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Does Personalized Embryo Transfer Help In Improving Pregnancy Outcome In Prior Ivf Failure ?

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ABSTRACT
Background: The clinical value of personalized embryo transfer (pET) guided by the endometrial receptivity analysis (ERA) tests for previous IVF failure cases is unclear. The aim of this study is to clarify the efficacy of ERA leading to personalization of the day of embryo transfer (ET) in previous IVF failure patients
Methods: A retrospective study was performed for 27 patients with previous IVF failure who underwent ERA between September 2017 and September 2021. Pregnancy outcomes in a previous vitrified-warmed blastocyst transfer (previous VBT) and a personalized vitrified-warmed blastocyst transfer (pVBT) in same patients were compared. The details of each pVBT were further analyzed between patients in a non-displaced group, which indicated "receptive" cases in ERA results and those who were in the displaced group, which indicated "non-receptive" cases.
Results: When the pregnancy rate, both per patient and per transfer cycle, of previous VBT and pVBT were compared, a significant increase in pVBT was observed between the two methods (5.3% vs. 62.8%, 4.4% vs. 47.9%, respectively). The pregnancy rates, implantation rates, and clinical pregnancy rates of the first pVBT were significantly higher in the displaced group than the non-displaced group. The cumulative ongoing pregnancy rate of the displaced group tended to be higher compared to that of the non-displaced group in the first pVBT, although the difference was not statistically significant (51.0% vs. 31.1%, p= 0.06).
Conclusions: Our study demonstrates that pVBT guided by ERA tests may improve pregnancy outcomes in previous IVF failure patients whose window of implantation (WOI) is displaced, and its effect may be more pronounced at the first pVBT. The displacement of WOI may be considered to be one of the causes of IVF failure, and its adjustment may contribute to the improvement of pregnancy outcomes in RIF patients.

Keywords: Window of Implantation (WOI); Recurrent Implantation Failure (RIF); Endometrial Receptivity Analysis (ERA); Vitrified-warmed Blastocyst Transfer (VBT); personalized Vitrified-warmed Blastocyst Transfer (pVBT).

I. INTRODUCTION

Human implantation is a highly complex and multifactorial process. Successful implantation requires the presence of a healthy embryo, a receptive endometrium, a synchronized and successful molecular dialogue between the embryo ans endometrium and immune protection from the host. Despite its many advances and achievements, reproductive medicine has long neglected the endometrial factor. Indeed, since the inception of this field, the oocyte/embryo has remained the central focus. In contrast, the maternal endometrium was considered a passive part of the reproductive process: a 'good embryo' (or four or five) was all that mattered. Yet, while embryology and embryo transfer technologies have improved considerably over the past 30 years, the efficacy of IVF remains low worldwide, with current live birth rates of 25–30% per started cycle according to Adamson et al., 2018(1). Part of this gap may derive from a failure to consider the endometrium.It is fair to say that any process relying on a collaboration between partners requires the function and coordination of both.

Advent of "Omics" that is, the analysis of biological samples using molecular profiling has revived interest in the study of ER particularly in the context of implantation failure (IF) in IVF. Endometrial receptivity is characterized by a finite and time-sensitive window of implantation (WOI) orchestrated by an incompletely defined complex of endocrine, paracrine, and autocrine factors . Recently, the endometrial receptivity analysis (ERA) using the transcriptomic signature of endometrial receptivity composed of 248 genes has been applied clinically. The ERA was developed as a means of personalizing embryo transfer (pET) timing, particularly in cases of RIF where endometrial receptivity may play a dominant factor.

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II. METHODS

The aim of the study was to see if pregnancy rate improved after using the personalized embryo transfer.All infertile women who underwent Endometrial Receptivity array (ERA) from September 2017 – September 2021 in IRM,MMM were taken into the study. It was a retrospective study.Women having prior IVF failure with one or more good quality embryos with self /donor oocytes were included. Patients with nonoperated hydrosalpinx, congenital uterine anomaly, untreated submucous myomas or endometrial polyps, endometrial hyperplasia, severe male factor infertility (<5 million spermatozoa/mL), and abnormal karyotypes of both partners were excluded. Cases with spontaneous pregnancy after ERA, and those who underwent only cleavage stage ETs, only natural cycle blastocyst transfers, or only fresh blastocyst transfers after ERA were also excluded from this study .

All patients with previous failed IVF with at least one vitrified-warmed blastocyst transfer (VBT) were included in this study. VBT performed before ERA was defined as previous VBT. All the details of previous VBT were collected. All the patients were routinely examined by vaginal ultrasound , hysteroscopy , for thyroid function,any medical disorders, thrombophilia (protein S, protein C, antithrombin III, coagulation factor XII, lupus anticoagulant, anticardiolipin antibodies) in case of RIF and were treated appropriately if any disorder was found. Confounding factors such as nonoperated hydrosalpinx, congenital uterine anomaly, untreated submucous myomas or endometrial polyps, endometrial hyperplasia, severe male factor infertility (<5 million spermatozoa/mL), and abnormal karyotypes of both partners were excluded. Cases with spontaneous pregnancy after ERA, and those who underwent only cleavage stage ETs, only natural cycle blastocyst transfers, or only fresh blastocyst transfers after ERA were also excluded from this study . Embryos were thawed and cultured to blastocyst stage with a diameter of 160–170 μm and after assisted hatching /without hatching one or two embryos more than 5BC were transferred considering the time from transfer to invasion according to ERA results.

In this study, the cases with ERA results of “receptive” were defined as the “non-displaced” group, and all other cases were defined as “displaced” group. Vitrified blastocysts were warmed and transferred according to ERA results. Patients with a receptive endometrium underwent VBT in an HRT cycle mimicking the ERA cycle. In patients with a modified implantation window, VBT was adjusted in subsequent cycles based on the personalized WOI identified by ERA (pVBT). VBT performed before ERA was defined as previous VBT.

Endometrial biopsies were collected from the uterine cavity with the use of Pipelles catheter on day Progesterone + 5 in a Harmone Replacement Therapy cycle.The day of endometrial biopsy in HRT cycle is after 5 full days of progesterone impregnation ,on 6^{th} day morning.After the biopsy,the endometrial tissue was transferred to a cryotube containing 1.5 ml RNA stabilizing agent,vigorously shaken for a few seconds, and kept at 4 degree centrigrade in refridgerator for 4 hours.The samples were then transported at room temperature to dualhelix and report was available after 2 weeks.ERA test diagnosed the endometrium to be receptive or non receptive.Non receptive endometrium was further classified as pre receptive or post receptive.Personalized embryo transfer was done in the subsequent cycles and the following were calculated - The pregnancy rates (PR) of previous VBT and pVBT were compared. Pregnancy outcomes of pVBT were also compared between patients in the non-displaced group and the displaced group. Clinical pregnancy was defined as the confirmation of a gestational sac in the uterine cavity by ultrasound analysis. Implantation rate (IR) was the number of gestational sacs observed by vaginal ultrasound at the fifth week of gestation. Ongoing pregnancy rate (OPR) was defined as each pregnancy showing a positive heartbeat at ultrasound after 12 weeks of gestation. Clinical miscarriage rate was the number of spontaneous pregnancy losses in which one or more gestational sacs were previously observed. Ectopic PR was the number of pregnancies outside the uterine cavity, diagnosed by ultrasound, surgical visualization, or histopathology. Cumulative ongoing pregnancy rate (COPR) was the number of patients with ongoing pregnancy. The pregnancy outcomes of all recruited patients were followed up until September 2021.

III. DISCUSSION

The human endometrium is a dynamic tissue; it undergoes changes at multiple levels during the menstrual cycle in response to ovarian hormones and paracrine secretions. The endocrine and paracrine secretions control gene expression of the different endometrial cell types.

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The proliferative phase, controlled by estrogen allows for the proliferation of stromal cells and glands and elongation of the spiral arteries. The postovulatory progesterone rise brings about secretory changes and the endometrium acquires a receptive phenotype permitting implantation of the blastocyst. This period of receptivity is known as the "window of implantation" (WOI). The WOI opens on day 19 or 20 of the cycle and remains open for just 4–5 days at the time when progesterone reaches peak serum concentrations. During the phase of receptivity, the endometrium undergoes morphological, cytoskeletal, biochemical, and genetic changes to become functionally competent. The ability to identify the endometrial WOI in the clinical setting would enhance the outcome of fertility treatments such as IVF.

The ERA test hints at the volatility and dependency of the results on the methods used to test the genes, the complexity of the mathematical model, the methods and timing of biopsy, corrective methods to the biopsy material, relationships to preovulatory progesterone levels (which are overlooked in most studies) and the validity of displacing the WOI in successive cycles by only 12–24 h. In addition, the implantation process includes crosstalk between the endometrium and the embryo before and during invasion Diedrich et al., 2007(2). This includes many distinct embryonal stages like apposition, adhesion and invasion which are regulated by many genes over a restricted period of days. The biopsies for gene expression evaluation are done on an endometrium that has not been affected by the embryo-endometrial crosstalk, which represents an obvious limitation of the whole concept. The transcriptomic signature of the WOI can be used to define an individual's personalized receptive window for use in IVF.Identifiying Endometrial receptivity changes in unexplained infertility,endometriosis,and other causes of infertility would help in providing treatment more efficiently.

The introduction of microarray technology has enabled rapid progress in the understanding of many biological functions and disease processes. Computing Omics with bioinformatic predictors has improved the diagnosis and subsequent treatment in diseases such as cancer.Success in this area coupled with identification of the transcriptomics of the receptive endometrium during natural and stimulated cycles led to the development of a molecular diagnostic test to identify the WOI – ERA.In the era of personalized medicine, a "one size fits all "policy is no longer acceptable. In IVF individualized ovarian stimulation, protocols are being promoted to optimize treatment. For lack of an objective and accurate test endometrial receptivity remained a gray area. ERA is a step forward in improving IVF results through identification of the WOI and personalizing embryo transfer. The test has been shown to be accurate and reproducible and does not have the limitation of inter cycle variability.

Much of the implantation process still remains to be unraveled. It has to be remembered that the embryo remains a major player in this equation and genetic testing of the embryo with array comparative genomic hybridization has shown improved IRs.However, there are no reports suggesting a 100% success even after doing a pET with a euploid embryo. Maternal factors especially the immune system involvement needs to be understood.

A study by Yuta Kasahara et al(3) demonstrates that personalized Vitrified BlastTransfer guided by ERA tests may improve pregnancy outcomes in RIF patients whose window of implantation (WOI) is displaced, and its effect may be more pronounced at the first personalized Vitrified BlastTransfer. The displacement of WOI may be considered to be one of the causes of RIF, and its adjustment may contribute to the improvement of pregnancy outcomes in RIF patients.

In a study conducted by Nalini Mahajan(4) et al displaced WOI was found more frequent in patients with RIF and it was concluded that it could be a responsible factor for their repeated implantation failure.

In a 5-year multicenter randomized controlled trial conducted by simon et al (5) comparing personalized, frozen and fresh blastocyst transfer cumulative pregnancy rate was significantly higher in the PET (93.6%) compared with FET (79.7%) ($P = 0.0005$) and fresh embryo transfer groups (80.7%) ($P = 0.0013$) .It demonstrates statistically significant improvement in pregnancy, implantation and cumulative live birth rates in PET compared with FET and fresh embryo transfer arms, indicating the potential utility of PET guided by the ERA test at the first appointment.

Similarly in a study conducted by hashimoto et al(6) for patients with unexplained RIF concluded that 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.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.

A study was conducted by Hromadova et al(7) to find out the percentage of patients with a non-receptive endometrium in the time of ERA and to learn what part of them got pregnant after the identification of their personalized implantation window. To achieve the clinical pregnancy 1.5 frozen embryo transfer in average was needed.A displaced implantation window was found in more than 1/3 of patients undergoing an assisted reproductive treatment. After the personalized FET the clinical pregnancy was noticed in 69.2% of them. This result supports an individual approach to patients in IVF programme besides other at the timing of embryo transfer after the identification of pWOI.

Clinical efficiency of embryo transfer performed in receptive vs non receptive endometrium diagnosed by the endometrial receptivity array test was conducted by Ruiz et al(8),study demonstrated that embryos transferred in a NR endometrium diagnosed by ERA have lower IR and PR and in this retrospective series never produced a live birth, whereas when a personalized ET is performed in the R endometrium, clinical results were above the standard (45% IR, 60% PR, and 74% OPR). These results highlight the relevance of the endometrial factor and its personalized diagnosis in ART.

Carrie Riestembery et al(9) conducted a study to compare the live birth rate between patients who undergo personalized embryo transfer (pET) after endometrial receptivity array (ERA) versus frozen embryo transfer (FET) with standard timing in first single euploid FET cycles. To report the rate of displacement of the window of implantation (WOI) in an infertile population without a history of implantation failure.The live birth rate did not differ between patients who underwent FET with standard timing and patients who underwent ERA/pET, 45/81 (56.6%) and 83/147 (56.5%), respectively.Their study does not support the routine use of ERA in an unselected patient population undergoing first autologous single euploid programmed embryo transfer.

IV. CONCLUSION

ERA is the most objective and accurate test available today diagnosing endometrial receptivity.It has been used to define an altered WOI,and thus establish a personalized WOI for each patient.IT has shown benefit in improving reproductive performance in patients with RIF.However,more studies are required to confirm these initial findings.It is limited by its invasive nature and associated costs.

REFERENCES

[1]. AdamsonG , de MouzonJ , Chambers G , Zegers-Hochschild F , Mansour R , Ishihara O , Banker M ,Dyer S. International Committee for Monitoring Assisted Reproductive Technology: World Report on Assisted Reproductive Technology, 2011. Fertil Steril 2018;110:1067–1080

[2]. Diedrich C , Fauser BCJM , Devroey P , G riesinger G , Evian Annual Reproduction (EVAR) Workshop Group. The role of the endometrium and embryo in human implantation. Hum Reprod Update 2007;13:365–377.

[3]. Yutu Kasahara,Tomoko Hashimiti,Ryo Yokomizo,Yuya Takeshige,Koko Yoshinaga,Mayumi TOya,Hideki Igarashi,Hiroshi Kishi et al .Evaluation of pregnancy outcomes of vitrified-warmed blastocyst transfer before ans after endometrial receptivity analysis in identical patients with recurrent implantation failure.Fertility and reproduction vol 3,no,02.,pp.34-41(2021)

[4]. Nalini Mahajan et al.Endometrial receptivity array:clinical application. Endometrial receptivity array: Clinical application Journal of Human Reproductive Sciences · July 2015 DOI: 10.4103/0974-1208.165153

[5]. Simon C,Gomez C,Cabanillas S,Vladimmirov L,Castillon G,Giles J,Boynukalin K,Findikli N,Bahceci M,Ortega L et al. A 5-year multicenter randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF RBMO2020 41:402–415

[6]. Hashimoto T,Koizumi M,Doshida M,Toya M,Sagara E,Oka N,Nakajo Y,Aono N,Igarashi H,Kyono K.Efficacy of the endometrial receptivity array for repeated implantation failure in Japan:A retrospective ,two centers study.Reprod Med Boil 2017;16:290-296.

[7]. Hromadova L,Tokavera I, Vesela K, Travnik P , Vesely J.Endometrial receptivity analysis – a tool to increase an implantation rate in assisted

reproduction.Ceska Gynekologie – Czech Gynaecology 2019;84:177-183.

[8]. Ruiz – Alonso M ,Diaz-Gimeno P, Gomez E, Rincon-Bertolin A, Vladimirov Y, Garrido N, Simon C.Clinical efficiency of embryo transfer performen in receptive vs non receptive endometrium diagnosed by the endometrial receptivity array test.Fertil Steril 2014b;102:e292.

[9]. Carrie Riestenberg,M.D.,Lindsay Kroener,M.D.,Molly Quinn, M.D., Kaycee Ching,B.S.,Gayane Ambartsumyan,M.D.Routine endometrial receptivity array in first embryo transfer cycles does not improve live birth rate fertstert.2020.09.140 jan 15,2021.