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MOLECULAR MARKERS OF ENDOMETRIAL RECEPTIVITY IN CLINICAL PRACTICE: POSSIBILITIES AND LIMITATIONS OF APPLICATION

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ABSTRACT

Endometrial receptivity is regarded as one of the key conditions for successful embryo implantation, especially in assisted reproductive technology programs. Even after the transfer of morphologically high-quality embryos, pregnancy does not always occur, which increases interest in evaluating the endometrium as an independent factor influencing reproductive outcomes. The formation of a receptive state is associated with the coordinated action of hormonal regulation, immune responses, cytokine signaling, gene expression, microRNAs, protein molecules, and the local microbiota. In this regard, molecular markers of receptivity are increasingly considered as a tool for clarifying the “window of implantation” and personalizing management strategies for patients with implantation failure. The aim of this review is to analyze the possibilities and limitations of using molecular markers of endometrial receptivity in clinical practice. The review considers the main groups of markers, including transcriptomic, proteomic, immunological, epigenetic, and microbiome indicators, as well as diagnostic approaches based on their assessment, including ERA and similar molecular tests. It is shown that these methods expand the understanding of the functional state of the endometrium and may be useful for individualized embryo transfer planning; however, their clinical significance remains a matter of debate. The limitations of their application include variability of results, dependence on the day of the cycle, the influence of hormonal protocols, inflammatory processes, and concomitant gynecological diseases, as well as insufficient standardization of data interpretation. It is concluded that molecular assessment of endometrial receptivity has potential for personalized reproductive medicine, but it cannot be considered a universal method for predicting implantation without taking into account the clinical context, embryo quality, and the patient’s condition.

KEYWORDS: endometrial receptivity, assisted reproductive technology, implantation, molecular markers, ERA, microRNAs, microbiota.

INTRODUCTION

Infertility remains a serious problem in reproductive medicine and continues to affect a significant number of couples. According to various estimates, approximately 8–12% of couples of reproductive age experience difficulties with conception, while recent reports indicate rates as high as 15–17% [2]. At the same time, some patients experience repeated unsuccessful embryo implantation attempts, which significantly reduces the effectiveness of assisted reproductive technologies and requires a more detailed understanding of the underlying causes [4].

Repeated implantation failure does not arise from a single factor but results from a complex interaction between the embryo and the endometrium. In clinical practice, this means that pregnancy may not occur even when embryos are of good quality [5]. In such cases, attention is increasingly focused on the condition of the

endometrium, primarily on its ability to “accept” the embryo. This refers to endometrial receptivity, a temporary and functional state in which conditions are created for blastocyst attachment and subsequent invasion [6]. Implantation itself is not a single-stage process. It includes several sequential stages: embryo adhesion, trophoblast invasion, and endometrial remodeling. Their normal progression requires the coordinated action of hormonal, immune, and molecular mechanisms. The so-called “window of implantation” is considered especially important: a short period in the secretory phase of the cycle when the endometrium is most sensitive to the embryo [10]. However, this period may shift or be functionally incomplete, becoming one of the causes of implantation failure. Despite significant progress in IVF and improvements in embryo quality, successful implantation rates remain far from ideal. This indicates that the problem lies not only in the embryo but also in the condition of the endometrium [13–15].

An analysis of current studies shows that increasing attention is being paid specifically to molecular markers. They are considered a possible way to determine whether the endometrium is ready for implantation not by indirect signs, but at a deeper level. This is not limited to a single indicator but includes a whole group of markers, such as genes, including HOXA10, cytokines such as LIF, adhesion molecules, microRNAs, and even features of the microbiota [14]. The emergence of molecular tests such as ERA has become an attempt to move from subjective assessment to more accurate and personalized diagnostics. However, their use in clinical practice still raises questions. Study results remain heterogeneous, and data reproducibility is limited. In addition, many studies have been conducted on small samples, which reduces their evidentiary value. The dependence of results on population and ethnic characteristics is also noted, which complicates the universal application of the obtained data [20].

As a result, the current picture remains rather contradictory: the mechanisms are actively studied, but clear approaches to their interpretation in clinical practice have not yet been established [22–25]. This makes the topic of molecular markers of endometrial receptivity in clinical practice relevant, since their potential is evident, but practical application remains limited. The aim of this review is to analyze current data on molecular markers of endometrial receptivity and to assess their possibilities and limitations in clinical practice in the treatment of infertility and repeated implantation failure.

CLINICAL SIGNIFICANCE OF ENDOMETRIAL RECEPTIVITY IN INFERTILITY

Endometrial receptivity is currently considered one of the decisive factors influencing the outcome of infertility treatment, since implantation does not always occur even after the transfer of high-quality embryos [17]. Despite the development of assisted reproductive technologies and improvements in embryo handling methods, consistently high pregnancy rates have not yet been achieved, which makes it necessary to search for causes related to the endometrium. The focus is now gradually shifting toward molecular mechanisms, although until recently the main emphasis was placed on morphology [19]. Several factors are being considered simultaneously: endometrial gene activity, microbial composition, and changes in hormonal status. However, in real clinical practice, these approaches are still used to a limited extent, since the data are not always consistent and do not produce the same results in different patients [20].

A number of authors, including Gokhberg Ya.A. et al., described the use of ERA as a method that allows more accurate determination of the optimal time for embryo transfer. This approach is based on the analysis of gene activity in the endometrium, which makes it possible to assess its functional state. According to the authors, the use of ERA is associated with an increased implantation rate and a reduced risk of miscarriage. At the same time, it is noted that the method remains limited in availability and requires further improvement. The same study also revises the earlier concept of uterine cavity sterility. Modern research methods have shown that the endometrium has its own microbiota [26]. Its composition is directly associated with pregnancy outcomes. Thus, when Lactobacillus predominates, the probability of successful implantation is higher, whereas increased diversity of other microorganisms is associated with reduced implantation efficiency and a higher risk of pregnancy loss. Other authors, Moreno I. et al., conducted a clinical study involving 106 women with recurrent pregnancy loss, most of whom were diagnosed with chronic endometritis. Microbiota analysis revealed the presence of Escherichia coli in 33% of patients, Chlamydia trachomatis in 30%, and Klebsiella pneumoniae in 23%. After antibacterial therapy, an increase in pregnancy and live birth rates was observed, indicating the significant role of inflammatory changes in the endometrium. Individual observations show that disruption of microbial balance affects not only the condition of the mucous membrane but also the molecular mechanisms of implantation. In particular, the expression of integrin αvβ3 and LIF changes, which may interfere with normal embryo attachment [25].

At the same time, a clinical study by Tkachenko A.A. et al., which included 320 patients, showed that embryo transfer performed with regard to the individual window of implantation determined using ERA can noticeably improve treatment outcomes. The pregnancy rate in this group reached 77.9%, whereas with the standard approach it was 57.6% ($p = 0.0007$). Similar differences were observed for other indicators: implantation occurred more often (54.1% versus 39.4%, $p = 0.0009$), and the live birth rate was also higher (71.3% versus 39.4%, $p < 0.0001$). These results are consistent with the data of Voros C. et al., who emphasized in their review the significance of molecular mechanisms of receptivity, including the role of microRNAs, in improving implantation efficiency and IVF outcomes.

An analysis of a larger sample of 3,605 patients showed that personalized embryo transfer has the greatest effect in women with repeated implantation failure. In this group, the clinical pregnancy rate increased to 62.7% compared with 49.3%, and the live birth rate increased to 52.5% versus 40.4%. In addition, a decrease in early pregnancy losses was observed. These findings are complemented by the results of Salmasi S. et al., who associate

changes in endometrial receptivity with the regulation of molecular pathways, including the involvement of microRNAs that influence implantation processes and pregnancy development. Overall, it has been established that with increasing patient age and a greater number of previous failed IVF cycles, displacement of the window of implantation is observed more often. This may explain the reduced effectiveness of standard treatment protocols and emphasizes the need for an individualized approach when choosing the timing of embryo transfer.

PHYSIOLOGY AND MECHANISMS OF ENDOMETRIAL RECEPTIVITY FORMATION

Today, endometrial receptivity is increasingly regarded as one of the main factors determining whether implantation will occur, since even a high-quality embryo does not guarantee pregnancy. In real clinical practice, the effectiveness of assisted reproductive technologies still remains far from the desired level, and this is largely related to the fact that embryo development does not always coincide in time with endometrial readiness [30]. Normally, the uterine mucosa becomes "receptive" only for a short period known as the window of implantation, during which the probability of embryo attachment is highest. During this period, various changes take place: endometrial tissue undergoes remodeling, pinopodes appear, adhesion molecules and signaling substances are activated, and the immune system shifts toward a more tolerant state [32–35].

However, in IVF cycles the situation may differ, because hormonal stimulation changes the natural hormonal background, and as a result, the window of implantation may sometimes shift or become less pronounced. Interestingly, studies on this issue show different results: some authors report impaired receptivity, whereas others do not find significant differences compared with the natural cycle [29]. Increasing attention is now being paid not only to morphology but also to molecular processes, such as gene activity, microRNAs, progesterone receptor function, and the composition of the endometrial microbiota. There is evidence that the predominance of Lactobacillus is associated with a higher probability of successful implantation.

In the review by Li J. et al. (2025), it is emphasized that the assessment of receptivity should take into account several levels at once, from genetic activity to biological markers, as this may help determine the optimal timing of embryo transfer more accurately. In addition, inflammation and hormonal disturbances should not be overlooked, as they may interfere with the normal endometrial response to progesterone and impair its preparation for implantation. Khamoshina M.B. et al. (2025) note that progestogens affect not only the structure of the endometrium but also immune processes, reducing inflammation and creating more favorable conditions for implantation. In essence, receptivity cannot be reduced to a single indicator; it is the result of the interaction of several systems at once. Hormones, cellular signals, and the immune response all matter here. If even one of these elements fails, implantation may be affected.

MOLECULAR MARKERS OF ENDOMETRIAL RECEPTIVITY: MAIN GROUPS AND THEIR CHARACTERISTICS

The formation of endometrial receptivity is associated with sequential changes during the menstrual cycle. First, the endometrium proliferates under the influence of estrogens; then, after ovulation, it enters the secretory phase under the influence of progesterone, and it is during this period that it becomes capable of accepting the embryo. If this phase transition is disrupted, implantation may fail even when the embryo is of good quality [19]. Decidualization is considered an important stage, during which stromal cells transform and create conditions for embryo invasion. At the same time, blood supply increases, vascular permeability changes, and local immune mechanisms are activated. Molecular factors also play a significant role: in the receptive endometrium, the expression of integrins, LIF, and HOXA10 increases, all of which are involved in adhesion and interaction with the trophoblast [28].

The "window of implantation" is considered separately as a short period in the middle of the secretory phase when the probability of embryo attachment is highest. In different women, this period may shift, which partly explains failures in IVF. In addition to hormonal and molecular processes, immune responses and the endometrial microbiota are also important [36]. The predominance of Lactobacillus is believed to be associated with more favorable outcomes, whereas dysbiosis is accompanied by inflammation and reduced receptivity. Overall, endometrial receptivity is formed through the interaction of hormones, cellular changes, and molecular signals, and even minor disturbances in these systems may affect the outcome of implantation.

MODERN METHODS FOR ASSESSING ENDOMETRIAL RECEPTIVITY: ERA, GENETIC, AND PROTEOMIC TESTS

Modern approaches to assessing endometrial receptivity have changed considerably: the focus is now increasingly shifting from morphology to molecular and genetic data, as shown in Table 1, which presents the characteristics of different tests [37]. In particular, the TAC-seq method has been proposed; it allows fairly accurate quantification of transcript numbers and, therefore, assessment of the expression level of key genes associated with receptivity. To process such data, the beREADY model was developed; it does not simply compare indicators but classifies samples according to stages of receptivity based on their genetic profile.

Table 1: Modern Methods for Assessing Endometrial Receptivity

Method	Type of Analysis	Number of Genes/Markers	Advantages	Limitations

ERA	Transcriptomics, microarray	≈238 genes	Personalization of the window of implantation	Invasiveness, controversial effectiveness
WIN-Test	qPCR	≈11 genes	Rapid analysis	Lower accuracy
ERPeak	qPCR	≈40 genes	Balance between accuracy and cost	Limited marker panel
TAC-seq, beREADY	RNA + UMI	Extended panel	High accuracy, elimination of PCR-related errors	Limited availability
RNA-seq	Whole transcriptome	Thousands of genes	In-depth analysis	High cost
Proteomics	Proteins/cytokines	Dozens to hundreds	Functional assessment	Limited standardization
Extracellular vesicles	RNA without biopsy	Hundreds of genes	Non-invasive approach	Still at the research stage
Endometrial organoids	In vitro modeling	—	Study of mechanisms	Not a clinical method

Interestingly, this approach does not work with individual markers but with whole gene sets, which makes it possible to capture gradual changes in the endometrium rather than only its "final" states. Unlike classical tests such as ERA, which analyzes approximately 238 genes, or more compact panels such as WIN-Test and ERPeak, this method uses a combination of markers selected through meta-analysis and supplemented with regulatory genes [40]. An important advantage of TAC-seq is the use of UMI tags, which help avoid errors associated with PCR amplification and provide a more accurate picture of gene expression. In a broader sense, transcriptomic studies have helped explain why even high-quality embryos do not always implant: much depends on the state of the endometrium, not only on the embryo. This is why research attention has gradually shifted toward maternal factors, including the genetic activity of tissues and their molecular readiness for implantation.

In addition, new models, such as endometrial organoids, have begun to be actively studied. This is shown in the work of Wang R. et al. (2023), where such models are used to reproduce receptivity processes in vitro more accurately. This makes it possible to observe how endometrial cells respond to hormones and embryonic signals, which was previously almost impossible.

Special attention should also be paid to studies devoted to impaired gene expression in endocrine disorders. For example, Díaz-Gimeno P. et al. showed reduced activity of IL-10, STAT3, HOXA10, and ITGB3, which is directly associated with impaired implantation. These data once again confirm that receptivity is not a single indicator but a whole network of interconnected processes. At the same time, the clinical use of tests such as ERA remains controversial: despite their popularity, some studies show that embryo transfer strictly based on test results does not always improve outcomes and sometimes does not produce the expected effect. This encourages the search for alternative or complementary methods, including proteomic and multi-omics approaches.

Analysis of endometrial extracellular vesicles is considered a promising direction, as it allows RNA assessment without invasive biopsy and may potentially enable diagnosis within the same cycle as embryo transfer. This approach identifies hundreds of genes with different expression patterns in women with successful and unsuccessful implantation, including previously unstudied transcripts. Non-coding RNAs are of particular interest because they may participate in signaling between the endometrium and the embryo and influence implantation processes.

Proteomic methods are also developing in parallel, allowing the assessment of protein markers and signaling molecules and complementing genetic data. It is important that gene expression is organized as coordinated networks rather than separate isolated processes; therefore, assessment should be comprehensive. Khamoshina M.B. et al. (2025) also made a separate contribution by showing that progestogens affect not only morphology but also the molecular and immune mechanisms of endometrial receptivity. As a result, it becomes clear that modern assessment methods are no longer just individual tests but a whole set of technologies that gradually bring personalized approaches closer to routine reproductive medicine.

Clinical Application of Molecular Markers in ART Programs

Maintenance of normal DNA methylation depends on the coordinated interaction of processes responsible for the addition and removal of methyl groups, and this balance directly affects the state of the endometrium and its readiness for implantation. Methyl groups are added to DNA by DNMT enzymes, whereas demethylation systems associated with TET proteins can remove or modify them; if DNMT1 activity is reduced, methylation marks may also gradually disappear passively [11]. During early embryonic development, almost all methylation "settings" are essentially erased, after which a new epigenetic profile is formed and then maintained during cell division. In the endometrium, the activity of DNMT3A and DNMT3B enzymes varies depending on the phase of the menstrual cycle, indicating that methylation is not static but is continuously remodeled together with gene expression [18]. The transition of the endometrium to a receptive state is accompanied by changes only in certain DNA regions,

but these regions are involved in key processes such as immune response, angiogenesis, cell adhesion, and extracellular matrix remodeling. When these epigenetic mechanisms are disrupted, for example through hypermethylation of the HOXA10 gene, normal implantation may be impaired, contributing to infertility. In clinical practice, this is already being considered in ART programs: molecular markers, including epigenetic changes, are increasingly used to assess receptivity and select the optimal timing for embryo transfer. Klimczak A.M. et al. showed that regulation through m6A methylation affects the estrogen–progesterone balance and is directly associated with the formation of endometrial receptivity.

From a clinical perspective, this is also important because in conditions such as polycystic ovary syndrome, hormonal dysregulation may alter gene expression and epigenetic profiles, worsening ART outcomes. Palomba S. et al. (2024) emphasize this issue when discussing therapeutic options and approaches to correcting receptivity. Thus, epigenetics should not be viewed merely as a background mechanism, but as a clinically relevant tool for assessing and potentially correcting the endometrial state, which is gradually being incorporated into personalized approaches to infertility treatment.

Limitations and Challenges of Using Molecular Markers in Clinical Practice

Despite active research into molecular markers, their practical application in ART still faces several limitations, and, as shown in Table 2, the results of different studies often do not coincide. For example, it has been shown that the levels of microRNAs and piRNAs in the culture medium may indeed reflect embryo quality, but these indicators are difficult to standardize and apply in routine practice [3]. Even when an association between the expression of certain molecules and blastocyst development is identified, the question remains as to how reproducible these data are across different laboratories and clinics.

Table 2 — Limitations and Challenges of Introducing Molecular Markers into Reproductive Medicine

Method / Marker	Type of Analysis	Clinical Application	Advantages	Limitations	Level of Evidence
ERA	Transcriptom ics, 238 genes	Determination of the window of implantation	Personalized embryo transfer	Invasiveness, controversial effectiveness	Moderate
miRNA, including miR-30d, miR223	Posttranscriptiona l analysis	Assessment of receptivity	High sensitivity	High variability	Low to moderate
piRNA	Non-coding RNAs	Assessment of embryo quality	Promising approach	Insufficient data	Low
LIF	Protein marker	Implantation	Key factor	Depends on multiple factors	Moderate
HOXA10	Gene expression	Endometrial receptivity	Association with hormonal regulation	Epigenetic variability	Moderate
VEGF	Angiogenesis	Endometrial blood supply	Important for implantation	Non-specificity	Moderate
Endometrial microbiota	Microbiome	Prediction of implantation	Novel approach	Lack of standardization	Low to moderate
Extracellular vesicles	Non-invasive RNA analysis	Diagnosis of receptivity	Minimal trauma	Experimental stage	Low

The situation is further complicated by the fact that implantation outcomes are influenced not only by the embryo but also by the endometrium, whose molecular profile constantly changes depending on the phase of the menstrual cycle. Studies of microRNAs have shown that their levels may fluctuate significantly even within a single cycle, making it difficult to determine the “ideal” moment for diagnosis [9]. This reduces the reliability of markers, since the same indicator may be interpreted differently depending on the timing of sample collection. Another problem is that many molecules, such as miR-30d or LIF, are indeed involved in implantation, but their effects are ambiguous and depend on many accompanying factors, including hormonal status and immune system activity. As a result, the same marker may show both positive and negative associations with pregnancy achievement.

It should also be noted that even widely used tests such as ERA do not provide a universal effect: Richter K.S. emphasizes in his review that improved outcomes are not observed in all patients, especially in cases of euploid embryo transfer. The ESHRE recommendations (2023) also indicate that molecular testing should be limited to specific clinical situations, such as repeated implantation failure. In addition, most methods are based on endometrial biopsy, which makes them invasive and requires a separate diagnostic cycle, increasing the burden on the patient. This, in practice, limits the broad implementation of such technologies, especially in standard ART protocols. Overall, these markers cannot yet be considered a universal tool. They provide valuable information,

but their use in real clinical practice remains complex: results may vary, and interpretation is not always straightforward.

Prospects for Development and Directions for Further Research

Current research on endometrial receptivity is increasingly shifting from the study of individual markers toward a more integrated understanding of this process. A personalized approach is becoming increasingly important, in which the timing of embryo transfer and treatment strategy are selected individually for each patient [41]. The development of high-precision genetic methods, including RNA sequencing and other transcriptomic technologies, remains a promising direction, as these approaches may allow more accurate determination of the window of implantation. At the same time, the search for new biomarkers capable of reliably predicting ART outcomes continues, since the existing indicators do not yet provide stable results.

As shown in Figure 1, the current direction of research is increasingly focused on multi-omics approaches that combine genomic, proteomic, and metabolomic data for a more complete assessment of the endometrial state. For this reason, receptivity is no longer considered a single isolated indicator. Rather, it is regarded as the result of multiple interacting processes that occur simultaneously and influence one another.

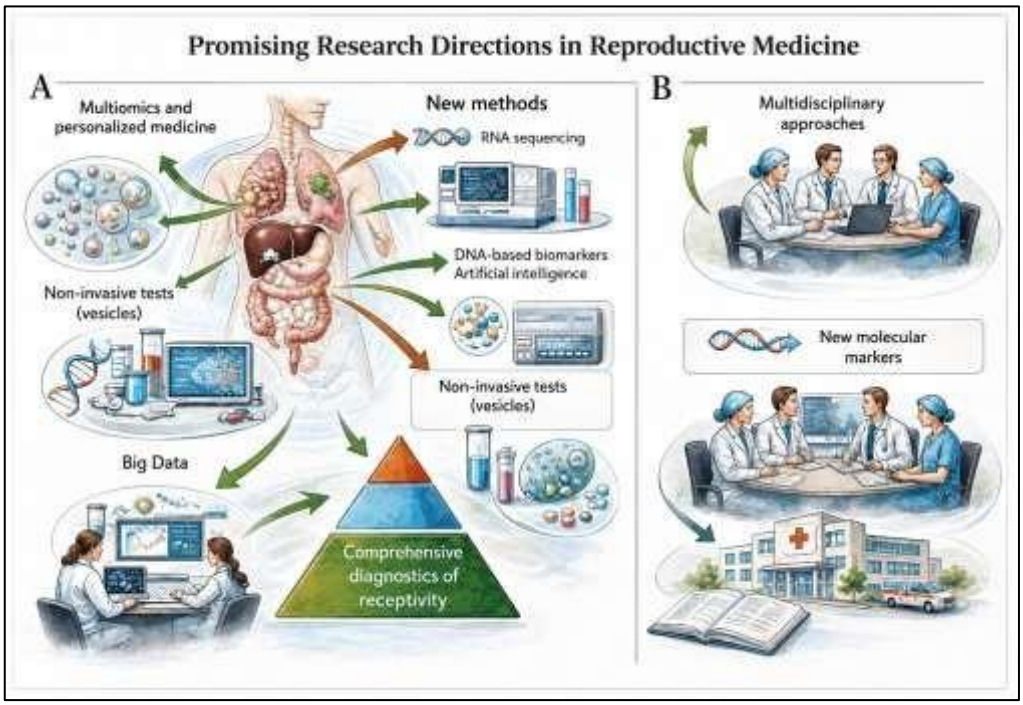

Figure 1 — Innovative Methods and Research Directions in Reproductive Medicine

An equally promising direction is the development of non-invasive diagnostic methods, including the analysis of endometrial fluid and extracellular vesicles, which may make it possible to avoid biopsy [42]. This approach can simplify diagnostics and make it more accessible for clinical use. Special attention is also being paid to the endometrial microbiota, since its composition, as current studies show, affects implantation and pregnancy development. In the future, this may lead to the development of new methods for correcting microbial balance in order to improve the effectiveness of ART programs. The studies by Zhylkybaeva I. et al. (2025) and Osakhtieva N.M. et al. (2025) emphasize the need for a comprehensive assessment of the endometrium, taking into account morphological, molecular, and immunological factors. At the same time, large randomized studies remain necessary to confirm the clinical significance of new technologies and determine their place in clinical practice. Further research will focus on the development of more accurate, accessible, and reproducible methods for assessing endometrial receptivity, which may improve the effectiveness of ART programs and reproductive outcomes.

CONCLUSION

Endometrial receptivity is formed through the coordinated interaction of hormonal, immune, genetic, epigenetic, and microbiome-related mechanisms; therefore, it cannot be assessed using a single isolated indicator. Molecular markers allow for a deeper analysis of the endometrial state, help clarify possible causes of implantation failure, and support individualization of embryo transfer strategies. At the same time, their use in clinical practice has limitations: results depend on the day of the cycle, the hormonal preparation protocol, inflammatory changes, concomitant diseases, and the quality of laboratory interpretation. Therefore, molecular diagnostics of receptivity may be a useful tool in personalized reproductive medicine, but it should not be regarded as a universal prognostic

criterion. The most justified approach is a comprehensive assessment in which molecular marker data are compared with the clinical picture, endometrial condition, reproductive history, and embryo quality.

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