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JOURNAL OF Gynecological Research and Obstetrics

ISSN: 2581-5288 DOI: https://dx.doi.org/10.17352/jgro

Research Article

Does personalized embryo transfer based on era improve the outcomes in patients with thin endometrium and Rif in Self Versus Donor Programme?

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Received: 16 October, 2020
Accepted: 27 October, 2020
Published: 28 October, 2020

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Keywords: ERA; Donor programme; Personalized ET; Thin endometrium; RIF

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Abstract

Aim: This study was designed to explore the influence of personalized Embryo Transfer (pET) with the guidance of endometrial receptivity array (ERA) on reproductive outcomes in patients with Recurrent Implantation Failure (RIF) and thin endometrium, and to determine its efficacy in self versus donor gamete programme.

Settings and designs: A retrospective study conducted from January 2014 until December 2019 at GG Hospital, Fertility research and women's speciality Centre, Chennai, India.

Methods and materials: 722 women who were inducted in this study were divided into four groups. Group A (n=179) comprised of patients using self-gametes and Group C (n=180) consisting of patients using donor gametes, patients under these groups underwent the ERA test. Both the groups were compared to their respective controls, Group B (n=181) and Group D (n=182).

Statistical analysis used: T-Test was performed using SPSS Software (12.0).

Results: Reproductive outcomes were observed to be statistically significant in patients who underwent ERA test (Group C) followed by pET. The PR was lesser in Group A (55.31%) than in Group C (68.33%). CPR was also higher in Group C (58.33%) than in Group A (48.6%). Hence, it is strongly recommended to perform pET based on ERA test for patients with thin endometrium and RIF by adjusting the progesterone exposure as per the need.

Conclusion: The present study shows that ERA test has superior benefits in patients who have previously failed despite using donor gametes. It is also apparent that ERA contributes a greater part by strengthening the reproductive outcomes in the donor gamete recipients.

Introduction

In recent times, there have been several ground-breaking techniques in the field of ART especially in screening pre-implantation embryos and assessing the potential of an endometrium for implantation. Despite advances in these arenas, the implantation process still remains an enigma throughout the IVF journey. It is an intricate process that involves synchronous dialogues between several chemical mediators and interplay of genes to assure the implantation of a chromosomally competent embryo into a receptive endometrium. When it comes to recurrent implantation failure in IVF, the definition still eludes us although largely it means, failure of three previous fresh or frozen embryo transfers using at least 3 or 4 good quality embryos [1-3]. It is now well known that there is an established receptive period during the mid-luteal phase of the menstrual cycle (days 19-23), designated as the Window of Implantation (WOI) [4]. Prior

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researches substantiate the fact that patients with impaired uterine environment exhibit a displaced WOI [5]. It has also been reported that WOI occurs 1-2 days earlier in women undergoing ovarian stimulation than in natural cycle [2]. In order to ascertain an appropriate marker for endometrial receptivity with higher accuracy, a molecular diagnostic tool called 'Endometrial Receptivity Array' (ERA) was developed. It appraises the expression of 238 genes which influence the development of endometrium during the WOI. The sensitivity and specificity was noted to be 99.75% and 88.57%, respectively. The results were reproducible in the same patients after 2-3 years from the date of the first test [6-8]. ERA test determines the duration of progesterone exposure required by the endometrium to produce a receptive niche which gives rise to personalized embryo transfer (pET) [5]. Among various factors which hinder successful reproductive outcomes, thin endometrium has a negative influence on the implantation process, in most cases leading to recurrent implantation failure (RIF). Hence, ERA can be performed to confirm the receptivity of a thin endometrium before preparing for frozen embryo transfer (FET). It guides the process of pET if a displaced WOI is encountered in patients with RIF [9,10]. This retrospective study was designed to explore the influence of pET with the guidance of ERA on reproductive outcomes in patients with RIF and thin endometrium, and to determine its efficacy in self versus donor gamete programme.

Study design

This retrospective study was conducted from January 2014 until December 2019 at GG Hospital, Fertility research and women's speciality Centre, Chennai, India. The study population comprised of 722 women who had documented poor/thin endometrial lining and previous IVF failures. A poor endometrial lining was defined as an endometrial thickness measuring ≤0.7 cm on a trans-vaginal ultrasound during the peri-implantation period. The 722 women who were inducted in this study were divided into four groups. Group A (n=179) comprised of patients using self-gametes and Group C (n=180) consisting of patients using donor gametes, the patients under these groups underwent the ERA test as described below. Both the groups were compared to their respective controls, Group B (n=181) and Group D (n=182) in which ERA test was not performed. All the patients were given oral and written information regarding the procedure and consents were taken for the same. The baseline characteristics of the study population have been elucidated in Table 1.

The stimulation protocols employed for patients using self-gametes comprised of the long and short protocol based on factors such as age, previous reproductive outcomes, hormone values, quality and quantity of oocytes and embryos. The known poor responders with poor quality embryos, and also the patients who were assigned for PGT-A were excluded from the study.

Stimulation protocol

The hyper stimulation regimes in long and short protocols were similar consisting of day 2/3 scan followed by hormone analysis and if normal, stimulations were started on day 3 of the cycle. The injections used were recombinant FSH for 4 doses (225-300 IU) (LG, Haryana)followed by addition of HMG (150 IU) (LG, Haryana) for 2 days and thereafter only HMG (300 IU) (LG, Haryana) until dominant follicles were visualised. In the antagonist protocol, Cetrotide 0.25mg (Merck, US) was added whenever the follicle size reached 1.4 x 1.4 cm until trigger. In the long protocol, the trigger was recombinant HCG of 250 IU (Merck, Germany) and in the short protocol, GnRH agonist inj. Decapeptyl 0.1 mg (Ferring, Germany)was given. For dual trigger HCG 250 IU was given along GnRH agonist.

Table 1: Baseline characteristics of the study population.

	SELF		DONOR	
Parameters	Group A	Group B (control)	Group C	Group D(control)
Total no of transfers	179	181	180	182
Mean age of patients	32.29±5.57	30.93±5.66	36.63±5.56	37.49±5.72
Mean duration of infertility (years)	7.54±4.83	7.73±5.55	10.23±4.56	11.61±5.47
Mean endometrial thickness (cm)	0.87±0.13	0.96±0.14	0.87±0.13	0.95±0.14
No of embryos transferred (mean)	2.46±0.51	2.48±0.83	2.62±0.51	3.16±0.83
No of day 3 transfers	33	19	29	33
No of day 5 transfers	59	93	39	29
No of day 3 + day 5 transfers	87	69	112	120

Era cycle

The ERA test was performed in a hormone replacement cycle. The women were given incremental doses of EstradiolValerate (2mg) (Zyduscadila, Sikkim) from day 2/3 of their menstruation phase until the mid-cycle assessment on day 12/13. Generally, the minimum dose is 6/8 mg andincreased up to a maximum dose of 12 mg. On day 16, a trigger of HCG 10,000 IU (Amlife, Gujarat) was administered along with starting dose of vaginal micronized progesterone 400mg. There on, micronized progesterone was given in both oral and vaginal suppository form from a minimum dose of 800 mg to a maximum dose of 1200 mg (Sun Pharmaceuticals, Gujarat). The procedure was performed on day 21 (P+5) of the cyclewhich involves a biopsy taken trans-vaginally using an endometrial sampler or Probet. The tissue was transferred to a cryotube containing 1.5 ml of RNA stabilizing agent (Igenomix, Delhi) and vigorously shaken for few seconds until thoroughly mixed. The sample was stored at 4°c until shipment at room temperature to Igenomix, Spain for the transcriptomic analysis. The results are usually classified as Receptive, Pre-receptive or Post receptive. The latter two recommendations by the lab are provided with the estimated time for pET. Sequential transfers were performed consisting of cleavage stage embryos on P+3 and blastocyst on P+5, whereas in single transfers, either cleavage stage embryos (P+3) or blastocyst (P+5) were transferred according to the personalized ERA profile. The primary outcomes were then measured as Pregnancy rate (PR), Clinical pregnancy rate (CPR), Implantation rate (IR), Miscarriage rate (MR) and Live Birth rate (LBR). Statistical analysis was performed using t-test in SPSS software (12.0).

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Results

A total of 722 patients with thin endometrium and RIF were recruited in this study. ERA test was performed for 359 patients and the results were documented (Table 2, Graph 1). In Group A (self), 45.25% of the patients exhibited receptive endometrium with early receptive (12.85%) and late receptive (2.79%). Non receptive endometrium was classified into pre-receptive (29.05%) and post- receptive (10.06%). On the other hand, patients under Group C (donor) returned with a receptive profile of 50.56% with 11.67% early receptive and 3.89% late receptive. 18.88% of the patients showed pre-receptive condition while post receptive was observed in 15.00% of the patients. The era profile of the study groups have been elucidated in table 2 and graphically represented in graph 1 Table 2.

Self (Group A And Group B)

In Group A and Group B (Control), PR was observed to be 55.31% and 51.90%, respectively. No statistical difference was recorded (P=0.521). The difference in the IR was statistically insignificant (P=0.81) between Group A (24.77%) and Group B (24.07%).CPR was higher in Group A (48.60%) than in Group B (43.09%). However, there were no significant differences observed (P=0.29). LBR in Group A was 85.06% and 75.64% in Group B. This yielded a statistically insignificant result with p-value 0.13. MR in Group A and Group B was 14.94% and 24.36%, respectively (P=0.192). The data have been elucidated in Table 3 and graphically represented Graph 2.

Donor (Group C and Group D)

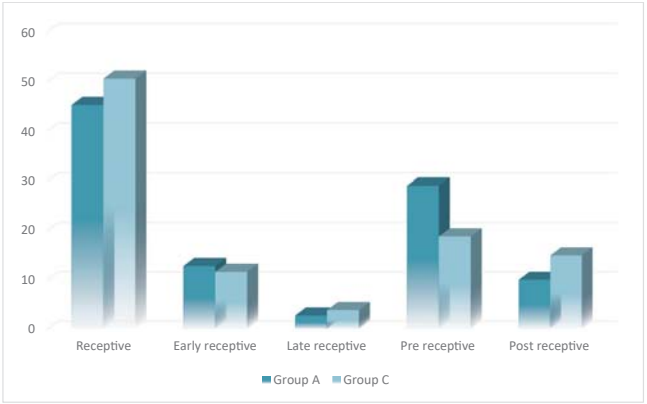
PR in patients who underwent ERA in Group C (68.33%) and in control Group D (52.19%) exhibited statistically significant difference (P=0.0017). IR was found to be statistically significant (P=0.0023) between Group C (30.31%) and Group D (21.51%). CPR was superior in patients under Group C with the rate of 59.44% as compared to Group D which showed 43.41%. This yielded a statistically significant range (P=0.002).There were significant differences documented in LBR and MR (P=0.05, P=0.028). LBR in Group C was 79.44% whereas in Group D it was 67.09%. MR in Group C and Group D was 20.56% and 32.91%, respectively. The data have been elucidated in Table 4 and graphically represented Graph 3.

Discussion

In a study conducted by Diaz-Gimeno, et al. to test the accuracy and reliability of the ERA test versus histological dating, they analysed 49 samples to compare the endometrial dating accuracy out of which 13 samples predicted through ERA identified the phase of the cycle more accurately than through the histological dating done by the pathologists. 16 samples were properly dated by using both the methods. They concluded that ERA exhibits a higher accuracy for endometrial dating throughout the luteal phase and endometrial receptivity than the anatomical approach that has been used since 1950s [11]. Ruiz – Alonsa, et al. submitted a report on the positive impact of pET on a patient with RIF. The underlying problem was likely found to be of endometrial origin. Hence, an endometrial biopsy was collected on day P+5 in an HRT cycle and received a pre receptive result. A two day displacement of WOI was diagnosed and personalized adjustments were done. pET was performed at P+7 with two blastocyst which resulted in twin pregnancy. This was followed by a pilot study through which they inferred that the personalization of the embryo transfer timing based on the ERA report can make a positive difference in reproductive outcomes in patients with RIF [12].

Table 2: ERA profile of patients under Group A and Group C.

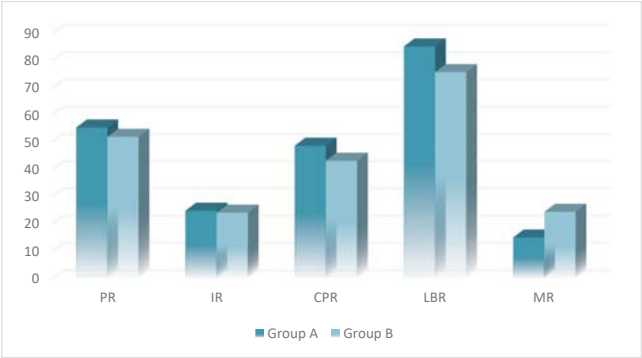
	GROUP A(N=179)	%	GROUP C(N=180)	%	p value
Receptive	81	45.25	91	50.56	0.34
Early receptive	23	12.85	21	11.67	0.71
Late receptive	5	2.79	7	3.89	0.57
Pre receptive	52	29.05	34	18.88	0.022
Post receptive	18	10.06	27	15	0.1633



Graph 1: Graphical representation of ERA results in Group A and Group C.

Table 3: Reproductive outcomes in patients under self-gamete programme.

Reproductive outcomes	GROUP A (SELF)	%	GROUP B (CONTROL)	%	p-value
Total no of cases	179		181		
Pregnancy rate	99	55.31	94	51.90	0.521
Implantation rate	109/440	24.77	104/432	24.07	0.81
Clinical pregnancy rate	87	48.60	78	43.09	0.29
Live birth rate	74	85.06	59	75.64	0.13
Miscarriage rate	13	14.94	19	24.36	0.192



Graph 2: Graphical representation of reproductive outcomes in Group A and Group B.

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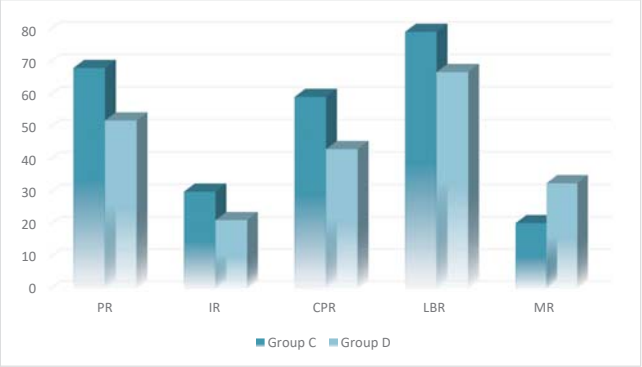
Table 4: Reproductive outcomes in patients under donor-gamete programme.

Reproductive outcomes	GROUP C (DONOR)	%	GROUP D (CONTROL)	%	p-value
Total no of cases	180		182		
Pregnancy rate	123	68.33	95	52.19	0.0017
Implantation rate	137/452	30.31	100/465	21.51	0.0023
Clinical pregnancy rate	107	59.44	79	43.41	0.002
Live birth rate	83	79.44	53	67.09	0.05
Miscarriage rate	22	20.56	26	32.91	0.028



Graph 3: Graphical representation of reproductive outcomes in Group C and Group D

Ruiz-Alonsa[1]stated that the WOI exhibited displacement in RIF patients reporting 25.9% of NR endometrium. They have also documented 50.0% PR and 38.5% IR by performing pET based on the ERA results. This was in accordance with the experiment conducted by Mahajan N, et al. in which they reported higher PR (68.5%) in patients underwent pET than in the control group who completed traditional ET (63.9%). They strongly suggest to carryoutERA test to diagnose displacement in WOI and to abide with pET for improved outcome. [5]Previous research confirms that the genetic abnormalities and aneuploidy lead to poor reproductive outcomes. However, in patients with euploid embryos combined with a non-receptive endometrium, pET can be performed using a modified progesterone protocol with the help of ERA to yield improved IVF outcomes [13]. Basil R, et al. put forth a diametric opinion stating that they were not able to demonstrate any improvement in PR by adjusting the time of subsequent FET according to the ERA results.[4] Nevertheless, in a review submitted by MahajanNand Sharma S in reference to a studywhich reported an overall PRof 33.3% in patients with thin endometrium, who underwent ET after ERA test. Hence, they stated that ERA can be used to confirm the receptivity of a thin endometrium before performing FET [9].

Kaur S and Naidu P in their case report have highlighted a case in which the patient had a history of thin endometrium which led to recurrent intra uterine insemination and IVF failures. The patient underwent ERA test before the subsequent FET, the test reported pre-receptive at P+5 and a repeat biopsy was advised at P+7 which confirmed a shift in the WOI. A personalized ET was carried out which indicated a positive beta-HCG result and a single gestational sac was observed [10]. In 2014, Cruz F and Bellver J submitted a case report which focused on live birth after embryo transfer with donor gamete in an unresponsive thin endometrium. The patient had faced multiple pregnancy losses in the previous cycles. The diagnosis of WOI in the endometrium using ERA test played a vital role in proceeding with the treatment; a single intrauterine pregnancy was detected resulting in the live birth of a healthy infant at 38 weeks gestation sans pregnancy complications [14].

The use of ERA in self gametes has been highlighted by several studies. However, its efficacy in donor programme with thin endometrium and RIF has been studied broadly for the first time. We undertook this study to determine the efficacy of pET based on ERA results in patients with thin endometrium and RIF using self versus donor gametes. Patients under Group A and Group B (control) used self gametes. Out of 179 patients who followed pET, 55.31% achieved pregnancy, but there was no statistical difference recorded (P=0.521). IR was statistically insignificant (P=0.81) between Group A (24.77%) and Group B (24.07%).CPR was higher in Group A (48.60%), however, there were no significant differences observed (P=0.29). Both LBR and MR yielded a statistically insignificant result with P=0.13 and P=0.192, respectively. Patients under Group C and Group D (Control) used donor gametes. The reproductive outcomes in 180 patients those who underwent pET reported significant results. PR in Group C (68.33%) and Group D (52.19%) exhibited statistically significant difference (P=0.0017). IR was statistically significant (P=0.0023) between Group C (30.31%) and Group D (21.51%). CPR was higher in patients under Group C (59.44%) as compared to Group D (43.41%). It was statistically significant (P=0.002). LBR in Group C (79.44%) and Group D (67.09%) was statistically significant (P=0.05). MR in Group C (20.56%) and Group D (32.91%) also yielded a statistically significant result (P=0.028). Hence, through this study we strongly recommend to perform pET based on ERA test for patients with thin endometrium and RIF by adjusting the progesterone exposure as per the need. It is also apparent that ERA contributes a vital role in the donor gamete recipients by strengthening the reproductive outcomes.

Conclusion

In conclusion, ERA is believed to be a promising molecular tool in the diagnostic platform and could establish a personalized window of implantation in patients with thin endometrium and RIF.The present study shows that ERA test has superior benefits in patients who have previously failed despite using donor gametes. Its relevance is expected to increase with emerging data which would apparently strengthen the pregnancy outcomes in the donor gamete recipients. However, a prospective study with a large sample size is required to highlight its importance more certainly.

References

1. Ruiz-Alonso M, Belsa D, Diaz-Gimeno P, Gómez E, Fernández-Sánchez M, et al. (2013) The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated Implantation failure. Fertil Steril 100: 818-824. Link: https://bit.ly/3kzhS2M

2. Das M, Holzer HE (2012) Recurrent implantation failure: gamete and embryo factors. Fertil Steril 97: 1021-1027. Link: https://bit.ly/31KSUWQ

3. Lessey BA (2011) Assessment of endometrial receptivity. Fertil Steril 96: 522-529. Link: https://bit.ly/3kBwMpp

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4. Bassil R, Casper R, Samara N, Hsieh TB, Barzilay E, et al. (2018) Does the endometrial receptivity array really provide personalized embryo transfer? J Assist Reprod Genet 35: 1301-1305. Link: https://bit.ly/3ovGQT3

5. Mahajan N, Kaur S, Ruiz-Alonso M (2018) Window of implantation is significantly displaced in patients with adenomyosis with previous implantation failure as determined by endometrial receptivity assay. J Hum Reprod Sci 11: 353-358. Link: https://bit.ly/34xLgRl

6. Von Grothusen C, Lalitkumar S, Boggavarapu NR, Gemzell-Danielsson K, Lalitkumar PG (2014) Recent advances in understanding endometrial receptivity: molecular basis and clinical applications. Am J Reprod Immunol 72: 148-157. Link: https://bit.ly/3oxKEmJ

7. Valdes CT, Schutt A, Simon C (2017) Implantation failure of endometrial origin: it is not pathology, but our failure to synchronize the developing embryo with a receptive endometrium. Fertil Steril 108: 15-18. Link: https://bit.ly/3e1ExCm

8. Eftekhar M, Tabibnejad N, Tabatabaie AA (2018) The thin endometrium in assisted reproductive technology: An ongoing challenge. Middle East FertilSoc J 23: 1-7. Link: https://bit.ly/2HDk230

9. Mahajan N, Sharma S (2016) The endometrium in assisted reproductive technology: How thin is thin? J Hum Reprod Sci 9: 3-8. Link: https://bit.ly/34zOFPR

10. Kaur S, Naidu P (2019) Why results of endometrial receptivity assay testing should not be discounted in recurrent implantation failure? Onco Fertil J 2: 46-49. Link: https://bit.ly/2HHNvIQ

11. Diaz-Gimeno P, Ruiz-Alonso M, Belsa D, Bosch N, Martínez-Conejero JA, et al. (2013) The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. Fertil Steril 99: 508-517. Link: https://bit.ly/35DDXqF

12. Ruiz-Alonso M, Galindo N, Pellicer A, Simón C (2014) What a difference two days make: "personalized" embryo transfer (pET) paradigm: A case report and pilot study. Hum Reprod 29: 1244-1247. Link: https://bit.ly/34zz5nd

13. Tan J, Khan A, Taylor B, Tallon N, Warraich G, et al. (2018) The role of the endometrial receptivity array (ERA) in patients who have failed euploid embryo transfers. J Assist Reprod Genet 35: 683-692. Link: https://bit.ly/3kza9C0

14. Cruz F, Bellver J (2014) Live birth after embryo transfer in an unresponsive thin endometrium. Gynecol Endocrinol 30: 481-484. Link: https://bit.ly/3ox1uCk

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