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Endometrial receptivity: The omics revolution

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ABSTRACT

Infertility, affecting millions globally, remains a significant challenge despite advances in Assisted Reproductive Technologies (ART) over the past four decades. While the success rates have improved, many couples still face challenges in conceiving. A major contributing factor is the limited understanding of infertility causes and the inefficiency of available treatment solutions. This article delves into the intricate processes of embryonic implantation and endometrial receptivity, crucial aspects of successful pregnancy.

The emphasis is placed on the frequently overlooked endometrial environment in the context of *In Vitro* Fertilization (IVF) procedures. Traditional methods of assessing endometrial receptivity, such as histological examination and hormonal level monitoring, have proven insufficient.

In the last years, omics approaches have generated a vast amount of highly valuable information, contributing significantly to the comprehension of the endometrial environment necessary for successful embryonic implantation. Genomic studies have unveiled specific loci related to endometrial disorders, epigenetic regulation studies have identified distinctive signatures associated with receptivity and endometrial pathologies, proteomic analysis has revealed protein expression changes during the menstrual cycle and metabolomic signatures in endometrial fluid may offer a direct insight into tissue function. Among these methodologies, transcriptomic analysis stands out as the most advanced. Particularly, high-throughput methods have proven to be robust in assessing functional states and pathologies leading to the development of commercial tests that evaluate endometrial receptivity. Recent advancements in single-cell and spatial transcriptomics provide great potential for the advanced study of endometrial function.

Current and emerging technologies employed in the exploration of the uterine compartment exhibit significant promise for advancing diagnostic methodologies and therapies addressing infertility. Despite existing challenges, we believe that the key to optimizing ART success rates lies in advanced assessments of the endometrial environment. As technology continues to evolve, the possibilities of precision medicine and personalized approaches offer hope and new opportunities for couples pursuing parenthood.

KEYWORDS

Endometrium, Gene Expression Profiling, Reproduction, Pregnancy.

MANUSCRIPT

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility impacts millions of people worldwide. The World Health Organisation estimates that 1 out of every 6 people are affected by the inability to have a child at some point in their life; this is regardless of where they live and what resources they have.

The advent of ART technology and the improvements in reproductive medicine in the last 40

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years have made possible the birth of more than 8 million babies. Although pregnancy rates have improved significantly, still the efficacy of the cycles is quite low and many couples struggle to conceive. Out of the 2.5 million cycles performed annually, only one fifth result in the delivery of a baby. The main reasons behind this ineffectiveness are that the infertility causes are currently understudied and that the variety of treatment solutions available is still reduced and quite inefficient[1].

The causes of infertility are varied and often complex, affecting both, men and women. One of the most challenging situations is the treatment of couples experiencing repetitive implantation failure (RIF) and recurrent pregnancy loss (RPL). RIF refers to as the failure to achieve a clinical pregnancy after two to three transfers with good-quality embryos[2]. RPL is referred to when having two or more consecutive pregnancy losses[3].

It is well known that one of the key processes for the success of the treatment is the implantation of the embryo into the uterine lining, the endometrium. Embryonic implantation is a pivotal process in human reproduction, it occurs when the developing embryo attaches and embeds itself into the endometrium, marking the initiation of pregnancy. The significance of this process lies in its fundamental role not only in the establishment of pregnancy but also enabling its successful progression[4,5].

For successful embryonic implantation, two essential elements are required: a competent embryo and an endometrium ready to receive it. Implantation involves a complex molecular and cellular dialog between the embryo and the endometrial matrix. This interaction is essential for the apposition, adhesion and invasion of the blastocyst in the human endometrium[6].

The synchronization of embryo development with endometrial preparation is a critical aspect of implantation, this precise coordination is fundamental to the success of the pregnancy. Numerous morphological and functional changes must take place in these two structures so that implantation can occur. Both, embryo and endometrium, have to reach states of development that allow the molecular signalling and communication required for implantation success[7]. On one side, the embryo has to be at the blastocyst stage of development, as this stage is most conducive to implantation. On the other side, the endometrium needs to reach a status that warrants an optimal environment for embryo implantation. This period of time where the endometrium is receptive to the embryo is called the window of implantation[5].

In an IVF treatment, most of the attention is focussed on the selection of the most competent embryo to be transferred to the uterus, and little relevance is given to the study of the endometrial environment. Uterine ability to receive the embryo is not routinely assessed.

Numerous investigations have reported that endometrial receptivity plays a crucial role in implantation. However, the accurate identification of the window of implantation is challenging. The process of endometrial receptivity acquisition is extraordinarily complex and tightly regulated, it involves a finely tuned interplay of hormonal fluctuations, structural modifications and molecular changes. The influence of hormones, particularly estrogen and progesterone, is critical for preparing the endometrium and transitioning it into a receptive state. Additionally, local factors like cytokines and growth factors also play a role in communication between the embryo and the endometrium[6].

Traditional approaches to endometrial evaluation, such as the histological examination of morphological changes in an endometrial biopsy or the monitoring of hormonal level changes in serum, do not seem to be accurate enough for the precise identification of the window of implantation. Other diagnostic methods like ultrasound, MRI, or advanced high-resolution ultrasound have been suggested as potent tools for evaluating endometrial tissue. Nevertheless, the predictive value of these techniques in anticipating endometrial receptivity or IVF outcomes remains unclear[8]. Hence, more sophisticated tests are necessary to ascertain the optimal timing for embryo transfer. Monitoring molecular alterations in the endometrium throughout the implantation window could offer a more dependable option compared to traditional morphological methods.

In the last years there has been a remarkable advancement in the techniques available for the study of the molecular mechanisms that underlie cell function, tissue physiology and hence the origin of disease. New tools generally grouped under the term of “omics” have been developed for the study of the genome, the transcriptome, the proteome, the epigenome and the metabolome, in some cases at the single cell level, as individual profiles or in combination (multiomic approaches)[9]. The advancements on bioinformatics analysis, artificial intelligence (AI) and algorithms for prediction, are very valuable tools for the analysis, interpretation and description of all data produced by these approaches, and also for its integration for the study of the interactome, the complete set of interactions of a particular tissue or system. The knowledge generated by these technologies is crucial for the advancement in our understanding of the tissues and the development of better diagnostic methods and treatments.

These powerful tools are being applied in many areas of medicine. In the field of reproduction, the study of the endometrium and the process of embryo implantation is starting to be deciphered by the application of these omics tools. Several groups have studied how the changes in morphology and function associated to endometrial pathologies or the process of endometrial receptivity acquisition are also reflected in changes in the genes, proteins and metabolites[10].

Genomic studies of the human endometrium are mainly focussed on GWAS approaches and have revealed specific loci or genomic alterations related to endometrial disorders such as endometriosis or endometrial cancer[11]. No genomic studies have been published so far for the prediction of endometrial receptivity.

Epigenetic regulation studies, however, have shown specific epigenetic signatures associated with variations in the expression of genes critical for the establishment of endometrial receptivity and also some associated with endometrial pathologies[12]. Other gene expression regulatory elements such as lncRNA, sncRNA and miRNA have also been found to be differentially expressed at different endometrial stages (secretory vs proliferative), receptivity status or reproductive conditions. It has been suggested that the identification of aberrant miRNA expression levels in serum may allow for clinical diagnosis of fertility and receptivity[13,14].

Proteomics has also been applied for the study of endometrial receptivity. Early research observed notable protein expression changes between the proliferative and secretory phases in fertile women. Despite some controversy due to differences in the proteins identified, certain proteins consistently found in various studies, which align with transcriptomic data, are deemed significant for endometrial receptivity[15].

In addition, the analysis of endometrial secretions has also been explored as an approach to study the uterine compartment. Analyses of the endometrial fluid composition though different spectrometric approaches along the menstrual cycle, in fertile and infertile women, or in different receptivity stages, have also shown differential profiles of secreted proteins[16]. Recently, Azkargota et al.[17] confirmed different protein composition of the endometrial fluid from implanting versus non-implanting IVF cycles, indicating the existence of endometrial status more favourable to implantation.

Metabolomics analyses have also been performed in endometrial samples in search for new biomarkers of endometrial receptivity with potential usefulness in the clinical context. The metabolome provides a more direct view of cellular function compared to the genome, transcriptome, or proteome. Despite its potential, its utilization in discovering new biomarkers for endometrial receptivity is not as advanced as other omics approaches. Unlike analysing tissues, the more commonly conducted metabolic analysis are based on biofluids, such as endometrial fluid. Endometrial fluid not only encompasses proteins but also includes lipids and other released metabolites within the uterine cavity. Lipidomic studies have shown variable levels of prostaglandins across the menstrual cycle, during the WOI, in endometrial disorders or RIF patients[18].

The transcriptomic analysis of the endometrium has been widely applied for the characterization of the molecular changes that underlie the morphological and functional modifications that this tissue experiments during the menstrual cycle, beginning initially with microarray studies[19], then applying high throughput RT-qPCR[20], RNA-sequencing[21] or microRNA sequencing[22]. Differential gene expression profiling has been described by many authors in different endometrial stages, pathologies, or treatments[21, 23–25].

Variations in the number and list of regulated genes exist among studies, mainly due to differences in experimental design, technology and sample processing. Despite these disparities, several studies and literature reviews aim to identify common regulated genes as potential biomarkers for receptivity[26].

Most studies report upregulation in the mid-secretory phase of numerous genes linked to implantation, indicating the need for transcriptional activation in the receptive endometrium. Overexpressed genes play crucial roles in implantation-related functions, including cell adhesion, lipid metabolism, ECM remodelling, immune response, intracellular signalling and response to external stimuli. Conversely, downregulated genes often encode DNA binding proteins, transcription factors, DNA-modifying enzymes or genes with unknown functions[15, 20].

The transcriptomic approach to the study of the endometrial tissue has been shown to be quite robust for the evaluation of functional states. A few diagnostic tools based on the application of transcriptomic technologies have been developed. Five molecular methods based on the transcriptomic analysis of the tissue have been published in peer reviewed papers and are currently commercially available for assessing endometrial receptivity. They allow the diagnosis of endometrial alterations as a cause of infertility diagnosis and the personalised treatment of the disorder identified:

1. Win-Test. Analyses by RT- qPCR the transcriptomic signature of 11 genes specifically modulated during the WOI coupled with an algorithm to identify the receptive state[27].

2. ERA, endometrial receptivity array is a molecular predictive tool that identifies the gene expression of 238 genes and employs artificial intelligence to determine the receptivity status of an endometrium. It was initially implemented using microarray technology and has been currently modified to apply NGS[28].

3. ER Map uses high throughput RT-qPCR combined with a predictive modelling algorithm for the accurate determination of the WOI. This test evaluates the expression of 40 genes involved in the development and acquisition of endometrial receptivity[20].

4. BeREady Test utilises target allele counting by sequencing (TAC-seq) to estimate the original molecule counts of mRNAs of 57 endometrial receptivity genes that have been identified as biomarkers of the different phases of the menstrual cycle[29].

5. The rsERT, combines the evaluation by RNA-Seq and machine learning of 175 biomarker genes to predict the WOI period and guide embryo transfer. This test has shown to improve the pregnancy outcomes of patients with RIF[30].

These tests offer valuable insights into the molecular status of the endometrium and its receptivity. By tailoring the timing of embryo transfer to the individual's receptivity profile, clinicians can optimize the chances of successful implantation and pregnancy in assisted reproductive treatments. The use of transcriptomics in endometrial receptivity assessments has proven more objective and concordant than traditional methods. The application of these tools has shown improvements in the results of the assisted reproduction treatments; some studies have emphasized the importance of precise and personalised analysis of the endometrium to achieve better implantation and pregnancy rates and also to reduce miscarriage rates[4,27,28,30]. This precision enables clinicians to tailor the timing of embryo transfer to an individual's receptivity profile, thereby optimizing the prospects of successful implantation and pregnancy in assisted reproductive treatments.

Endometrial receptivity tests have also been proven instrumental in the characterization of pathologies and the identification of specific molecular signatures associated with infertility complications such as RIF, endometriosis and RM, showing the power of these approaches for the understanding of infertility cases, its adequate diagnosis and further treatment[21]. Nevertheless, some controversial findings in the application of these tests have also been published[31].

Endometrial receptivity tests present a revolutionary stride in understanding endometrial receptivity, however, their clinical application is not without challenges. A more profound characterization of the menstrual cycle and of the molecular mechanisms behind endometrial receptivity are crucial for understanding how the normal endometrium is regulated and synchronised with the developing implanting embryo. This knowledge together with the ongoing evolution of technology is key for refining these tests, enhancing their accuracy and minimizing limitations. A nuanced approach, evidence-based guidelines, and a focus on refining methodologies will contribute to realizing the full potential of endometrial receptivity tests in improving fertility treatments and increasing success rates in implantation.

In recent years several groups are focussing on applying the latest technologies for the study of the human endometrium both in vivo and in vitro in an aim to understand tissues structure and physiology. The advancements in single cell transcriptomics have allowed high resolution transcriptomic-based molecular and cellular characterization of human endometrial transformation across the menstrual cycle providing insights into this essential physiological process. Wang et al.[32] studying endometrial biopsies from healthy ovum donors after the onset of their menstruation by single cell RNA-seq analysis have identified the specific profile of six cell types and the definition of 4 major transcriptomic phases across the cycle, one of them corresponding to the WOI. Their data suggest interesting functions of different cell types in the process of embryonic implantation such as immune cells in the decidualisation period.

Other high resolution approaches for the study of the physiology and disease of tissues include spatial transcriptomics. This technique opens up a unique opportunity to understand how tissues are structured and how cells interact with each other. The definition of the spatial arrangement of cells and their interaction in tissues as complex as the endometrium is key to define its function and physiology.

The Human Cell Atlas initiative aims to map all cells in the human body using genomic technologies[33]. In the case of the endometrium, the group of Roser Vento-Tormo have generated a cellular map of the human endometrium that account for the temporal and spatial changes of this tissue during the menstrual cycle [34]. They have used single cell and spatial transcriptional profiling to study endometrial biopsies for donors screened for potential endometrial disorders and the whole endometrium and myometrium of donors with non-gynaecological disorders. They reported spatio-temporal changes in gene expression characteristic of cell types and menstrual cycle stages as well as differential expression associated with specific endometrial disorders such as endometriosis or endometrial cancer. This specific and in depth

profiling of the uterus of healthy women and the establishment of the normal endometrium signature will serve as a reference for the study of endometrial disorders.

In addition to deepening our understanding of the molecular mechanisms underlying endometrial function, emerging technologies may offer exciting opportunities for the development of therapies for enhancing endometrial receptivity.

One promising approach explored recently involves the transplantation of mesenchymal stem cells (MSCs) into the endometrium as a strategy to address endometrial dysfunction. MSCs have the ability to differentiate into endometrial cells. Studies in animal models and clinical trials have demonstrated that this approach can augment endometrial thickness and receptivity[35]. The use of growth factors and cytokines has also been shown to have a significant impact in endometrial function and implantation[36]. Another very interesting approach that is being the focus of many research studies is the utilization of exosomes for the treatment of endometrial dysfunction. Exosomes are minute, membrane-bound vesicles released by various cell types, containing a diverse array of biomolecules, including proteins, lipids, and nucleic acids. Exosomes play pivotal roles in intercellular communication and the regulation of cellular functions, which can be used for therapeutic purposes. Current findings propose that exosomes may hold diagnostic and therapeutic promise in addressing endometrial dysfunction[37].

In the decades to come, new high-throughput omics technologies and therapies will enable a better understanding of the complex and dynamic changes involved in receptivity and implantation. Omics approaches are expected to innovate further, leading to a deeper and more holistic description of cell and tissue biology and transforming our understanding of health and disease. Progress is expected in various areas, such as enhancements in efficiency, cost reduction and the integration of several testing methods into a single assay. Improvements in computational approaches that allow integrated analyses across various modalities are also envisaged and will be crucial for uncovering interdependencies within and among each molecular layer. Additionally, making more commercially available high resolution methods such as single-cell and spatial multi-omics assays will enhance their accessibility and application by a broader research community. These advancements in technology and computation will ultimately lead to an improved comprehension of cell and tissue function. This will be key in deciphering the origins of pathogenesis and disease, establishing more effective diagnosis methods and therapeutic approaches and providing guidance for precision medicine.

The field of ART needs to increase its success rate, patients deserve to be offered effective treatments, established after adequate diagnosis of the origin of their difficulty to conceive. It would be advisable for health professionals, and scientists, to explore new ways of improving success rates, by applying new approaches to increase implantation and thus reproductive outcomes, especially in complex cases such as RIF patients, unexplained infertility or RM. These couples are exposed to repeated cycles of assisted reproduction techniques with small success rates, producing in them not only high levels of psychological stress but also intense financial pressure. Advancements in the study of uterine environment and personalised approaches resulting from the knowledge that is expected to be generated in the coming years will enhance the chances of implantation success, offering hope and new possibilities to couples on their journey to parenthood.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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