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Efficacy of the endometrial receptivity array for repeated implantation failure in Japan: A retrospective, two-centers study

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Abstract

Aim: This study aimed to assess the efficacy of the endometrial receptivity array (ERA) as a diagnostic tool and the impact of personalized embryo transfer (pET) for the treatment of patients with recurrent implantation failure (RIF) in Japan.

Methods: Fifty patients with a history of RIF with frozen-thawed blastocyst transfers were recruited from July, 2015 to April, 2016. Endometrial sampling for the ERA and histological dating and a pET according to the ERA were performed. The receptive (R) or non-receptive (NR) status of the endometrium as a result of the first ERA, endometrial dating, and pregnancy rates after the pET were analyzed.

Results: Of the patients with RIF, 12 (24%) were NR. Among them, eight (66.7%) were prereceptive. A clinical follow-up was possible in 44 patients who underwent the pET. The pregnancy rates were 58.8% per patient and 35.3% per first pET in the R patients and 50.0% per patient and 50.0% per first pET in the NR patients. Discrepancies between the ERA results and histological dating were seen more in the NR patients than in the R patients.

Conclusions: For patients with unexplained RIF, there is a significance in searching for their personal window of implantation (WOI) using the ERA, considering the percentage of those who were NR and the pregnancy rates that resulted from the pET. By transferring euploid embryos in a personal WOI, much better pregnancy rates are expected.

KEYWORDS

endometrial receptivity array, histological dating, implantation window, personalized embryo transfer, recurrent implantation failure

1 | INTRODUCTION

Recurrent implantation failure (RIF) is a major issue of infertility that is not yet fully investigated and is determined when there are failed implantation cycles after several in vitro fertilization (IVF) attempts. Implantation failure usually is considered to have occurred after more than three cycles of IVF with the transferral of morphologically good embryos.[1] There are several causes of RIF, such as pathologic alterations of the endometrial cavity (ie hyperplasia, submucosal myomas, endometrial polyps, endometritis, synechia), hydrosalpinx, embryonic aneuploidy, thrombophilias,[2] and systemic factors, such as thyroid dysfunction.

Although embryonic aneuploidy is likely to be the major contributor to human implantation failure, especially in cases of advanced maternal age,[3] it has been reported that the proportion of euploid embryos failing to implant has been ~40%,[4] which might suggest the importance of the endometrium and its receptivity status as another dominant factor for implantation failure.[5]

The window of implantation (WOI) is a short period of the menstrual cycle in which the endometrium acquires a functional, but transient, status that supports blastocyst acceptance in a synchronic way and it is regarded as opening on days 19-20 of the cycle and lasting 4-5 days at the time when progesterone (P) reaches peak serum concentrations.[6]

Recently, a Spanish team developed a tool that is able to detect a receptive endometrium with the use of a specific transcriptomic signature.[7] It consists of a customized array, including 238 genes that are expressed at different stages of the endometrial cycle, and is linked to a computational predictor that can identify the receptivity status of an endometrial sample and assess the personalized WOI of a patient.[7] The endometrial receptivity array (ERA) was shown to be more accurate than endometrial histology,[8] and importantly, these results were reproducible in the same patients 29-40 months after the first test.[8]

In this study, the authors assessed the efficacy of the ERA as a diagnostic tool, as well as the impact of personalized embryo transfer (pET) for the treatment of RIF, in Japan.

2 | MATERIALS AND METHODS

2.1 | Patients and samples

Among the 65 patients who agreed to undergo an ERA in the authors' centers from July, 2015 to April, 2016, a total of 50 patients with RIF and a past history of repeated implantation failure with at least three good-quality embryo transfers were eligible for this study. All the patients were routinely examined by vaginal ultrasound (hysteroscopy if necessary), for thyroid function, thrombophilia (protein S, protein C, antithrombin III, coagulation factor XII, lupus anticoagulant, anticardiolipin antibodies), and were treated appropriately if any disorder was found.

This study was approved by the Institutional Review Board of Kyono ART Clinic, Sendai and Takanawa, Japan. All the patients who were involved in this study allowed the researchers to use their medical record data for research in an unidentifiable manner. Written, informed consent was obtained from all the patients prior to the ERA in the two centers.

2.2 | Endometrial sampling and processing

The ERA was performed in either a hormonal replacement therapy (HRT) cycle or a natural cycle. In a HRT cycle, after appropriate priming with estradiol (by transdermal patch, estradiol valerate, or both when necessary) for ~2 weeks, leading to a trilaminar endometrium of ≥6 mm and confirming the appropriate hormonal status, P was administered (either by micronized suppositories or by chlormadinone acetate) for five full days, and on day P+5, an endometrial biopsy was performed. In a natural cycle, after the detection of a luteinizing hormone (LH) surge (LH+0) or artificially induced ovulation by the administration of human chorionic gonadotropin (hCG+0), an endometrial biopsy was performed on day LH+7 or hCG+7. The endometrial biopsy was performed from the uterine fundus by using a catheter called "ENDOSUCTION" (Hakko Company, Ltd., Nagano, Japan) either on day P+5 in the HRT cycles or on day hCG+7 or LH+7 in the natural cycles, as described previously.[2] The biopsied endometrial sample was put into a cryotube containing 1.5 mL RNAlater (Quiagen, Tokyo, Japan) and then shaken for a few seconds. It was kept at 4°C for 4 hours and shipped at room temperature for the ERA analysis (IGENOMIX, Valencia, Spain).[2] Also, the authors provided endometrial samples for histopathological examination.

2.3 | Window of implantation recommendation according to the endometrial receptivity array prediction

The sequencing expression of the 238 genes that are involved in endometrial receptivity was analyzed by using a customized DNA microarray and the endometrial receptivity status was assessed by the ERA computational predictor, as described previously.[2] The ERA assessment of receptive (R) or non-receptive (NR) was provided. The pET was performed on the day that was designated by the ERA. For the NR patients who did not agree to undergo a second ERA or for those who already had the final assessment by their first ERA test, the pET was performed according to the first ERA diagnosis.

The profiles and pregnancy rates of groups R (those who were receptive at the first ERA) and NR (those who were non-receptive at the first ERA) were analyzed. "Clinical pregnancy" was defined as the confirmation of a gestational sac in the uterine cavity by ultrasound analysis.

2.4 | Endometrial receptivity array and histological dating

The associations between the ERA results and histological dating also were examined. Two independent pathologists analyzed the biopsied endometrial samples and assessed the endometrial dating, as well as the presence of other histopathological findings, such as endometritis.

The pathologists who assessed the endometrial dating were not informed about the ERA results, but were informed that the endometrial biopsy was performed on P+5 in the HRT cycles or either on hCG+7 or LH+7 in the natural cycles. The authors defined the differences in endometrial dating, as follows: for the R group, histological dating other than the postovulatory day (POD) 5; for the NR group, histological dating that was different from the result of the ERA (ie histologically POD 5 in spite of the ERA diagnosis of NR). If the dating was assessed as histologically POD 6 (or POD 5-6) and the ERA diagnosis was postreceptive, the histological dating result was regarded as consistent because the pathologist detected a delay in the endometrium; for those with an ERA result of P+5.5 who were diagnosed as POD 5 histologically, the definition was "suboptimally consistent" because of the difficulty in detecting 12 hours of delay by histological analysis alone.

2.5 | Statistical analysis

The statistical analysis was performed by using the Mann-Whitney *U* test, chi-square analysis, or Fisher's exact test, as well as the ANOVA where appropriate. A *P*-value of <.05 was considered to be statistically significant.

3 | RESULTS

3.1 | Patient profiles

The average age of the 50 patients with RIF was 38.82±3.90 (28-51) years old; 19 patients were multigravida and five were multipara, whose past histories of failed frozen-thawed (vitrified-warmed) blastocyst transfers and total failed embryo transfers were 4.64±2.06 cycles and 7.34±3.34 cycles, respectively. The mean follow-up period was 12.83±2.56 (8.5-17) months. The first ERA was done either in HRT cycles (45) or in natural cycles (five). One patient received oocyte donation (OD) in another country. Those cases with congenital uterine malformation, endometrial hyperplasia, submucosal myomas, endometrial polyps, and hydrosalpinx were not included in this study.

3.2 | Endometrial receptivity array results and pregnancy rates

The first ERA resulted in the diagnosis of 38 (76%) R patients and 12 (24%) NR patients. The profiles of the R patients and the NR patients are compared in Table 1, in which there was no significant difference between the two groups. There was no multipara patient in the NR group.

Among the 12 NR patients, eight (66.7%) were prereceptive, three (25%) were postreceptive, and one (8.3%) was proliferative. Among the eight prereceptive patients, four were diagnosed as P+5.5, while four were suspected as P+6 and were recommended to have a new biopsy 1 day after (on day P+6). Four out of the 12 NR patients underwent a second ERA and three turned out to be R on the specified day (hCG+6; P+6).

Clinical follow-up was possible in 44 patients (34 patients in group R, 10 patients in group NR) who underwent a pET on the day that was indicated by the ERA. Six patients had not yet undergone a pET during the follow-up period. An average of 1.03±0.19 embryos were transferred per pET. The authors make it a rule to transfer single embryos whenever possible in order to prevent multiple pregnancies, following the guidelines of Japan Society of Obstetrics and Gynecology.[9]

The clinical pregnancy rates were 58.8% (20/34) per patient and 35.3% (12/34) per first pET in the R group and 50.0% (5/10) per patient and 50.0% (5/10) per first pET in the NR group (Table 2). All the pregnant cases in the NR group achieved pregnancy in their first pET

TABLE 1 Patient profiles of the receptive (R) and non-receptive (NR) groups

Characteristic	R Group	NR Group	*P*-value
Patients (N)	38	12	–
Age (years): Mean±SD	38.42±3.40	40.08±5.16	.20[a]
Multigravida patients: N (%)	14 (36.8)	4 (33.3)	.90[b]
Multipara patients: N (%)	5 (13.2)	0 (0.0)	.44[b]
Previous ET: Mean±SD	7.18±3.37	7.83±3.35	.52[a]
Previous FBT: Mean±SD	4.47±1.97	5.17±2.33	.41[a]
Natural-cycle ERA: N (%)	3 (7.9)	2 (16.7)	.74[b]
HRT-cycle ERA: N (%)	35 (92.1)	10 (83.3)	.74[b]
EM thickness (mm) at first ERA: Mean±SD	11.02±2.43	11.04±3.06	1.00[a]
Serum E2 (pg/mL) at ERA: Mean±SD	461.76±359.84	453.98±372.49	.96[a]
Serum P (ng/mL) at ERA: Mean±SD	13.58±5.07	26.48±34.81	.29[a]

E2, estradiol; EM, endometrium; ERA, endometrial receptivity array; ET, embryo transfer; FBT, frozen-thawed blastocyst transfer; HRT, hormone replacement therapy; P, progesterone; SD, standard deviation. [a]Mann-Whitney's *U* test; [b]Chi-square test.

TABLE 2 Pregnancy rates of the receptive (R) and non-receptive (NR) groups (all ages)

Characteristic	R Group	NR Group	*P*-value
Patients (N)	38	12	–
Age (years): Mean±SD	38.42±3.40	40.08±5.16	.20[a]
Patients with pET after ERA: N (cycle)	34 (59)	10 (18)	–
Pregnancy rate (per patient): N (%)	20/34 (58.8)	5/10 (50.0)	.89[b]
Pregnancy rate after first pET: N (%)	12/34 (35.3)	5/10 (50.0)	.64[b]
Implantation rate: N (%)	20/61 (32.8)	6/19 (31.6)	.92[b]
Miscarriage rate: N (%)	6/20 (30.0)	2/5 (40.0)	1.00[c]
Take-home baby rate: N (%)	14/59 (23.7) (6 live births, 8 ongoing)	3/18 (16.7) (1 live birth, 2 ongoing)	.76[b]
Interval from first ERA to first pET (months): Mean±SD	3.24±2.83	2.40±1.31	.66[a]
Interval from first ERA to pregnancy (months): Mean±SD	4.38±3.16	2.10±.74	.14[a]

ERA, endometrial receptivity array; ET, embryo transfer; pET, personalized embryo transfer; RIF, repeated implantation failure; SD, standard deviation. [a]Mann-Whitney's *U* test; [b]Chi-square test; [c]Fisher's exact test. Forty-four patients with RIF underwent pET (77 pET cycles). An average of 1.03±.19 embryos was transferred per ET.

(Table 2). The implantation rates were 32.8% (20/61) in the R group and 31.6% (6/19) in the NR group (Table 2). Biochemical pregnancies were not included. The one OD recipient in the NR group who had >10 failed frozen-thawed blastocyst transfer cycles (of which three were OD cycles) achieved pregnancy by pET after the second ERA diagnosis of P+6. The intervals from the first ERA to pregnancy were shorter in the NR group, compared to the R group, but this was not statistically significant (Table 2). The miscarriage rate was 30.0% (6/20) in the R pregnancies and 40% (2/5) in the NR pregnancies (Table 2). Among the eight cases of miscarriage, chromosomal analysis of the chorionic villi was performed in one NR case, which turned out to be abnormal.

As embryonic aneuploidy increases with an advanced maternal age and is suspected to contribute largely to implantation failure, the authors analyzed the clinical outcomes of the R and NR groups in relation to patients who were aged under 40 years old (Table 3). The clinical outcomes were better in the patients who were under 40 years old, compared to all ages (Tables 2 and 3), but showed the same tendency.

3.3 | Histological dating and the endometrial receptivity array

Also analyzed were the associations between the ERA and histology. There was no inflammatory histopathology, nor any malignancy.

TABLE 3 Pregnancy rates of the receptive (R) and non-receptive (NR) groups (aged <40 years old)

Characteristic	R Group	NR Group	*P*-value
Patients (N)	21	5	–
Age (years): Mean±SD	36.10±2.76	36.20±4.38	.43[a]
Patients with pET after ERA: N (cycle)	19 (34)	3 (3)	–
Pregnancy rate (per patient): N (%)	12/19 (63.2)	2/3 (66.7)	1.00[b]
Pregnancy rate after first pET: N (%)	7/19 (36.8)	2/3 (66.7)	.54[b]
Implantation rate: N (%)	12/36 (33.3)	3/4 (75.0)	.14[b]
Miscarriage rate: N (%)	3/12 (25.0)	0/2 (.0)	1.00[b]
Take-home baby rate: N (%)	9/34 (26.5) (4 live births, 5 ongoing)	2/3 (66.7) (1 live birth, 1 ongoing)	.21[b]
Interval from first ERA to first pET (months): Mean±SD	3.79±3.45	1.33±.58	.10[a]
Interval from first ERA to pregnancy (months): Mean±SD	4.50±3.48	1.50±.71	.12[a]

ERA, endometrial receptivity array; pET, personalized embryo transfer; SD, standard deviation. [a]Mann-Whitney's *U* test; [b]Fisher's exact test.

TABLE 4 Histopathological dating and the first endometrial receptivity array (ERA) results of the receptive (R) and non-receptive (NR) groups

Group	Histological dating	Histological decision	ERA result	ERA dating (the day suggested for pET)	Concordance
NR					
1	POD 5	Receptive	Prereceptive	P+6 suspected	×
2	ND	–	Proliferative	Proliferative	–
3	POD 4	Prereceptive	Prereceptive	P+6 suspected	○
4	ND	–	Postreceptive	hCG+6 suspected	–
5	POD 5	Receptive	Prereceptive	P+5.5	△
6	POD 5	Receptive	Late receptive	P+4.5	△
7	POD 5	Receptive	Prereceptive	P+5.5	△
8	POD 5	Receptive	Prereceptive	P+5.5	△
9	POD 5	Receptive	Prereceptive	P+6 suspected	×
10	POD 6-7	Postreceptive	Postreceptive	P+4 suspected	○
11	POD 5	Receptive	Prereceptive	P+6 suspected	×
12	POD 5	Receptive	Prereceptive	P+5.5 suspected	△
R	Histological dating	Histological decision	ERA result	ERA dating	○
13	POD 5	Receptive	Receptive	P+5	○
14	POD 5	Receptive	Receptive	P+5	○
15	POD 5-6	Postreceptive	Receptive	P+5	×
16	POD 5	Receptive	Receptive	P+5	○
17	POD 5	Receptive	Receptive	P+5	○
18	POD 5	Receptive	Receptive	P+5	○
19	POD 5	Receptive	Receptive	P+5	○
20	POD 5	Receptive	Receptive	P+5	○
21	POD 5-6	Postreceptive	Receptive	P+5	×
22	POD 5	Receptive	Receptive	P+5	○
23	POD 5	Receptive	Receptive	P+5	○
24	POD 5-6	Postreceptive	Receptive	P+5	×
25	POD 5	Receptive	Receptive	P+5	○
26	POD 5	Receptive	Receptive	hCG+7	○
27	POD 5	Receptive	Receptive	P+5	○
28	POD 5	Receptive	Receptive	P+5	○
29	POD 5	Receptive	Receptive	P+5	○
30	POD 5	Receptive	Receptive	P+5	○
31	POD 5	Receptive	Receptive	P+5	○
32	POD 5	Receptive	Receptive	P+5	○
33	POD 5	Receptive	Receptive	P+5	○
34	POD 5	Receptive	Receptive	hCG+7	○
35	POD 4	Prereceptive	Receptive	P+5	×
36	POD 5	Receptive	Receptive	P+5	○
37	POD 5-6	Postreceptive	Receptive	hCG+7	×
38	POD 5	Receptive	Receptive	P+5	○
39	POD 5	Receptive	Receptive	P+5	○
40	POD 5	Receptive	Receptive	P+5	○
41	POD 5	Receptive	Receptive	P+5	○
42	POD 5	Receptive	Receptive	P+5	○

(Continues)

TABLE 4 (Continued)

Group	Histological dating	Histological decision	ERA result	ERA dating (the day suggested for pET)	Concordance
43	POD 5	Receptive	Receptive	P+5	○
44	POD 5	Receptive	Receptive	P+5	○
45	POD 5	Receptive	Receptive	P+5	○
46	POD 5	Receptive	Receptive	P+5	○
47	POD 5	Receptive	Receptive	P+5	○
48	POD 5	Receptive	Receptive	P+5	○
49	POD 5	Receptive	Receptive	P+5	○
50	POD 5	Receptive	Receptive	P+5	○

○, concordant; △, suboptimally concordant; ×, discrepant. hCG, human chorionic gonadotropin; HRT, hormone replacement therapy; LH, luteinizing hormone; ND, not described; P, progesterone; pET, personalized embryo transfer; POD, postovulatory day. Pathologists were not informed about the ERA results, but were informed that the endometrial biopsy was performed on P+5 in the HRT cycles or either on hCG+7 or LH+7 in the natural cycles.

Concordance (including optimal and suboptimal) of the histological dating and the ERA was observed in 80% of the total cases that was studied (33 in the R group and seven in the NR group) (Table 4). More discrepancies between the histological dating and the ERA results were observed in the NR group than in the R group, but this was not statistically significant (25% [3/12] vs 13.2% [5/38]; *P*=.60, chi-square test).

4 | DISCUSSION

To the best of the authors' knowledge, there has been no other study in Japan to report on the effectiveness of the ERA as a diagnostic tool and pET that is guided from the results of an ERA for patients with RIF.

Although the number of studied cases was limited, it was found that 24% of the patients with RIF were NR and that the greater portion of the NR patients were prereceptive, as reported previously.[2] Also, the implantation rates of the R and NR groups and the pregnancy rate by the first pET in the NR cases were equivalent to those results that have been reported previously.[2]

The conditions of this study's population were different from the previous study[2]: a high-aged population that included patients who were >40 years, a high percentage of single embryo transfers, and only one OD recipient. A higher age in women is related to a higher aneuploidy rate; thus, by combining pre-implantation genetic screening analysis with the ERA, much better pregnancy rates are expected.

Although not statistically significant, all the pregnant cases of the NR group achieved pregnancy in their first pET and thus the interval from the first ERA to pregnancy was shorter in the NR group, compared to the R group (Table 2). This indicates that a displacement of the WOI could be the crucial cause of implantation failure in the NR group, while some may mention that an endometrial biopsy might have favorably affected the first pET in the NR group. There have been suggestions that the local injury that is induced by an endometrial biopsy (scratching) might improve embryo implantation in the following embryo transfer cycle[10] and some think that the pregnancy rates of pET after an ERA have been affected by endometrial scratching itself. The Spanish team followed its R patients for 6 months and found that the clinical results had not improved in the first month after the endometrial biopsy for the ERA test and that the pregnancy rates per month in which the first pET was done after the ERA were constant up to 6 months, therefore confirming that the results were not related to local injury.[2]

There were limitations to this study; that is, the short follow-up period, limited study number, no control ERA results for patients without RIF, and a hysteroscopy was not routinely done unless any alteration was suspected by ultrasound analysis. The status of each embryo (euploidy) was not confirmed in this study, but this was also the same as reported previously.[2]

The superiority of the ERA test against endometrial histology was shown in a previous report,[8] in which it was mentioned that the reasons why histology is worse than the ERA was more understandable after analysis of the subjective histologic features and that the transitions between the prereceptive/receptive or receptive/postreceptive stages are more difficult to distinguish by pathologists.[8] In contrast, in this study, the concordance (including optimal and suboptimal) of histological dating and the ERA was observed in 80% of the cases, but this might be related largely to the fact that the pathologists in this study had information about the timing of when the endometrial biopsy was performed, making it easier to predict the dating. In a different study, the pathologists were blinded to the subject and to the endometrial phase.[8] Additionally, more discrepancies were found in the assessment of histological dating, compared to the ERA results, in the NR patients than in the R patients, although this was not statistically significant. Indeed, some of the ERA results were diagnosed as P+5.5 or P+4.5 and it can be difficult to assess the WOI by only classic histological dating with such accurate timing. Also, subjective judgments and bias are unavoidable in histological diagnosis. Given the limitations in this research, the authors believe that further study is necessary in order to assess the cost–benefit ratio of the ERA in future.

It certainly is important to scrutinize the various causes of implantation failure, but for patients with unexplained RIF, there is a

significance in searching for their personal WOI, considering the percentage of NR patients and the pregnancy rates resulting from pET. The ERA and pET were effective for a subset of patients with unexplained RIF, and by transferring euploid embryos in a personal WOI, much better pregnancy rates are expected.

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DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights*: All the procedures that were followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study, which was approved by the Institutional Review Board of Kyono ART Clinic, Sendai and Takanawa, Japan. This article does not contain any study with animal participants that has been performed by any of the authors.

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