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ENHANCED OUTCOMES IN RECURRENT IMPLANTATION FAILURE: A CASE STUDY ON THE APPLICATION OF ENDOMETRIAL RECEPTIVITY ANALYSIS (ERA)

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ABSTRACT

This article addresses the impact of the endometrial receptivity array (ERA) methodology to increase implantation success rate after several implantation failure on embryo transfer. The cause of this failure may vary from the assumed inconsistency of the endometrial biopsy, the variable number of genes found to be dysregulated in endometrium samples without the embryonal-induced effect. This review aims to investigate if ERA was effective in optimizing the reproductive outcomes in a systematic way. As controlling for the embryo's quality would allow for a more accurate assessment, we only analyzed the effects of ERA in euploid embryo transfer (EET) cycles. The intra-patient variations in the test need to be addressed. In summary, like all other add-ons, it is doubtful whether the ERA test use can significantly enhanceimplantation success rates. **Summary:** Couples could be counselled to undergo ERA during assisted reproductive technology treatment if a number of failed implantations in assumed inconsistency of the endometrial biopsy, the variable number of genes found to be dysregulated in endometrium samples without the embryonal-induced effect. At presentIn summary, like all other add-ons, it is doubtful whether the ERA test use can significantly enhance implantation success rates, but in this particular study, the result was satisfactory, although the outcome of further research is awaited.

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INTRODUCTION

Recurrent implantation failure (RIF) presents a significant challenge in the field of reproductive medicine, affecting a considerable number of couples undergoing in vitro fertilization (IVF).RIF is a failure to achieve a pregnancy following 2–6 IVF cycles, in which more than 10 high-grade embryos were transferred to the uterus was defined by various clinicians as RIF (Tan *et al.*, 2005). Treatment of infertile couples has progressed immensely during recent years. More than 3 million ART cycles are now reported each year worldwide (ICMART 2022) with a reported 769 977 babies born. Registry figures are thought to represent around 75% of all ART treatments. Thus, around 4 million ART cycles are estimated each year, with about 1000 000 babies born. The most 'officially' active countries in the world are Japan (454 893 cycles in 2018) (Ishihara et al., 2021) and the USA. (www.cdc.gov/art). However, according to the ICMART data China is now performing around 1 000 000 cycles per year (ICMART 2022). The Endometrial Receptivity Analysis (ERA) is a sophisticated diagnostic approach designed to pinpoint the optimal timing for embryo transfer, thereby enhancing the chances of successful implantation and live birth rates in in vitro fertilization (IVF) treatments. Initially conceived to aid patients experiencing recurrent implantation failure, the utility of ERA has expanded to benefit a broader spectrum of IVF candidates (*Mahajan et al.).*

The ERA employs Next-Generation Sequencing (NGS) to meticulously analyze the expression levels of 238 genes that are crucial indicators of the endometrium's receptivity state. This comprehensive gene expression analysis facilitates a deeper understanding of the endometrial environment's readiness to accept an embryo (Ruiz-Alonso *et al.*, 2013). This case study illuminates the impact of integrating Endometrial Receptivity Analysis (ERA) into the treatment plan for a couple with a decade-long history of primary infertility attributed to both male and female factors.

Clinical Presentation

A 37-year-old female and her 47-year-old male partner were referred to our clinic, reporting a history of primary infertility lasting more than ten years. The female patient's medical examinationand ultrasound revealed anovulation, both ovaries with 2-3 AFC (Antral Follicle Count), a significantly low anti-Müllerian hormone (AMH) of 0.7 ng/ml indicating poor ovarian reserve and 3 to 4 small intramural fibroids. The male partner was diagnosed with severe asthenoteratozoospermia. Their journey through infertility treatments included over six IVF attempts across various countries, with no successful pregnancies. These attempts comprised one cycle in South Africa in 2015, two cycles in Angola in 2017 and 2018, and three cycles in India during 2021 and 2022. All attempts resulted in recurrent implantation failure (RIF) with poor embryo quality.

Chronology of past failed implantations cycles history

In October 2015, two blastocysts' embryos were transferred, on day 12th post ET, her β-hCG result was 0.2. mlU/mL. During 2017 patient stimulated, 6 oocytes collected out of them only 2 fertilized and transferred on day 3, luteal phase support of progesterone 400mg/day was given, β-hCG realized on day 15th post transfer result was 0.5mlU/mL. On July 10th, 2021, the patient underwent a hysteroscopic myomectomy to remove two submucous fibroidsand endometrial scratching prior to embryo transfer. Still in 2021, she underwent two IVF cycles; the first using her own eggs and the second utilizing oocyte donation (OD), patient underwent a hysteroscopic myomectomy to remove two submucous fibroids and endometrial scratching prior to embryo transfer. The first with own oocyte had a β-hCG result of 3 mlU/mL, and the second using egg donor the result was 1mlU/mL. In 2022, they underwent three additional stimulations using a novel protocol aimed at poor ovarian responders called "pooling," an alternative method devised to improve IVF outcomes by accumulating oocytes over multiple cycles. This approach was based on the Bologna criteria for poor responders (Frattarelli et al. (2008a). Despite this strategy, only one egg was retrieved in each of the cycles conducted and two Blastocysts grade 4AB was transferred in November 2022 which resulted in a negative pregnancy test with β-hCGof1mlU/mL.

Investigation and Clinical Outcomes

In the clinical investigation of this case, the initial step involved conducting an Endometrial Receptivity Analysis (ERA), which indicated that the patient's endometrium was post-receptive. This suggested a displacement in the window of implantation. The gene expression profile from this analysis recommended a follow-up endometrial biopsy to be performed one day earlier than the initial one (P+4), aiming to refine the embryo transfer timing based on a more accurate assessment of endometrial receptivity. Despite the specific recommendation derived from the ERA results for a personalized approach to embryo transfer, the patient elected to proceed with the embryo transfer as initially planned. This decision resulted in a negative pregnancy outcome, as confirmed by a subsequent β-hCG test. A second ERA test was then conducted, with the biopsy taken on March 21, 2023. The results, which were available on March 31, 2023, identified the endometrium as being in a pre-receptive phase. Based on this finding, it was advised to adjust the embryo transfer timing to the period between the two analyzed biopsies (108 ± 3 hours), aiming to target the precise window of implantation more accurately. Following the recommendations from the second ERA, the embryo transfer was executed within this newly identified optimal timeframe. This strategic adjustment led to a successful pregnancy, as evidenced by a positive β-hCG reading of 617mlU/mL. A viability ultrasound performed five weeks later confirmed the success, revealing a single intrauterine gestational sac with a detectable fetal heartbeat.

DISCUSSION

The ERA has emerged as a pivotal tool in identifying the optimal window of implantation (WOI), a period during which the endometrium is most receptive to embryo implantation. This case illustrates the utility of ERA in adjusting embryo transfer timing based on the endometrium's receptivity profile, leading to a successful pregnancy after several failed attempts. The successful application of ERA in this case highlights its value in identifying the optimal window for embryo transfer in patients with RIF. This molecular diagnostic tool, by elucidating the endometrium's receptivity status, facilitates a more personalized approach to IVF treatments. The discussion extends to the broader implications of ERA's use, supported by evidence from clinical trials and studies demonstrating its efficacy in improving live birth rates for patients undergoing IVF, particularly those with a history of RIF.(Diaz-Gimeno, et al.). Studies support the premise that ERA-guided personalized embryo transfer protocols significantly improve outcomes for patients with previous implantation failures, underscoring the potential for ERA to enhance clinical practice (REFDiaz-Gimeno, et al.) Despite its demonstrated benefits, the application of ERA in routine IVF practice remains a subject of debate (Díaz-Gimeno et al. 2013). Critics argue that the technology may not be universally beneficial, particularly for patients without a history of implantation failure. Simon et al. (2018) suggest that the utility of ERA may be most pronounced in a subset of patients with recurrent implantation failure, especially those with otherwise unexplained infertility and multiple failed IVF cycles despite the transfer of euploid embryos. This case reflects the targeted application of ERA, providing valuable insights into its potential to address specific patient needs.

CONCLUSION

This case study substantiates the importance of adopting a personalized approach in the treatment of infertility, especially for couples experiencing RIF. The integration of ERA into the diagnostic and treatment arsenal for IVF represents a significant advancement in reproductive medicine, offering renewed hope and improved outcomes for patients struggling with the challenges of achieving successful implantation and pregnancy. Finally, the successful use of ERA in this case invites further exploration into its broader applicability, including its potential integration into standard practice for all patients undergoing IVF. Also, further randomized controlled trials are needed to fully understand the scope of ERA's benefits across different patient populations.

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