Review Article

Endometrial Receptivity Analysis (ARA) in Women with Repeated Implantation Failure (RIF) Under Intracytoplasmic Sperm Injection (ICSI): A Review

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Abstract

Endometrial receptivity is the key factor of successful implantation that ties directly to achieving pregnancy. In many decades, well-meaning endeavors aimed at untangling the myriad biological mazes concerning not just endometrial receptivity but also embryo implantation have borne fruit in terms of knowledge. However, that knowledge does not translate into effective practices in the clinic and indeed actual challenges posed by Repeated Implantation Failure within the wider context of Assisted Reproductive Technology. Here, Intracytoplasmic sperm injection (ICSI) proved to be a significant helper where successful implanted embryos did not materialize over several attempts repeated implantation failure (RIF) varied greatly between different populations and was something eventually found out to be an extremely complicated etiology involving multiple factors. This literature review puts together all the study results about endometrial receptivity analysis, showing important markers, molecular interactions, and possible treatment plans; at the same time finding gaps in knowledge and suggesting paths for future study. It also combines recent research findings on endometrial receptivity analysis (ERA) and what it means for making outcomes better in women with RIF who are going through ICSI.

Keyword: Endometrial receptivity analysis, Repeated implantation failure, Intracytoplasmic sperm injection, Assisted reproductive technology.

Introduction

Successful embryo implantation primarily depends on the receptivity of the endometrium. [1] Also noted that though several markers of endometrial receptivity have been associated with pregnancy outcomes, their ability to predict such outcomes is often limited. This observation therefore pushes the need for more molecular tests capable of providing more reliable prognostic information about endometrial receptivity [1]. The complex molecular communications that constitute endometrial receptivity involve a blend of hormones, cytokines, and growth factors. These are discussed by Singh et al. [2], who further indicate why implantation managers have not yet been extensively researched as potentially improving treatment regimens. Dekel et al. [3] also pointed out how knowledge about mechanisms that make an injured endometrium act receptive could be useful in delivering assistance when clinically practicing reproductive technologies. Embryo implantation forms a significant part of reproduction and compromise in this step is mainly responsible for loss of pregnancy. Synchronized development of an embryo competent for implantation and the differentiation of the uterus to the receptive state

are crucial in this process [4]. The endometrium can only be described as receptive for limited time periods shall we say, roughly at day 4.5 of pregnancy in mice when it was tested. During the implantation window in mammals, many characteristic changes in morphology occur in the uterus that is indicative of the uteri becoming receptive for embryo implantation [5, 6].

Chronic endometritis (CE) is a very common finding in the population of women with RIF. Studies have reported that about 30.3% of these patients can be diagnosed with CE. Investigations revealed that CE is associated with low implantation rates, hence it is presumed to be involved significantly in condition RIF [7]. Results regarding the treatment of CE proved promising, leading to better clinical pregnancy and live birth outcomes in subsequent In Vitro fertilization (IVF) cycles when treated with antibiotics [7,8]. This shows why assessment of the uterine environment is necessary before further attempts at ART are made; this assessment should include hysteroscopic evaluation for underlying infections [7].

There have been strides in the understanding of endometrial receptivity, but several gaps persist. The relationship between levels of progesterone and endometrial receptivity regarding RIF should be further explored, especially concerning the timing of the interventions. Also, the molecular mechanisms leading to endometrial deregulation in patients with RIF and Recurrent Miscarriage (RM) require thorough exploration so that possible measures can be developed [2]. Personalized approaches such as ERA may have potential, but big-scale studies are needed wherein trials on various populations test these claims. Studies in future also need to focus on how advanced maternal age affects endometrial receptivity and development interventions for ameliorating declines in fertility that are associated with increased maternal age [9].

Genetic and Molecular Biomarkers

Recent studies have the focus of genetic biomarkers related to endometrial receptivity. A meta-signature of genes is presented by Altmäe et al. [10], capable of serving as biomarkers in the evaluation of endometrial receptivity, offering valuable insight into its molecular underpinnings. Results indicate that promising technology for genetic profiling can be used to inform treatment strategies in fertility management and possibly make approaches in reproductive health more personalized. Embedding such results, development on microRNAs regarding embryo implantation unfolds as another prospective research area [11]. Liang et al. [12] suggests that the appraisal of endometrial microRNAs could evolve into non-invasive biomarkers for receptivity assessment, therefore increasing precision in assessments carried out within assisted reproductive technologies. The insertion of molecular biology into the analysis of endometrial receptivity stands vital to better fertility outcomes.

Integrins have therefore emerged as major players in the window of endometrial receptivity, perhaps the best-known one being the αvβ3 integrin. It can be said that women with normal expression of these proteins have much higher rates of clinical pregnancy and live births compared to those with low expression, hence suggesting that integrin assessment may be used in future as a test to identify women who are at risk for implantation failure during ICSI cycles [13]. Letrozole is also suggested to work therapeutically by upregulating the integrins and making the endometrium more receptive improving all aspects of IVF result. This requires prospective studies to validate this intervention

RIF management when applied within ICSI protocol [14].

Another important analysis looked at the endometrial gene expression profiles of women who have RIF and RM against a backdrop of fertile controls. The notable differences in gene expression seen signify periconceptional endometrial deregulations which may lead to implantation failure. This study highlights particular cellular functions and pathways that get altered in patients with RIF and RM, implying that such molecular changes might act as indicators for evaluating endometrial receptivity. Knowing these variations is key for creating focused treatments meant to enhance implantation success [15].

The successful result of in vitro fertilization (IVF) greatly relies on the development of a chromosomally normal embryo and its implantation into a receptive endometrium. Preimplantation genetic testing for aneuploidy has formed the basis of widespread acceptance to ascribe viability to embryos. The Endometrial Receptivity Array (ERA) did so since 2011 by providing useful information regarding whether or not optimal timing for endometrial receptivity to an embryo, or the "window of implantation," is present. Molecular arrays used in ERA analyze endometrymal proliferation and differentiation aiming at screening inflammatory markers. Unlike PGT-A, there is some controversy regarding the utility of ERA in the scientific community [16]. Most studies that have questioned the efficacy of ERA concluded that it does not improve pregnancy outcomes in patients who harbor good prognosis. In contrast, studies that included the ERA in patients with repeated implantation failure and the transfer of verified euploid embryos showed better outcomes [17].

Addressing Clinical Challenges

The clinical challenge seen often in failure of implantation is primarily due to poor receptivity of the uterus. In this study, Hashimoto et al. [18] assessed the performance of the endometrial receptivity array (ERA) as a diagnostic tool for patients with recurrent implantation failure. Their results showed that the ERA could significantly increase success rates of embryo transfers by allowing personalization of treatment approaches. The same paper also put forth, Ruan et al. [19], a discussion on what role ion channels may play in modulating endometrial receptivity; thus, finding and suggesting biomarkers through which implantation could be improved. Grasping such molecular mechanisms clearly is fundamental towards crafting both diagnostic and therapeutic interventions.

Another major factor that plays a role in endometrial function and receptivity is aging; particularly, women who are ICSI participants. Results from studies correlate advanced maternal age with alterations in endometrial biology that might plaque receptivity resulting in failure of implantation. This clearly indicates the need for future investigations concerning the mechanisms on how the older female participants have to undergo RIF regarding endometrial aging and its fertility effects [20]. Improvements under declines related to age regarding endometrial receptivity are needed ART outcomes.

Impact of Reproductive Disorders

Another major area is the impact of diseases, like endometriosis, on receptivity. In this review by Lessey et al. [21], they show how endometriosis may cause progesterone resistance and hence, affect receptivity as well as fertility. This underscores the potential detraction that unites the systematic need for a thorough

assessment of endometrial receptivity in contemporary disorders of reproduction. Further, Šalamun et al. [22] study GLP-1 effects on endometrial quality and receptivity in PCOS-affected women. Their results also highlight that metabolic factors significantly influence endometrial receptivity; therefore, probable therapeutic channels could indeed be tested.

High progesterone levels during controlled ovarian stimulation (COS) have been proven to adversely affect embryo quality, mainly the development of optimal blastocysts, which are very important for successful implantation. From this study, we can advocate for continuous monitoring of progesterone levels throughout any IVF cycle and accordingly advise a freeze-all strategy whenever there is elevated progesterone so as to optimize endometrial receptivity in subsequent cycles [23]. This major finding thus demonstrates a very critical gap in our understanding of the fine links that exist between progesterone dynamics and endometrial receptivity in the setting of RIF .

Endometrial receptivity is related to ovarian steroids, estrogen and progesterone, and their downstream mediators. The actions of these steroids are mainly on the nuclear receptors: estrogen receptor and progesterone receptor, with E2 predominantly using ERα over ERβ and the latter for PR. As transcription factors, these nuclear receptors then organize the expression of multiple molecules under them that include adhesion molecules, homeobox genes, matrix metalloproteinases or MMPs, LIF among many others [24].

The embryo implant within described as three phases during the so-called window; pre-implantation on day 4, peri-implantation on day 5, post-implantation on day 6 in gestating mice. Molecules characteristic of endometrial receptivity such as E-cadherin show high expressions where HoxA10 displays low levels of expression at all these key times relative to this process. For example, the expression of E-cadherin which β-catenin positively regulates reaches a high point during pre-implantation where it functions as an adhesion molecule promoting homotypic adhesion among the epithelial cells at the closed lumen of the mouse uterus. After pre-implantation this expression gets down regulated very much to allow trophoblastic cell invasion [25].

IVF/ICSI protocols using GnRH analogues merit attention primarily for their effects on endometrial receptivity. The antagonist protocols seem to reduce the risk of hyperstimulation without apparently compromising the clinical outcome. This is of great importance to women with RIF as to optimize endometrial receptivity, it is mandatory to have appropriate stimulation protocols [26]. The future studies should be directed toward finding out the specific effects of these protocols on endometrial receptivity.

Endometrial Receptivity Array (ERA)

The endometrial receptivity array (ERA) has come to be regarded as a useful diagnostic test for optimizing the timing of embryo transfer in women with RIF. Preliminary data support the notion that personalized embryo transfer (pET) according to ERA results may improve implantation success by aligning transfer with the individual receptivity profile of the endometrium [18, 27]. This individualized approach may lead to better clinical outcomes and, thus, underscores the need for personalized strategies in the effective management of RIF.

The Endometrial Receptivity Array (ERA) has been considered as a new molecular diagnostic test that finds the best time for embryo transfer by studying the gene expression profile of endometrial tissue. This large review looks at the

importance and use of ERA in cycles of euploid embryo transfer, where correct chromosomal number embryos are essential for successful pregnancy outcomes. It therefore improves implantation rates and decreases pregnancy loss by evaluating development, methodology, clinical applications, effectiveness, and challenges of ERA. Key findings show that ERA has much better accuracy in spotting the implant window than old ways; this leads to better results in ART cycles [28]. Even with such good results, the review acknowledges other challenges like cost, accessibility, and no standardization. Recommended clinical practices emphasize integrating ERA into routine ART protocols, patient counseling—comprehensive and multidisciplinary collaboration. This review has outlined promising prospects that include technological advances to make ERA more cost-effective, the development of refined gene expression profiles, and the potential integration with other emerging ART technologies [29].

Research has also brought up the fact that immune dysregulation could be involved in RIF. One study, however, proved the efficacy of immunosuppressive treatment tacrolimus on those women having high T helper cytokine ratios implying that immune response modulation would result in better pregnancy outcomes [30]. Otherwise, the relationship between immune factors and embryo implantation is not well explored but brings potential for new therapeutic applications upon revealing these dynamics. The endometrial microbiome now gains growing interest in RIF. Recent research has outlined successful implantation as potentially influenced by microbial welfare and individual bacterial species related to reproductive success [31, 32]. In brief, this research could prove that bacterial imbalance contributes to RIF and thus visit changes might be considered a breakthrough solution for dysfunctions during implantations.

Preimplantation genetic screening (PGS) by array comparative genomic hybridization (CGH) has been proved to the method of choice for better outcomes in women with RIF. Transfer of euploid embryos has been correlated with improved pregnancy rates, thus confirming the role of genetic factors in successful implantation [33]. This finding lays the basis for genetic screening to be integrated as a standard treatment protocol within RIF management and again calls for personalizing approaches in ART. Emerging therapies that go beyond conventional treatments and improve pregnancy rates in women with RIF include intrauterine platelet-rich plasma infusions (PRP) treatments [18, 34]. This would mean PRP infusions improve uterine conditions favorable to implantation. Personalized embryo transfer, or pET, takes into consideration the results of ERA and improves results of patients with RIF. The authors consider the result of this study as a further step in confirming that the correct identification of the BIM is ICSI cycle gives the best opportunity for successful embryo transfer. This would then mean a personalized approach to improving endometrial receptivity [35].

Conclusion

Endometrial receptivity analysis will prove to be a rather complicated and dynamic area with great promise for improving fertility outcomes. Merging molecular biology, genetic profiling, and cutting-edge diagnostics is likely to push the frontier of knowledge and management of endometrial receptivity. Bridging these gaps while also opening new research avenues would mean a lot toward improving clinical practices in reproductive health that serve individuals on their path to conception. The management of

repeated implantation failure as a multi-faceted challenge calls for an integrated approach. Research results put at the fore at improvement of implantation outcomes, addressing chronic endometritis, optimizing receptivity per se, and immune & microbial considerations as determinants in achieving successful implantation. Future research shall fill these existing gaps in knowledge and formulate novel strategies for women suffering from RIF as the reproductive medicine arena progresses. Endometrial receptivity analysis provided an important chance to improve the clinical results of women with RIF getting ICSI. By combining results about integrin expression 3, progesterone 1 gene levels and 2 personalized embryo transfer ways we can take a step closer to better care for people with implantation problems. Ongoing study in these fields is key for creating focused treatments that help endometrial receptivity and overall success rates in assisted reproductive technologies.

Conflict of interest

None

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