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REVIEW PAPER/GYNECOLOGY

Personalized embryo transfer (pET) guided by endometrial receptivity (ER) assessment — a possibility to increase effectiveness of IVF procedures. Review of available methods

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ABSTRACT

The continuous development of assisted reproductive techniques (ART) implies the search for solutions that could increase the effectiveness of available methods. In the context of *in vitro* fertilization (IVF), a significant proportion of failures are due to unsuccessful embryo transfers. At this stage the most important issue is proper dialogue between implanting embryo and the maternal endometrium. Therefore, it seems justified to assess endometrial receptivity (ER), defined as the tissue's ability to accept an embryo to attach and invade into the mucosa. Window of implantation (WOI), is a certain period in which implantation of the properly developed embryo is possible. The cause of endometrial receptivity disorders is believed to be the disturbed expression of cytokines and endometrial surface proteins, the presence of which has been proven in commonly diagnosed diseases such as endometriosis or chronic endometritis. Despite many years of research on endometrial receptivity, the area of diagnostic methods enabling clinical monitoring of ER still remains undeveloped. The aim of

this study is to review the utility of selected markers and the available methods of ER assessment, ranging from noninvasive ultrasound, through endometrial fluid analysis, to genomic studies based on endometrial biopsy, in order to increase the effectiveness of IVF. Such an approach could potentially be a significant step towards personalizing medical procedures especially in patients diagnosed with repeated implantation failure (RIF).
Key words: in vitro fertilization; embryo transfer; personalized medicine; endometrium; endometrial receptivity

INTRODUCTION

Reproductive health is undoubtedly one of the factors that constitute human well-being. The problem of infertility affects a significant percentage of the world's population. It significantly reduces the quality of life and deepens the demographic crisis [1]. According to World Health Organization (WHO) data between 48 million couples and 186 million individuals suffer from infertility globally. A properly running implantation process is essential in achieving clinical pregnancy. For many years, conducted research focused on embryonic defects as the main causative factor of implantation failure. The available *in vitro* fertilization (IVF)-related procedures allow the genetic selection of aneuploid embryos, but despite that fact the pregnancy rates remain at constant levels in recent years. It is estimated that the cause of implantation failure may be related to the condition of the endometrium in 2/3 of cases [2]. Endometrial receptivity (ER) is defined as the tissue's ability to accept an embryo to attach and invade into the mucosa resulting in establishing an ongoing pregnancy [3]. For fertilization to take place, the embryo at the appropriate stage of development must appear in the uterine cavity at a strictly defined, individually differentiated time called window of implantation (WOI), in which numerous hormonally controlled cellular, molecular and biochemical processes determine the proper development of the endometrium [4, 5]. In natural cycle, this period occurs in mid-secretory phase, between days 6–10 after ovulation and is limited to approximately 48 hours [6]. The cause of endometrial receptivity disorders is believed to be disturbed expression of cytokines and endometrial surface proteins. Such alternations were also observed in several conditions such as endometriosis or chronic endometritis (CE). Moreover, both aforementioned diseases are associated with higher prevalence of infertility resulting in necessity of ART implementation compared with the general population. The establishment of ER assessment schemes and their implementation as a constant element in IVF protocols poses an opportunity to synchronize the transfer with the individual moment of maximal endometrial receptivity of a given patient. Such personalized

embryo transfer (pET) is likely to increase the effectiveness of the procedure. The potential clinical benefits of endometrial assessment are numerous. It is believed that decreased or altered ER may be the cause of defective implantation, resulting in early pregnancy loss or further complications of the gestation as gestational hypertension or pre-eclampsia [7].

DESCRIPTION OF THE CURRENT STATE OF KNOWLEDGE

During the physiological menstrual cycle, the female endometrium cyclically proliferates, transformates and secrets under the influence of ovarian hormones. Biochemical and morphological changes, resulting in its thickening and a change in the pattern, lead to the normal receptivity [8]. The first attempts to assess the histological maturity of the endometrium and its correlation with the day of the onset of menstruation were made by Rock and Bartlett [9]. Their study showed 16% agreement of biopsy estimates with the actual occurrence of menstruation, 17% of patients had their periods later and 68% earlier than expected [9]. Based on these results, Noyes et al. [10] developed histological criteria on the ground of own studies, that have been the standard assessment of endometrial maturity for many years. With the introduction of new examination techniques and the emergence of requirements for an individual assessment of patients' endometrium in IVF procedures, the universal criteria for histological evaluation have become outdated and insufficient. Among others Murray et al. [11] showed that the histological dating of the endometrium is not sufficiently accurate and reliable to allow its clinical use in the management of patients with reproductive failure, as the variable duration of endometrial maturation applies to fertile women as well as to those with fertility disorders. Attention was paid to the individual variability and some systemic conditions that may reduce the credibility of obtained results.

Certain conditions may reduce ER and impair female fertility by shifting or narrowing the WOI. According to Zhao et al. [12] lower expression of Hypoxia-inducible factor-1α (HIF-1α) in patients with polycystic ovary syndrome (PCOS) might be the cause of endometrial disfunction, due to proven in previous studies crucial role of this protein in establishment of proper ER during WOI. Endometriosis, as a chronic inflammatory disease is proved to be associated with an overexpression of endometrial B-cell lymphoma 6 (BCL6) [13] as well as Sirtuin 1 (SIRT1) [14]. Both appear to be biomarkers of this disease and are key factors involved in the pathogenesis of progesterone resistance. Furthermore, according to Almquist et al. [15] overexpression of BCL6 is associated with poor pregnancy rates in IVF cycles. Histone deacetylase 3 (HDAC3) is shown in the study of Jae-Wook Jeong and his team [16] to be downregulated in endometrium of women with endometriosis. It is a causative

factor for increased fibrosis and disturbed hormonal impact on endometrium, that impairs its receptivity. This study also emphasizes the possibility that excessive fibrosis of various pathogenesis within the endometrium may translate into a decrease in ER and constitute one of the so far unexplored causes of infertility. Based on this discovery, a discussion about other potential causes of increased endometrial fibrosis has opened and sets trends in new research [17]. Described by Osiński et al. [18] significant increase in 3β-hydroxysteroid dehydrogenase type II (HSD3B2) and estrogen receptor 1 (ESR1) transcripts in follicular eutopic endometrium from infertile women with endometriosis might also have a negative impact on biological effect of E2 in endometrium, further impairing implantation mechanisms and the development of possible pregnancy. The inclusion of the indicated molecules in future tests may increase the prognostic value of ER assays. Also, chronic endometritis (CE), is characterised by an abnormal expression of cytokines and other molecules that regulate receptivity of the endometrium. The most sensitive way of diagnosing this pathology seems to be immunohistochemistry (IHC) for Syndecan-1 (CD138), a marker for plasmatic differentiation [19]. By examining seventy-five patients with CE and RIF Wang et al. [20] showed, that they have decreased endometrial TGF-β and IL-10 expression and increased IL-17 expression compared to patients with male factor infertility. The consequence is promotion of proinflammatory phenomena resulting in a defective ER.

Currently, wide range of methods to assess ER are available. From noninvasive ultrasound, through endometrial fluid analysis, search for biochemical markers or study of molecular markers in endometrial samples, to genomic studies based on endometrial biopsy. Ultrasonography is an easily accessible and universal tool enabling the assessment of the endometrium in the peri-implantation period. Evaluation of certain parameters in 3D power Doppler scans may add further benefits. In the study of Mercé et. al. [21] 80 infertile patients underwent their first IVF cycle. On the day of human chorionic gonadotropin (hCG) administration endometrial pattern, endometrial thickness, endometrial volume (EV), and PDA vascularization index (VI), flow index (FI), and vascularization flow index (VFI) were measured. Results showed that EV and 3D power Doppler indexes such as VI, FI and VFI are useful in assessing ER in IVF/ICSI and embryo cycles, as they were statistically significantly higher in the group of patients who became pregnant. However according to mentioned study there was no statistically significant difference in endometrial thickness and endometrial pattern between pregnant and nonpregnant groups. Similar data is provided by Rashidi et al. [22] in prospective study of 150 infertile patients undergoing IVF/ICSI. It concludes that the ultrasonographic characteristics of the endometrium, such as thickness and pattern on the day

of hCG administration, were of no prognostic value in terms of the occurrence of pregnancy. A potentially reliable source of information on the status of the endometrium is endometrial fluid, the relatively non-invasive collection of which, with proven pregnancy safety in this cycle [23], is a chance to assess the ER. A comprehensive proteomic analysis of human endometrial fluid aspirate led to the successful identification of 803 different proteins in the International Protein Index (IPI) human database [24]. It may constitute the basis for further research to detect reliable ER markers, but nowadays no grounds for introducing any specific marker into clinical diagnostics are available [25]. As a summary of described methods serves a study of Li Wang and colleagues [26], conducted on 396 women, half of whom were diagnosed with unexplained infertility, and the rest were fertile controls. The blood flow, endometrial thickness and EV did not differentiate patients from both groups, unlike VI, FI and VFI which were much higher in fertile patients. Also, the levels of markers obtained from the uterine fluid of the patients, including integrin avb3, VEGF, TNF-a, and LIF levels were significantly higher in the control group. The best parameters for predicting ER in WOI was FI (AUC = 0.894, sensitivity 93.8%, and specificity 83.1%) and among biomarkers integrin avb3 had the best predictive value, (AUC = 0.921, sensitivity 96.7%, and specificity 89.5%) [26].

The previous researches proved the purposefulness of endometrial biopsy analyzes in terms of the presence of molecular biomarkers and their possible correlation with the histological picture. Prospective case control study carried out by Franasiak et al. [27] proved that the usage of leukemia inhibitor factor (LIF) combined with αvβ3 integrin as biomarkers of ER can be useful in predicting poor reproductive outcomes in both monitored natural and stimulated cycles. Decreased concentration of both molecules was observed in women with unexplained infertility. Despite this, insufficient convincing evidence from the studies on larger sample size implicates the lack of clinical tests based on molecular markers.

A breakthrough in the approach to ER assessment and personalization of IVF procedures by determining patient's individual WOI, was the presentation by Diaz-Gimeno et al. [28] of a brand-new diagnostic test — endometrial receptivity array (ERA). It is based on the evaluation of 238 selected genes expression in endometrial sample and can determine endometrial status of the patient by comparing obtained results with control samples. Using this method, it becomes possible to detect WOI shifts in a patient and to synchronize the **ET [proszę wyjaśnić skrót??]** with the presence of endometrium at the time of its maximal receptivity. This enhances the probability of proper implantation and is a step towards personalizing medical procedures in order to increase the effectiveness of embryo transfer.

Another advantage of the ERA is the reproducibility of the results in the middle secretory phase in successive cycles or over long periods [29]. In randomized controlled trial conducted on 458 infertile patients undergoing IVF procedures, cumulative pregnancy rate was significantly higher in the pET guided by ERA testing (93.6%) compared with frozen ET (79.7%) and fresh embryo transfer groups (80.7%) [30]. Such results indicate the potential utility of pRT guided by ERA test at the first appointment.

A beREADY test based on the highly sensitive Targeted Allele Counting by sequencing (TACseq) methodology facilitates the ability to analyze the expression of 57 genes related to ER in endometrial sample [31]. All the genes are involved in endometrial growth, maturation and receptivity. Using robust rank aggregation analysis, a statistically significant meta-signature of 52 up-regulated and five down-regulated genes in mid-secretory vs ‘pre-receptive’ endometrium was identified [32]. The expression of among others membrane associated proteins, secreted enzymes, binding proteins, secreted immune response proteins, different enzymes, transcription factors is tested. A beREADY test provides 93% to 96% compliance with the ERA results and enables the classification of the patient's endometrium as pre-receptive, early-receptive, receptive, late-receptive or post-receptive [33]. As part of the result, the receptivity score, the recommended time of progesterone administration and the estimated time of obtaining receptivity in the case of pre-receptive results are determined. Therefore, it is possible to adjust the transfer day to the receptive period (WOI) and maximize the chances of successful implantation just as in case of exemplary Be-ready test result presented at Figure 1.

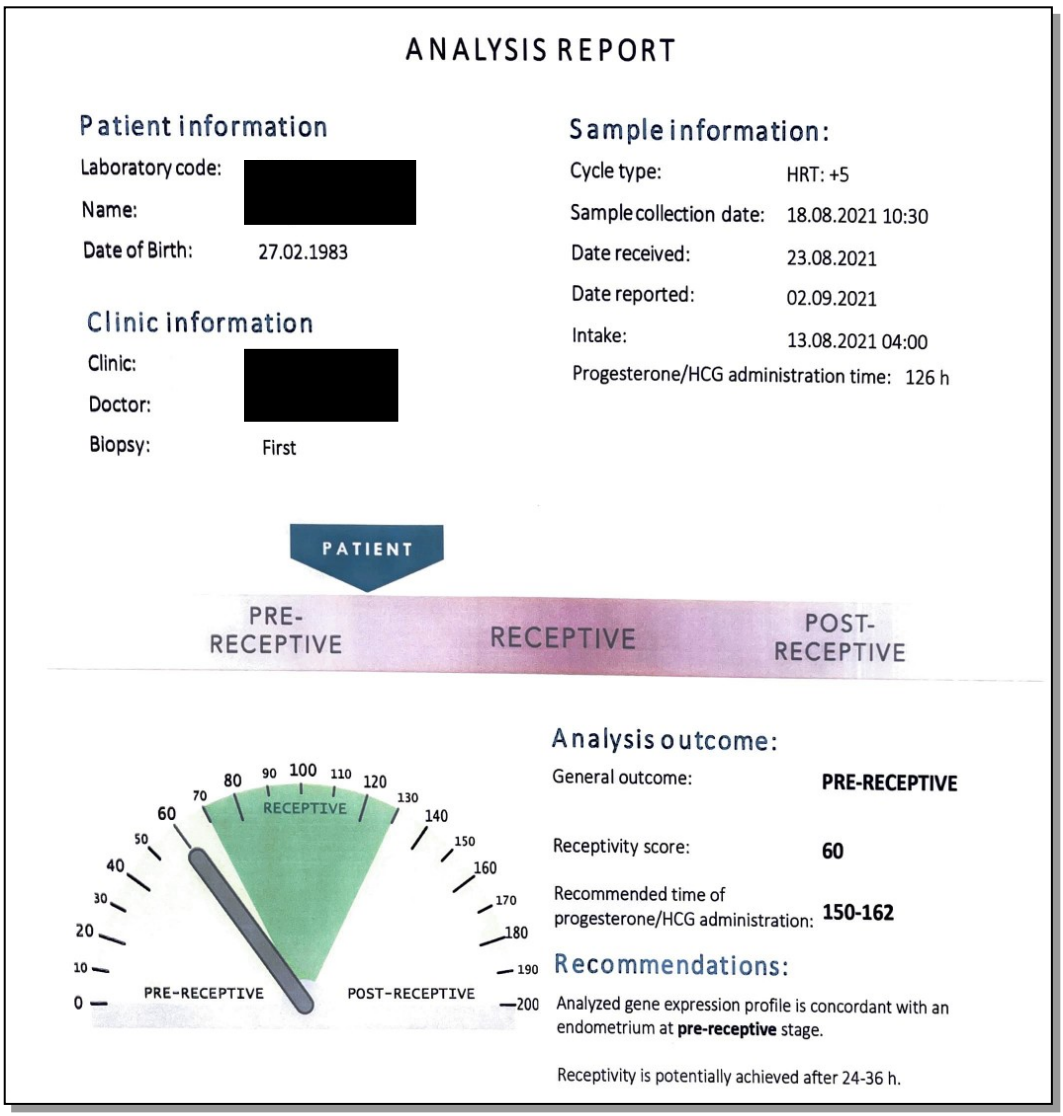

Figure 1. Exemplary Be-ready test result. Endometrium in a pre-receptive state; HCG — human chorionic gonadotropin

Testing for BCL6 overexpression in endometrial samples has high positive value for diagnosing endometriosis and associated progesterone resistance [34]. Both of them may lead to decreased ER. Moreover, according to Likes et al. [35] patients with detected BCL6 overexpression might benefit from medical or surgical treatment before undergoing IVF procedure by achieving higher live birth rates. The study proves that women with higher level of BCL6 in endometrial sample treated by medical suppression and those undergoing laparoscopy for endometriosis had a significantly higher LBR, (5/10; 50%; 95% CI 23.7 to 76.3%) and (11/21; 52.4%; 95% CI 32.4 to 71.7), respectively, compared to controls (4/54; 7.4%; 95% CI 2.9 to 17.6).

Table 1. Characteristics of papers included in the study

Mercé et.al.	Three-dimensional ultrasonography and power Doppler angiography (3D US-PDA) Parameters: endometrial pattern, ET, EV, PDA VI, FI, VFI	Spain	80 infertile women, mean (±SD) age (34.5 ± 3.5) (range: 27 to 41 years)	Endometrial or miometral anomalies Congenital uterine abnormalities	Chi-square test, Fisher's exact test Receiver operaing characteristic (ROC) curve	EV and the endometrial VI, FI, VFI – statistically significantly increased in the group of patients who became pregnant
Rashidi et.al.	Ultrasonography: Endometrial pattern, ET	Iran	150 infertile patients The mean ± S.D.) age was 30.8 ± 5 years	history of uterine surgery, uterine anomalies, endometrial pathologies, hydrosalpinges, tubal factor in infertility, abnormal laparoscopic findings	Chi-square test, Fisher's exact test Receiver operaing characteristic (ROC) curve	ET and endometrial pattern - no prognostic value in terms of the occurrence of pregnancy
Li Wang et.al.	Detection of uterine fluid biomarkers (integrin avb3, vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF-a), and leukemia inhibitory factor (LIF)) by enzyme-linked immunosorbent assay (ELISA) Three-dimensional ultrasonography and power Doppler angiography (3D US-PDA)	China	392 women (196 infertile, 196 fertile)	gynecological surgery, thyroid disease, pelvic inflammatory dis- eases, endometriosis	Chi-square test, Fisher's exact test Receiver operaing characteristic (ROC) curve	Blood flow of uterine artery and subendometrial region, ET, and EV did not differ between the two groups The endometrial VI, FI, and VFI and the integ- rin avb3, VEGF, TNF-a, and LIF levels in uterine fluid were significantly higher in fertile women com pared with unexplained infertile women (p < .05),
Franasiak et.al.	Endometrial biopsy - Immunohistochemistry (IHC) and messenger RNA by real time reverse transcriptase–polymerase chain reaction (PCR) (quantitative real-time reverse transcriptase–PCR)	USA	55 infertile women (1 year of unexplained infertility) 20 paid controls	PCOS , uterine fibroids Irregular menses Abnormal sperm parameters	Student's t-test using 95% confidence (P< .05) for significance, Fisher's exact test- comparisons of categorical data	leukemia inhibitor factor (LIF) combined with αvβ3 integrin - biomarkers of ER, usefulin predicting poor reproductive outcomes
Simón et.al.	Endometrial biopsy ERA test	Spain, Bulgaria, Turkey, Japan, Brasil, Belgium, Panama, Australia	458 infertile patients (pET guided by the ERA n=148, frozen embryo transfer (FET) n=154, fresh embryo transfer ET (n=156))	recurrent miscarriage, >3 failed IVF cycles with good-quality embryos Transferred, severe male factor infertility	Chi-squared test, two-sided Fisher's exact test to compare the study groups Differences were estimated as relative risks with 95% CI.	statistically significant improvement in pregnancy, implantation and cumulative LB rates in pET compared to FET and ET

EV — endometrial volume; VI — PDA vascularization index; FI — flow index; VFI — vascularization flow index; SD — standard deviation; PCOS — polycystic ovary syndrome; pET — personalized embryo transfer

CONCLUSIONS

A significant proportion of unsuccessful IVF procedures are due to missed embryo transfers. Implantation failure may be related to the condition of the endometrium in 2/3 of cases, what makes the assessment of ER potentially crucial in increasing the effectiveness of IVF. Reliable assessment of the endometrium could enable the embryo transfer personalization, contributing to the increase in the effectiveness of implantation and would lead to growth of pregnancy rates. Regarding to the cited research results presenting and evaluating the numerous available methods, it seems justified to propose a comprehensive assessment of the endometrium in order to guarantee patients the highest possible effectiveness of the IVF procedure. Methods based on the analysis of the genes expression related to endometrial receptivity seem to be the most objective and clinically useful. There are many studies on the effectiveness of ERA test, however, there still remain a need to evaluate the beREADY test clinical utility in randomized controlled trials.

Patients with a history of RIF in IVF procedures, as well as patients with endometriosis, in whom the exact mechanism of infertility is presumably multifactorial and has not been concretely defined, seem to be a particularly interesting target groups for further research. The potential clinical benefits of endometrial assessment are numerous, as it is believed that decreased endometrial receptivity may also be the cause of defective implantation, resulting in early pregnancy loss, or incompletely correct implantation leading to the development of pre-eclampsia.

Conflict of interest

All authors declare no conflict of interest.

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