.0%) and LBR (29.9% vs. 9.7%) were significantly higher in the pET group compared to the non-pET patients [26]. Furthermore, a study from China reported that an RNA-Seq-based endometrial receptivity test tool, which uses transcriptomic biomarkers, was effective in improving the clinical PR in women with RIF [27].

The primary limitations of this study stem from its retrospective nature. Additionally, the study was conducted with a small population from a single clinic. Despite these limitations, the strength of this study lies in its uniqueness; it is one of the few studies that have investigated the factors influencing clinical and ongoing PRs in women with RIF undergoing the ERA.

While the ERA may be viewed as an unproven technology, it can also be seen as a worthwhile option for women with intractable RIF. Furthermore, given the scarcity of studies addressing the efficacy of the ERA in women with RIF, a need exists for additional well-designed studies to confirm the clinical value of the ERA and identify specific populations that may benefit from this technology.

## Conflict of interest

Byung Chul Jee has served as an editor of *Clinical and Experimental Reproductive Medicine* since 2018. However, he did not participate in the selection, evaluation, or decision-making process concerning the peer reviewers of this article. No further potential conflicts of interest pertinent to this article have been disclosed.

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Conceptualization: BCJ. Data curation: HKL, KYM. Formal analysis: HKL, KYM, BCJ. Methodology: BCJ. Project administration: BCJ. Writing-original draft: HKL, KYM. Writing-review & editing: HKL, KYM, HP, BCJ.

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