CASE REPORT

Endometrial Receptivity Array—A Promising Remedy for Women Afflicted with Recurrent Implantation Failure: A Case Report

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Abstract

Aim and background: An endometrial receptivity array (ERA) is a test for assessing the endometrium's gene expression profile concerning receptivity for embryo implantation. The primary significance of the ERA test is its ability to objectively assess the window of implantation (WOI), thereby facilitating the development of the personalized embryo transfer (pET) concept.

Case description: A patient, aged 38 years, married for 16 years, a case of secondary infertility, had three unsuccessful attempts of intrauterine insemination and six unsuccessful attempts of *In vitro* fertilization (IVF). Given her history of recurrent implantation failures (RIF), she underwent the ERA test. The ERA indicated a pre-receptive result. She conceived in the very first attempt of ERA-guided pET. The patient delivered a female child at 34 weeks by a lower segment cesarean section.

Conclusion: The ERA test accurately and sensitively identifies endometrial gene expressions, enabling the decision of the most suitable time for embryo transfer.

Clinical significance: *In vitro* fertilization success rates could rise if the endometrial factor were personalized using an objective and reproducible diagnostic method like ERA in RIF patients.

Keywords: Case report, Endometrial receptivity array, *In vitro* fertilization, Personalized embryo transfer, Recurrent implantation failure, Window of implantation.

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Introduction

Successful implantation necessitates the presence of a viable embryo, an endometrium that is receptive, synchronized and effective molecular communication between the two, and immune protection from the host. Recurrent implantation failure (RIF) poses a significant challenge. *In vitro* fertilization (IVF) is associated with frequent implantation failures.

It has been demonstrated that chromosomal abnormalities in the embryo contribute to as much as 60% of RIF.[1] It is important to note that not all IVF failures are attributable to embryonic defects. Consequently, transferring a euploid embryo cannot provide a flawless success rate of 100%. In about 40% of embryo transfers, euploid blastocysts do not implant.[2–4]

The release of endocrine and paracrine factors governs the regulation of gene expression across various endometrial cell types.[5] The endometrium acquires a receptive phenotype in response to progesterone, permitting blastocyst implantation. A window of implantation (WOI) is the temporal window of opportunity (30–36 hours) when the endometrium transforms, becoming receptive to the blastocyst. This brief window occurs in a natural cycle from luteinizing hormone (LH) +6 to LH +9 or in a hormone replacement therapy (HRT) cycle from progesterone (P) +4 to P +7.[6] During the WOI, the endometrium is most receptive.[6] In one out of every four RIF patients, the WOI is individualized and even shifted rather than being constant in all women.[7,8] The lack of successful implantation of an euploid embryo indicates a probable nonembryonic origin, and the lack of synchronization between the embryo and the WOI may contribute to RIF.[9]

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Recurrent implantation failure patients demonstrate a different endometrial gene expression profile. The failure of implantation can be attributed to the displacement and/or disruption of the WOI as a result of molecular diseases that are not directly related to timing.[10] Infertile patients with a displaced WOI may experience positive outcomes with endometrial receptivity array (ERA)-guided personalized embryo transfer (pET).

As stated by Ruiz-Alonso et al., the ERA is composed of a customized array comprising 238 genes that exhibit expression during various phases of the endometrial cycle. This array is integrated with a computational predictor, enabling the identification of the receptivity of the endometrium with the determination of the personalized WOI for a woman, irrespective of the histological characteristics of the endometrial sample.[8]

We discuss a case of a patient with previous 6 IVF failures who conceived in the first attempt of ERA-guided pET.

Case Description

The patient, aged 38 years and had been married for 16 years, had secondary infertility, which included a prior occurrence of one abortion. The patient experienced three unsuccessful attempts of intrauterine insemination and six unsuccessful attempts of IVF. The patient experienced a single instance of conception by IVF employing a Frozen-Thawed Embryo Transfer cycle approximately 5 years ago, tragically leading to a spontaneous abortion. The patient exhibited regular menstrual cycles. Due to the patient's history of RIF, she received counseling regarding the ERA test and a pET as per the results.

The baseline investigations conducted were as follows:

Anti-Müllerian hormone	1.365 ng/mL
Antral follicle count	8
Follicle-stimulating hormone	7 mIU/mL
Luteinizing hormone	3.69 mIU/mL
Estradiol	26.74 pg/mL
Thyroid-stimulating hormone	2.93 μLU/mL
FT3	4.85 pg/mL
FT4	1.12 ng/dL
Serum prolactin	2.8 ng/mL
Random blood glucose	85 mg/dL
HbA1c	5.29%
CB-NAAT	*Mycobacterium tuberculosis* not detected
Antiphospholipid antibodies—IgM and IgG	Negative

The ultrasound results revealed normal findings. A hysteroscopy was performed, and no abnormal findings were observed. The results of the semen analysis conducted on the husband indicated the presence of oligozoospermia.

Oocyte retrievals were done thrice. The ERA was conducted and indicated a pre-receptive result (Fig. 1).

A recommendation was made to carry out a pET, specifically targeting the transfer of a blastocyst, within a time frame of 135 ± 3 hours following initiation of progesterone supplementation.

Embryo transfer was conducted within the context of an HRT cycle. The procedure for the ERA was replicated during the HRT cycle.

On the 11th day of estradiol supplementation, an endometrial thickness of 9.5 mm and zone 4 vascularity was obtained. A serum progesterone measurement yielded a result of 0.404 ng/mL. The administration of microionized vaginal progesterone was started at a dosage of 400 mg every 12 hours through the vaginal route. The pET involved the transfer of a blastocyst, which was conducted within a specific time frame of 135 ± 3 hours following the initiation of progesterone supplementation (Fig. 2).

The patient conceived in the very first attempt of ERA-guided pET, which was confirmed by the assessment of beta-HCG conducted on the 14th day following the transfer of the embryo.

Beta-HCG on day 14—496 mIU/mL.

Beta-HCG on day 16—801 mIU/mL.

The antenatal period was uneventful. The patient delivered a female child, birth weight 2.1 kg at 34 weeks, by a lower segment cesarean section (LSCS).

Discussion

An ERA is a test for assessing the endometrium's gene expression profile concerning receptivity for embryo implantation. The ERA test's primary significance is its ability to objectively assess the WOI, thereby facilitating the development of the pET concept.

Endometrial receptivity array has a place in RIF where endometrial factors could be the contributory cause. Optimal indications of ERA are RIF, or euploid embryos failure to achieve a pregnancy, IVFOD (oocyte donation) failure with the transfer of good quality embryos, and persistent thin or thick endometrium. Patients with adenomyosis, endometriosis, and chronic endometritis have altered endometrial receptivity; hence, using ERA can be beneficial.

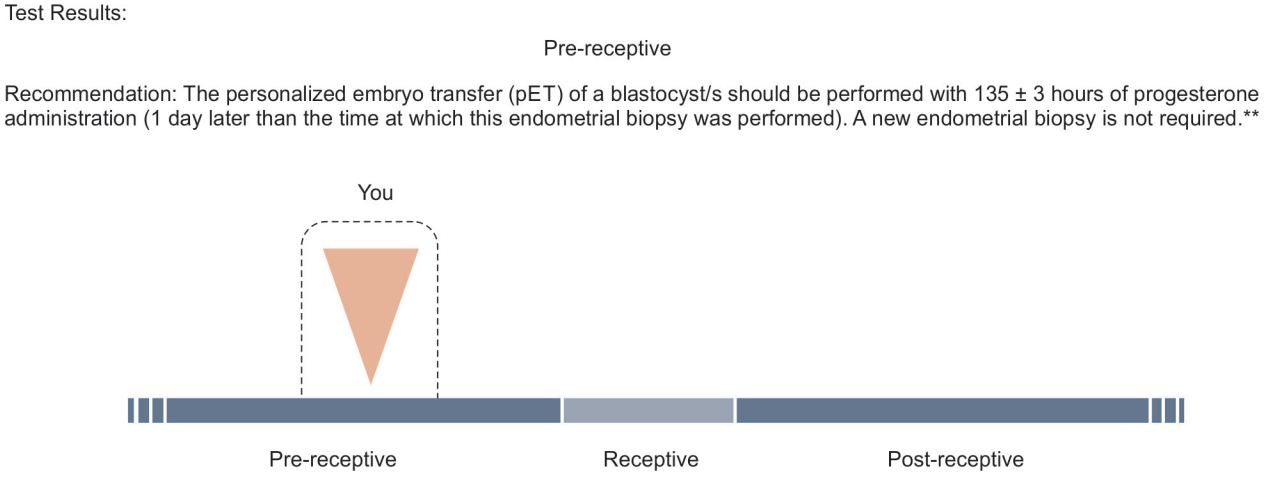

Fig. 1: ERA report indicating a pre-receptive result

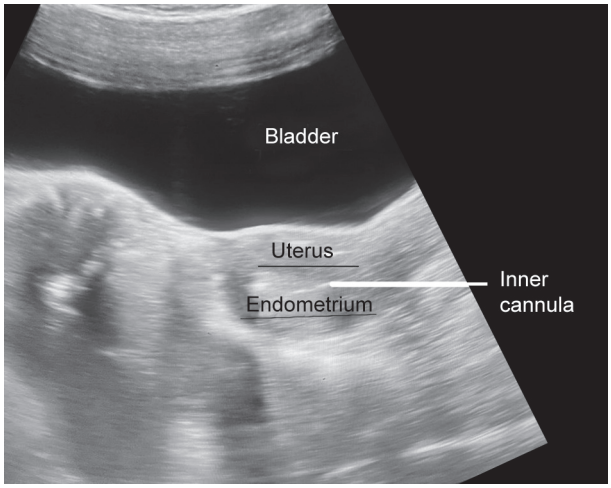

Fig. 2: Ultrasound-guided embryo transfer

The ERA test categorizes the endometrium as receptive or non-receptive (pre-receptive or post-receptive). It proposes a recommendation for pET, quantified in hours, based on the specific day of progesterone supplementation. In a subsequent cycle, receptive ERA patients would proceed with standard embryo transfer (sET) using the identical method on the same day as during ERA. On the other hand, those with non-receptive (NR) results would receive recommendations on how to modify the ET timing for a pET.

Endometrial receptivity array test is objective, accurate, and reproducible and does not have the limitation of inter-cycle variability. With a sensitivity of 0.99758 and a specificity of 0.8857 for predicting a receptive endometrium, ERA outperforms other techniques in terms of accuracy.[11] The findings are reproducible in an individual 29–40 months following the initial examination.[12]

Ruiz-Alonso et al. in 2014 documented a case involving the unsuccessful outcome of four self-IVF cycles and three IVF cycles with OD. The ERA reported a displacement of the WOI to P ± 7. Following a pET, a twin pregnancy and delivery were accomplished.[13]

Ruiz-Alonso et al. conducted a study on 17 OD women with 1–6 unsuccessful implantations with standard embryo transfer (ET). Once the patients' WOI was diagnosed, they underwent pET. These individuals attained a 60% clinical pregnancy rate (PR) with pET, whereas standard ET in an ERA-diagnosed non-receptive endometrium resulted in a 19% PR.[13]

In their publication, Ota et al. in 2019 documented the achievement of pregnancy in a Japanese woman through the application of ERA-guided pET following 11 prior implantation failures.[14]

Simrandeep and Padmaja in 2019 documented three instances of RIF in Indian women. Two of these cases had previously undergone ERA at another medical facility. The recommended pET protocol for a shifted WOI was not adhered to, leading to another unsuccessful outcome. After implementing pET, clinical pregnancies were successfully attained in both patients.[15]

Simón et al., in a multicenter open-label randomized controlled trial, has demonstrated the efficacy of ERA-guided pET even in women embarking on their initial IVF cycle.[16] Simón et al. found a statistically noteworthy rise in the frequencies of cumulative live birth rates after 12 months in patients in whom ERA-guided pET was resorted to instead of a standard ET.

The research conducted by Yan Jia et al.,[17] Simón et al.[16] and Jayesh Amin Sr. et al.,[18] evaluating the ERA test reported a notable increase in implantation and clinical PR among individuals who received the ERA test in comparison to those who did not undergo the test.

Riestenberg et al. discovered no statistically noteworthy differences in clinical PRs among groups receiving ERA and those not receiving ERA. These findings indicate that the routine use of ERA does not yield enhanced pregnancy outcomes for individuals undergoing their first embryo transfer.[19]

Conclusion

The ERA test accurately and sensitively identifies endometrial gene expressions, enabling the decision of the most suitable time for embryo transfer. By using pET guided by ERA, non-receptive RIF patients can attain PRs and implantation rates on par with receptive RIF patients.

Incorporating preimplantation genetic testing for aneuploidy to ensure the euploid state allows for a thorough assessment of the endometrial component. Consequently, the potential impact of pET on reproductive outcomes may hold greater significance.

Clinical Significance

In vitro fertilization success rates could rise if the endometrial factor were personalized using an objective and reproducible diagnostic method like ERA.

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