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Factors influencing endometrial receptivity in women with recurrent implantation failure

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Abstract

Background Embryo implantation involves two key elements: a good quality embryo and receptive endometrium. Endometrial receptivity abnormalities are known as one of the possible causes of recurrent implantation failure (RIF), especially when the embryo is euploid. This study was aimed to evaluate the impact of age and other clinical factors on endometrial receptivity in women with RIF.

Methods 68 women with RIF (defined as at least three unsuccessful transfers of good quality embryo of at least 1BB category of blastocysts) and 49 controls (women undergoing IVF treatment because of idiopathic infertility or male factor) were included to the study. After preparation of the endometrium by the hormone replacement therapy endometrial biopsies were taken from each patient and sequenced with beREADY test TAC targeting 67 biomarker genes for endometrial receptivity. Depending on the test result patients were classified into one of four different groups: pre-receptive ($n=16$), early-receptive ($n=54$), receptive ($n=44$) and late-receptive ($n=3$).

Results In women with RIF pre-receptive endometrium has been detected substantially more often than in controls – 13 (19,1%) vs. 3 (6,1%) patients ($p=0,043$). Early-receptive endometrium was diagnosed in the majority of patients with idiopathic infertility – 12 (66.7%) vs. 6 (33.3%) women ($p=0.042$) and with polycystic ovary syndrome (PCOS) – 12 (70,6%) vs. 3 (17.7%) women ($p=0,0447$). We found significant association between abnormal endometrial receptivity and patient's age and duration of infertility. Young women were diagnosed significantly more often as normal or late-receptive, whereas older women with longer history of infertility as early-receptive and pre-receptive.

Conclusions In patients with RIF in comparison to other women undergoing IVF procedures, patient's age and infertility duration are the most important factors related to endometrial receptivity abnormalities, indicating that older women with a longer history of infertility may benefit the most from endometrial receptivity testing.

Trial registration Not applicable.

Keywords Endometrial receptivity, Recurrent implantation failure, Chronic endometritis, Window of implantation, Personalized embryo transfer

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Background

Embryo implantation, essential for successful pregnancy, is a very complicated process, depending on a specific "cross-talk" between embryo and endometrium [1]. This process involves two key elements: a good quality embryo and receptive endometrium [2]. Endometrial receptivity is defined as the ability of the endometrial tissue to support successful embryo implantation [3]. The moment, when endometrium becomes receptive for embryo, is referred as the window of implantation (WOI) and is considered to begin seven days after the luteinizing hormone (LH) peak during the natural cycle, lasting for about 48 h [4]. However, some studies suggest that its length may vary from two up to six days [5]. Transcriptional studies of the endometrial biopsies have demonstrated that the WOI can be shifted or displaced in time, causing asynchrony between the endometrial and embryonal development and in consequence implantation failure [6–8].

Recurrent implantation failure (RIF) is the lack of pregnancy after several transfers of good quality embryos. The exact definition of RIF varies significantly between different studies, however the most commonly used description indicates three or more consecutive failed in vitro fertilization (IVF) attempts with at least three high quality fresh or frozen embryos transferred [9]. Recently, the ESHRE Working Group on Recurrent Implantation Failure recommended a new definition of RIF to be adopted in clinical practice: RIF describes the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and/or interventions. The authors recommend also to set an individual threshold for the cumulative chance of successful implantation, including several factors, i.a patient's age and genetic status of the embryo [10].

There is a wide range of possible causes of RIF, including immune, genetic, anatomical, hematological and endocrine factors, as well as chronic endometritis (CE) [11–15]. Nevertheless, some studies suggested that even two-thirds of implantation failures are thought to be secondary to suboptimal endometrial receptivity [16]. Although, endometrial receptivity testing is now available in clinical practice, giving an opportunity for personalized embryo transfer (pET) and possible improving infertility treatment outcomes, its true clinical value, target patients' groups and correlations with clinical and epidemiological factors have not yet been unequivocally established.

CE is a persistent inflammatory disorder of the endometrial tissue, characterized by superficial endometrial edema, disturbed maturation between epithelium and stroma and infiltration of endometrial stromal plasma cells [17]. It is estimated that chronic endometritis can be diagnosed in up to 55–60% of patients with idiopathic infertility, RIF and women suffering from recurrent pregnancy loss [18, 19]. Studies have also shown that women with CE undergoing IVF treatment have lower pregnancy rates in comparison to women without the disease. Importantly, adequate antibiotic therapy may lead to the complete normalization of endometrial lining with restoration of its function and normal receptivity at WOI [20, 21]. The current gold standard for the diagnosis of CE is endometrial biopsy with the detection of CD138 positive (CD138+) plasma cells within endometrial stroma [22–25].

The aim of this study was to evaluate if endometrial receptivity abnormalities are more common in patients with RIF than in other women undergoing IVF treatment and also which epidemiological and clinical factors (such as patient's age, duration and cause of infertility and the diagnosis of CE) are related to these abnormalities.

Methods

Study population and protocol

In this case-control observational study adult women with the diagnosis of RIF undergoing IVF treatment in OVIklinika Infertility Center in Warsaw, Poland between January and December 2022 were included in the study. The results obtained from RIF patients were compared with those obtained from women undergoing IVF treatment due to idiopathic infertility or male factor as the control group. RIF was defined as at least three unsuccessful transfers of good quality embryo of at least 1BB category of blastocysts according to the Gardner classification [26]. We didn't perform preimplantation genetic testing of the embryos. Nevertheless, in our clinic karyotype testing of the patient and her partner is routinely performed before IVF treatment and patients with any genetic abnormalities were excluded from the study. Similarly, patients with clinically relevant myomas (especially types 0,1,2,3, 2–5 and 3–5) were excluded from the study.

The preparation of the endometrium was accomplished via the hormone replacement therapy. From Day 2 of the menstrual cycle, 4 mg of an oral micronized estradiol (Estrofem 2 mg, NovoNordisk) was administered twice a day. At Day 9–12, after confirming that endometrial thickness in ultrasound assessment reached at least 7 mm, the patients continued with 10 mg dydrogesterone tablets (Duphaston 10 mg; Mylan) three times daily and 200 mg vaginal progesterone (Lutinus 100 mg, Ferring GmbH) twice daily for 5 days. Endometrial biopsy was performed after 120 h of progesterone administration. Endometrial preparation protocol for the subsequent embryo transfer was exactly the same to ensure reliability of endometrial receptivity testing, however the duration of progesterone administration could be different

depending on the results of the test (e.g. for pre-receptive endometrium it is 140–144 h).

Endometrial tissue biopsies were collected by aspiration biopsy with a use of Pipelle® flexible suction catheter (Laboratoire CCD, France). The tissue samples were divided into two: one was fixed in 10% formaldehyde for immunostaining using mouse monoclonal antibody CD138/syndecan-1 (B-A38) by Cell Marque (Roche Diagnostics, Switzerland) and evaluated by the pathologist by counting CD138-positive plasma cells in 40 nonoverlapping random stromal areas (by 400x magnification). CE was diagnosed after the presence of ≥ 5 CD138 + cells per $10mm^2$, based on the existing literature [27–30]. The latter tissue sample was fixed according to the manufacturer's protocol and sent to Competence Centre on Health Technologies in Tartu, Estonia, where endometrial receptivity assay - beREADY test was performed.

Clinical and demographical characteristics of patients involved in the study (age, cause and duration of infertility, concomitant disease – polycystic ovary syndrome (PCOS), endometriosis, anti-Müllerian hormone (AMH) level are presented in Table 1. PCOS was diagnosed on the basis of the Rotterdam criteria described earlier and recommended by the international guidelines since 2018 [31, 32]. Endometriosis was diagnosed either by ultrasound/magnetic resonance imaging or during laparoscopy. Diminished Ovarian Reserve (DOR) was defined as AMH blood serum level < 1,0 ng/mL.

The study was approved by the local Bioethics Committee at the Institute of Mother and Child, Warsaw, Poland, and written informed consent was obtained from all participants. The study was performed in accordance with the guidelines described in the Declaration of Helsinki [33].

Endometrial receptivity assay – beREADY test

BeREADY test is based on Illumina sequencing-based TAC-seq technology (Targeted Allele Counting by sequencing), enabling biomolecule analysis down to a single-molecule level [34]. The 72 genes analyzed with this test contain the core set of 68 endometrial receptivity-associated biomarkers, and four housekeeper genes [35, 36]. The development of beREADY test and its confirmatory data are described in previously published studies [34–38].

We assigned all patients to one of four groups based on their beREADY test result: pre-receptive, early-receptive, receptive and late-receptive. These categories reflect different stages of endometrial receptivity: (1) pre-receptive - indicating endometrium before the optimal WOI; (2) early-receptive - meaning the onset of endometrial receptivity; (3) receptive - indicating full readiness for embryo implantation and (4) late-receptive - meaning that endometrium has started to pass the optimal window for implantation.

Statistical analysis

All statistical analyses were carried out using SAS 9.4 statistical software (SAS Institute Inc., 100 SAS Campus Drive, Cary, NC 27513 – 2414, USA). For variables with normal distribution, average values were compared using the t-student's test, whereas for variables with skewed distributions, significance was assessed with the Mann-Whitney U test. For categorized data, between-group comparisons were performed using chi-square test or Fisher's exact test. For more than two group comparisons Kruskal-Wallis test was carried out. The value of $p < 0.05$ was considered as the significance level for the above-mentioned analyses.

Results

In total, 117 patients were included in the study: 68 women with RIF and 49 patients in the control group. Among them 16 (13,7%) women were diagnosed as pre-receptive, 54 (46,1%) as early-receptive, 44 (37,6%) as receptive and 3 (2,6%) as late-receptive. The demographic and clinical characteristics of the study participants are presented in Table 1.

According to the beREADY test results pre-receptive endometrium was diagnosed significantly more often in patients with RIF than in the control group – 13 (19.1%) vs. 3 (6.1%) patients respectively ($p = 0.035$). There were

Table 1 Clinical and demographic characteristics of study participants

	RIF $n = 68$	Control group $n = 49$	Chi^2 or U-Mann-Whitney*	*P*-value
Age (years)	35.46 ± 4.17	34.63 ± 4.36	0.84*	0.152
Duration of infertility (years)	5.1 ± 2.93	3.45 ± 2.21	11.99	**< 0.001**
AMH (ng/ml)	2.957 ± 2.018	2.629 ± 2.35	1.578*	0.221
Male factor	30 (44.12%)	15 (30.61%)	12.2	**0.016**
Idiopathic infertility	22 (32.35%)	11 (22.45%)	12.03	**0.018**
Tubal factor	5 (7.35%)	3 (6.12%)	0.026	0.871
DOR	10 (14.71%)	14 (28.57%)	3.36	***0.067***
Endometriosis	6 (8.82%)	8 (16.33%)	1.522	0.217
PCOS	11 (16.18%)	6 (12.24%)	0.355	0.552

AMH – antimüllerian hormone; DOR – diminished ovarian reserve; PCOS – polycystic ovary syndrome

Table 2 Receptivity classes according to the beREADY test results in the study groups

	RIF $n=68$	Control group $n=49$	Chi^2	*P* value
Pre-recetive	13 (19.12%)	3 (6.12%)	4.44	**0.035**
Early receptive	30 (44.12%)	24 (48.98%)	0.27	0.603
Receptive	23 (33.82%)	21 (42.86%)	0.99	0.320
Late receptive	2 (2.94%)	1 (2.04%)	0.09	0.758

no differences between the groups in other classes of endometrial receptivity (Table 2).

Subgroup analysis demonstrated that among patients with PCOS 12 (70.6%) patients were diagnosed as early-receptive and 3 (17.7%) women as pre-receptive, occurring significantly more often in comparison to women without PCOS ($p=0.0447$). Similarly, the vast majority of patients with idiopathic infertility had early-receptive endometrium – 12 (66.7%) women vs. 6 (33.3%) patients with known cause of infertility ($p=0.042$). There was no difference between RIF patients and control group in the incidence of PCOS and endometriosis, but there was a trend for DOR diagnosis in the RIF group: 10 (14.7%) vs. 14 (28.6%) women ($p=0.0685$).

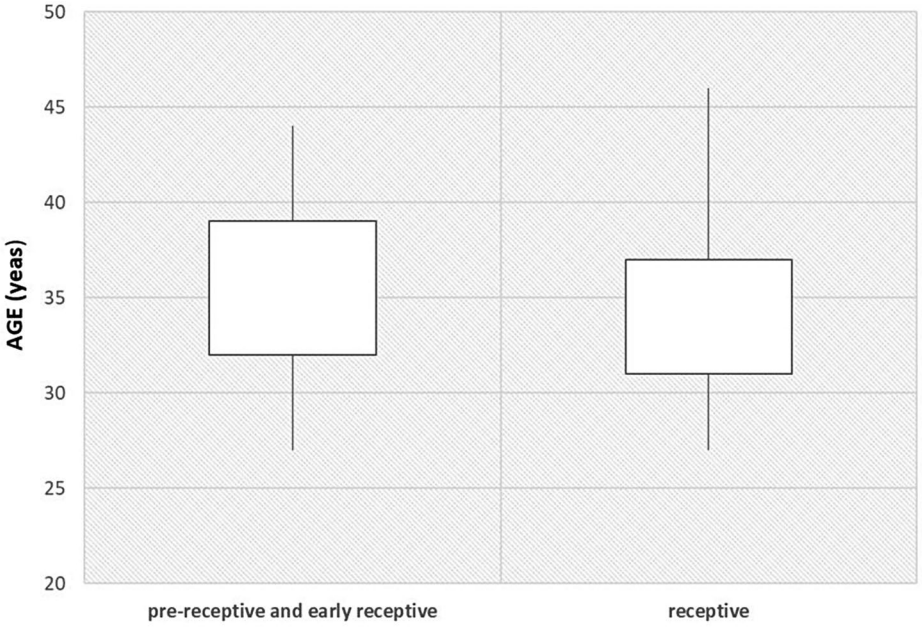
The overall incidence of CE in the study population was 6,8% and it did not differ between the groups: 4 (5,9%) patients in the RIF group vs. 4 (8,2%) women in the control group ($p=0.63$). CE status did not correlate with endometrial receptivity, however it might be due to a small number of cases.

There was a significant correlation between endometrial receptivity and patient's age, as well as duration of infertility. Patients diagnosed as pre-receptive and early-receptive were significantly older, whereas younger women had significantly more often normal or late-receptive endometrium (Fig. 1). Similarly, longer duration of infertility was related to pre-receptive and early-receptive endometrium (Fig. 2).

Discussion

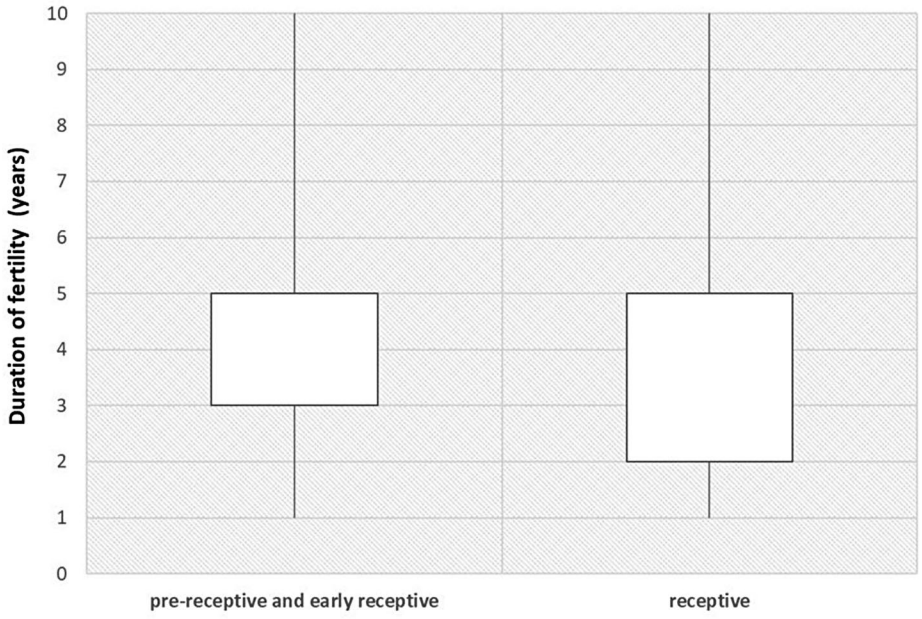
Presented study demonstrated that endometrial receptivity abnormalities are diagnosed significantly more often in women with RIF than in other patients undergoing IVF treatment. Moreover, the risk for displaced WOI increases with patient's age and duration of infertility, leading to more often diagnosis of pre- or early-receptive stages of endometrial samples.

Before the introduction of the first endometrial receptivity assay – ERA (Endometrial Receptivity Array) test by Igenomix in 2011, clinicians assessed endometrial



Mann-Whitney U test				
Rank sum pre-receptive and early receptive	Rank sum receptive	U	Z	P
4428.5	2126.5	1136.5	2.35	**0.018**

Fig. 1 Endometrial receptivity and patient's age



Mann-Whitney U test				
Rank sum pre-receptive and early receptive	Rank sum receptive	U	Z	p
4062	2154	1119	2.19	**0.028**

Fig. 2 Endometrial receptivity and duration of infertility

receptivity by histological examination or ultrasound scan by measuring endometrial thickness [39]. Histology assay based on Noyes' criteria, estimating endometrial maturation by the use of its microcells reaction on progesterone became widely used, however this estimation is based on subjective nature of histologic assessment, where endometrial receptivity is determined by much more factors than simply an appropriate maturation response to progesterone [40–43]. Therefore substantial effort has been made to describe molecular changes in the menstrual cycle and identify these responsible for the development of the WOI [44, 45]. With the help of whole transcriptome studies, the differentially expressed gene profiles have been detected between proliferative, early-, mid- and late-secretory endometrium, and diagnostic tests such as ERA or beREADY have been elaborated and implemented into the clinical practice [46, 47]. Their implementation as an integral element of IVF treatment poses an opportunity to synchronize the embryo transfer with the best timing for the maximal endometrial receptivity of a given patient [48]. Several clinical studies have shown that also some therapeutic interventions, such as blocking activation of oxytocin receptors by an oxytocin receptor antagonist has the potential influence on endometrial receptivity by increasing endometrial perfusion and enhancing endometrial decidualization [49].

It has been estimated that displaced WOI occurs at around 10% of women undergoing IVF treatment and in at least 25% of women with RIF [7, 50, 51]. Certain conditions, like PCOS, endometriosis and CE are also shown to shift the WOI and impair endometrial receptivity. In our study the vast majority of patients with PCOS had abnormal endometrial receptivity. Multiple factors are related with the shift of the WOI in women with PCOS, including obesity, hyperinsulinemia, abnormal expression and function of glucose transporters in endometrial tissue, elevated oxidative stress and reduced expression of hypoxia-inducible factor 1 (HIF-1) locally in uterus [52–57]. There is now available overwhelming evidence supporting endometrial dysfunction as one of the factors underlying decreased fertility rate in patients with PCOS [58]. Impaired endometrial receptivity in PCOS is a consequence of both primary (not related to the ovulatory factor) and secondary abnormalities (subsequent to all clinical and biochemical alterations known to be diagnosed in women with PCOS) [58, 59]. Primary endometrial abnormalities include abnormal expression of proteins involved in cell cycle regulation, cellular

transport, DNA repair, apoptosis and mitochondrial metabolism. Abnormal expression of estrogen, progesterone and androgen receptors, as well as their co-regulators are linked to impaired endometrial function [58, 59]. Secondary endometrial abnormalities in women with PCOS are effects of hyperandrogenism, insulin resistance, obesity and other biochemical and metabolic features [58, 59]. Although, various pharmacological and non-pharmacological strategies with a strong biological rationale have been proposed to improve endometrial receptivity in women with PCOS, to date no intervention is supported by an adequate body of evidence, limiting their use in clinical practice [60]. Because of many molecular abnormalities in PCOS patients, there might be concern about the adequacy of used assay in this group of patient. BeREADY test has been however evaluated in the group of PCOS women and there were no differences between PCOS patients and healthy women in the expression of studied biomarker genes for endometrial receptivity, thus it was concluded that PCOS status does not affect the expression profiles of biomarkers included in the developed assay [36].

CE is one of the most important factors that may negatively impact endometrial receptivity, but it is also one that is relatively easy to remove by antibiotic treatment [61]. A higher incidence of CE has been observed in women with infertility, implantation failure, and recurrent pregnancy loss and live birth rates in women with a history of recurrent pregnancy loss or RIF and untreated chronic endometritis are very poor (7%) [19, 20, 62]. On the other hand, available research reports suggest that ongoing pregnancy rates are improved significantly after antibiotic therapy and resolution of the prevailing inflammatory condition [20, 63]. Wang et al. demonstrated decreased endometrial transforming growth factor β (TGF-β) and interleukin-10 (IL-10) expression and increased interleukin-17 (IL-17 expression in patients with CE and RIF compared to women undergoing IVF because of male factor infertility. These changes, associated with CE lead to proinflammatory endometrial response resulting in a defective endometrial receptivity [64]. Kuroda et al. confirmed the significant relationship between CE and a personalized WOI, as identified by results of endometrial receptivity analysis by ERA test [27]. Ota et al. presented a case of discrepancy between three ERA tests in women with RIF complicated by CE [65]. In our study there was no significant correlation between CE and beREADY test result, however this might be due to a small number of patients with CE in the study group.

An interesting finding of presented study is a high rate of abnormal endometrial receptivity in patients with idiopathic infertility. Endometrial receptivity assay is not routinely performed in the diagnostics of infertile couples, however our study shows that it might be considered when other abnormalities have been excluded.

Presented study demonstrates that pre-receptive and early-receptive endometrium are detected significantly more often in older women. This finding is consistent with other studies [66–71]. A recent endometrial transcriptomic data analysis revealed that age-related changes begin at the age of 35 years and include upregulation of genes involved in ciliary formation as well as growth factor regulation [66]. Animal models have uncovered the potential risk of tissue fibrosis, dysregulation of the decidualization process and immune imbalance, causing deterioration of endometrial receptivity as age increases [72, 73]. Additionally, impaired cellular senescence phenomenon is a well described mechanism of aging endometrium [67]. Fogle et al. revealed statistically significant associations between age and expression of homeobox A10 (HOXA10) in the endometrial explant culture system concluding that uterine age may play a role in endometrial receptivity [68]. Fujii et al. identified that both aging and endometrial microbiota are related to pre-receptive endometrium [69]. Zhao et al. in recently published meta-analysis demonstrated slightly lower implantation rates and clinical pregnancies, significantly increased miscarriage rates and decreased live birth rates in women with advanced age in comparison to younger women after oocyte donation, indicating that advanced maternal age is related to the decline of endometrial receptivity [70]. To the contrary, Guo et al. investigated expression of HOXA10 and osteopontin in three different age groups and found no differences, suggesting that the age of the patient does not influence their endometrial receptivity [71]. Thus further studies are required to explain this important field of interest.

As mentioned above, recently the ESHRE Working Group on Recurrent Implantation Failure implemented a new definition of RIF, taking into account not only the number of failed embryo transfers, but most of all patients characteristics [10]. The authors recommend setting an individual threshold for the patient, depending mainly on patient's age and the genetic status of the embryo, because among ART patients, the chance of successful implantation will differ significantly [10]. Our study confirmed age as one of the most important factor influencing endometrial receptivity and thus, the chance of pregnancy. On the other hand, the lack of preimplantation genetic testing of the embryos in RIF patients in our study, must be considered as a limitation, because the quality of the embryo (euploidy/aneuploidy) is crucial for pregnancy outcomes [74].

The main purpose of implementing endometrial receptivity assay into the clinical practice is to guide pET, meant to synchronize the embryo transfer with the individual timing for maximal endometrial receptivity, thus

improving the chance for successful pregnancy. Recently pET has caused a lot of debate, because the results of the studies are contradictory. Jia et al. investigated the effectiveness of endometrial receptivity analysis-guided embryo transfer in a cohort of Chinese patients with RIF and found that it resulted in significant improvement in pregnancy and implantation rates when compared with conventional frozen-thawed embryo transfer (FET) [75]. In a 5-year multicenter randomized controlled trial Simon et al. demonstrated statistically significant improvement in pregnancy, implantation and cumulative live birth rates in pET compared to FET [76]. A meta-analysis published in 2022 and including 11 studies revealed that pET significantly increases the chance for pregnancy for non-receptive patients with RIF of endometrial origin [77]. On the contrary, Doyle et al. performed another randomized control study and found that using endometrial receptivity testing to guide the timing of embryo transfer did not significantly improve live birth rates in comparison to the standard timing for transfer [78]. Edimiris et al. presented one center experience with pET and concluded that in patients with RIF, the endometrial receptivity analysis showed a high incidence of displaced WOI. However, pET did not improve pregnancy outcome [79]. Cozzolino et al. published a paper indicating that using ERA test for pET not only did not improve reproductive outcomes, but worse outcomes were detected when ERA testing was used [80]. Finally, recently published meta-analysis including 8 studies and nearly 2800 patients also did not reveal any change in pregnancy rates after using ERA for pET [81]. The vast majority of these studies were performed using ERA test, whereas to the best of our knowledge four other endometrial receptivity assays are now available, including beREADY, ER Map test (IGLS), WIN-Test (INSERM) and rsERT (Yikon Genomics Company) [51, 82, 83]. When compared to rest of the tests beREADY test is based on the TAC-seq technology, that eliminates the PCR-caused bias in results. Moreover, the selection of genes is based on the results of comprehensive meta-analysis of endometrial receptivity biomarkers [35]. This approach may allow for a more adequate analysis, but it needs further investigation. The second aspect is that endometrial receptivity testing may be more relevant in some narrower groups of patients, e.g., older women with longer history of infertility, as in the presented study. Further research is however needed to determine what group might benefit the most from endometrial receptivity analysis. Yet another issue is that all current endometrial receptivity tests require a tissue biopsy which excludes the possibility of embryo transfer in the same cycle and thereby the testing is vulnerable to possible cycle-to-cycle variations in the WOI as well as biases if taken biopsy does not reflect whole tissue [38].

Conclusions

Presented study demonstrates that displaced WOI is detected significantly more often in patients with RIF in comparison to other women undergoing IVF procedures. The prevalence of endometrial receptivity abnormalities is associated with patient's age and infertility duration indicating that older women with a longer history of infertility may benefit the most from endometrial receptivity testing. Yet, there is a need for further studies, aimed to personalize the treatment of infertile couples, based on individual determination of WOI.

Abbreviations

AMH	anti–Müllerian hormone
CE	chronic endometritis
DOR	diminished ovarian reserve
ERA	Endometrial Receptivity Array
FET	frozen–thawed embryo transfer
HIF	1–hypoxia inducible factor 1
HOXA	10–homeobox A10
IL	10–interleukin 10
IL	17–interleukin 17
IVF	in vitro fertilization
LH	luteinizing hormone
PCOS	polycystic ovary syndrome
pET	personalized embryo transfer
RIF	recurrent implantation failure
TAC	seq–Targeted Allele Counting by sequencing
TGF	β–transforming growth factor
WOI	window of implantation

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Author contributions

Conceptualization- K.O., K.P., A.S. and P.L.; methodology, K.O., K.P., A.S., P.L.; formal analysis, K.O.,K.P., J.S., P.L.; writing— original draft preparation, K.O., K.P.; writing—review and editing, P.P., A.S., E.A., T.I., P.L; supervision – P.L. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the local Bioethics Committee at the Institute of Mother and Child, Warsaw, Poland, and written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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