Endometrial receptivity – can it be diagnosed and controlled? And why does it matter?

Receptywność endometrium – czy potrafimy ją zdiagnozować i kontrolować? Czy ma to znaczenie?

Mateusz Mikołajczyk, Jana Skrzypczak

Division of Reproduction, Poznan University of Medical Sciences, Poland

Abstract

Infertility remains a challenge to modern medicine. Despite extensive diagnostic and therapeutic procedures, the achievement of pregnancy remains an elusive goal in some patients. The endometrium is one of the key factors in embryo implantation. Older methods of describing endometrial receptivity, like histology or ultrasound, did not bring noticeable improvement in pregnancy rates. New technologies, including genomics, proteomics, lipidomics, and secretomics promise to improve the detection of the implantation window in the endometrium and result in better counseling of patients with infertility.

Key words: **infertility** / **endometrium** / **window of implantation** / **receptivity** / / **proteomics** / **secretomics** / **lipidomics** / **genomics** / **metabolomics** /

Streszczenie

Niepłodność jest jednym z głównych wyzwań współczesnej medycyny. Pomimo szerokiego wachlarza procedur diagnostycznych i terapeutycznych uzyskanie ciąży u niektórych par pozostaje niespełnione. Kluczowym czynnikiem odgrywającym rolę w implantacji jest endometrium. Starsze metody opisywania receptywnego endometrium, takie jak ocena histologiczna czy ultrasonograficzna, nie przyczyniły się do zauważalnego wzrostu liczby ciąż. Nowe techniki, takie jak oznaczanie za jednym razem wielu genów, białek, produktów lipidowych czy procesów metabolicznych, obiecują poprawę nie tylko w wyznaczaniu okna implantacyjnego w endometrium, ale i w poradnictwie par z niepłodnością.

Słowa kluczowe: **niepłodność** / **endometrium** / **okno implantacyjne** / **receptywość** / / **proteomika** / **sekretomika** / **lipidomika** / **genomika** / **metabolomika** /

Corresponding author:
Mateusz Mikołajczyk
Division of Reproduction
Polna 33, 60-535 Poznań, Poland
Tel. 0048616599302
e-mail: matmik@gmail.com

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Introduction

Infertility is classified as a disease by the World Health Organization. It is defined as inability to conceive offspring after 12 months of unprotected intercourse [1]. Ovulation, patent Fallopian tubes, normal sperm parameters and good timing are among the necessary factors for natural pregnancy to occur [2].

Since the advent of IVF programs, we have been very successful in inducing ovulation, improving sperm parameters or even using a single sperm to fertilize the embryo. Owing to IVF, we no longer depend on the patency of the Fallopian tubes, as we can create embryos in vitro and place them in the uterine cavity. The rates of successful ovulation induction and embryo creation exceed 90% [3]. Therefore, since we can control or bypass most of nature's flaws in the reproductive process, one could expect very high pregnancy rates with IVF cycles but in reality they rarely exceed 40% [3].

Why is that? Successful pregnancy begins with successful implantation. Implantation depends on two factors: healthy embryo and receptive endometrium. The impact of embryo quality cannot be overestimated. Declined oocyte function after the age of 35 is a well-recognized phenomenon, with higher number of reported genetic alterations [4].

To add to the problem, we have very high aneuploidy rates in embryos, reaching even 50% in older patients [5]. Do we have tools to assess the quality of the embryo? Morphologic indices including fragmentation status, multinucleation, balstomere number and blastocyst formation, and, a recent advance, time-lapse assessment, have been used as prognostic features for IVF outcome for many years [6, 7]. It did improve the number of pregnancies but still failed to produce a noticeable leap in implantation percentages [8]. With many of the embryo harboring an aneuploidy, the promise of improving the chances of successful implantation with Preimplantation Genetic Screening (PGS) for either the polar bodies or single balstomere seemed a valid one [9]. However, after initial favorable results, randomized controlled trials failed to show significant improvement in implantation rates [10]. We have come to realize that omission from the analysis of the key player in the implantation game, i.e. the endometrium, has been a mistake.

Why does endometrium matter? Observational studies

The first lessons about the role of endometrium during implantation came from incidental findings of embryos discovered within human hysterectomy specimens that were removed during surgery [11, 12]. The embryos, depending on the day after ovulation, showed different stages of implantation. Further studies showed that the timing of the intercourse does influence the chances not only for the pregnancy to begin, but also to survive [13]. With sensitive βHCG assays and lessons learned from the IVF programs, we know that the period of maximal receptivity for the embryo is relatively short (4-5 days) and spans from 7-9 days after ovulation [14, 15].

What happens in this timeframe? We now know that endometrial preparation for the acceptance of an embryo involves not only numerous morphological changes in the luminal as well as glandular endothelium, but also changes in the stroma, vasculature, genetic and protein profiles throughout the entire endometrial thickness.

Histology

Human endometrium is known to be quite a unique tissue in the human organism. It undergoes complex changes in response to steroid hormones, progressing from thin endometrium at the beginning of the proliferative phase to thick tissue in the middle of the secretory phase. Since the 1950s, we have been relying on histologic assessment of the endometrium to confirm its proper development and, consequently, proper receptivity [16]. A term 'luteal phase deficiency' (LPD) was coined, blaming infertility problems on either poor development of the endometrium or low progesterone levels [17]. Thus, many women were subjected to endometrial biopsies, progesterone measurements in the second half of the cycle, and "supportive" treatments with progesterone derivatives. However, in 2004, a series of publications in Fertility and Sterility finally exposed what many researchers of this filed had been suspecting [18,19], that the luteal phase defect, as judged by histologic indices, could no longer be considered a cause for infertility due to the fact that 50% of women with normal fertility potential exhibited signs of LPD [20]. Furthermore, it was proven that there was a considerable intra- and inter-observer variability regarding the histologic assessment of endometrial development [18].

Scanning electron microscope

With the development of modern devices like the scanning electron microscope (SEM), we ceased to be confined to the relatively low powered magnification and two-dimensional limitations of a light microscope. We were able to gaze at the 3D surface of the endometrium. It turned out that the endometrial surface, which is first to make contact with the embryo, has some interesting projections on its surface. Pinopodes, first described by Psychoyos and then popularized as the endometrial receptivity marker of the endometrium by Niklas [21], were demonstrated to exhibit various stages of development throughout the endometrial cycle, with full development coinciding with the so-called "implantation window". However, as time went by, more and more researchers began to question the role of pinopodes in assessing endometrial receptivity [22]. It was also proven that the name "pinopodes", suggesting some pinocytic function, is completely without merit [23].

Ultrasound

Advances in the field of modern ultrasound equipment have allowed for relatively non-invasive assessment of the endometrium. The characteristic appearances of endometrium in different phases of the cycle have become a cornerstone for ad hoc endometrial analysis. The thin, hypoechoic endometrium of the proliferative phase, gives rise to thick, hyperechoic secretory phase endometrium. From these observations a notion spanned, that pregnancies cannot occur unless a certain thickness of the endometrium is observed during ultrasound examination. However, as with many things in biology, there are no definite truths. Although the chances of pregnancy are increased with the endometrium of more than 7mm, sometimes the pregnancy can survive with endometrial thickness of just 3.7 mm [24]. Also, proper thickness of the endometrium does not guarantee successful implantation. Since two-dimensional thickness of the endometrium could not predict the implantation, volumetric systems were employed and soon they also failed to improve

the detection of receptive endometrium [25, 26]. Numerous other studies focusing on the echogenic patterns within the endometrium, or the blood flow in the uterine arteries or the power flow determinants at the level of myometrial-endometrial border, also did not yield significant improvements in our understanding of what makes a receptive endometrium [27].

Molecular markers

Implantation of the blastocyst into the human endometrium begins with the initial contact of the apical luminal endometrial layer with the embryo surface. The contact can be facilitated or hindered by adhesion molecules present on the endometrial surface. To date, many molecules, including LIF, MUC-1, glycodelin, various integrin patterns, interleukins, MMP, have been studied [28–32]. With specific papers focusing on differences in the expression of various molecules in the menstrual cycle, we gained new insights into how the initial steps of the implantation processes work. However, despite intensive research, there is no molecule that has gained the status of the true "receptivity marker". To illustrate how difficult it is to assess the function of certain molecules and their role in the receptivity, a tale of MUC-1 is in order. MUC-1 is a transmembrane molecule that, owing to its length, was thought to be the first molecule to come into contact with embryo receptors [33]. Initially, the papers reported the presence of an aberrant expression of this molecule in infertile patients [34]. Studies in animal models revealed that the molecule was removed from the endometrium during implantation [35]. Furthermore, the molecule was thought to have a role in recognizing abnormal embryos, and lack or improper function of MUC-1 was attributed to recurrent abortions [36]. To add to the confusion, commercially available kits that aimed to measure the quantity of the MUC-1 failed to take into consideration the high glycosylation status of the molecule. Studies by Aplin showed that in human endometria, contrary to animal studies, MUC-1 is removed only from the contact area adjacent to the blastocyst [37]. Therefore, previous studies reporting variations in the immunolocalization of the MUC-1 molecule were mistaken. Similar stories could have been written about each molecular marker of endometrial receptivity tested, with initial triumphant stories, and subsequent corrections. This shows how complex the endometrium could be, and how difficult it is to study.

Here come the modern days: the "-omics" era.

Until recently, the search for genetic markers of endometrial receptivity has been chaotic at best. Each researcher picked a specific gene, supposedly associated with the implantation window, and produced a paper on it. However, it soon became clear that, due to the large number of genes and the fact that many of them work in unison, this method would not bring any conclusions in the search for understanding of the endometrium and its changes during the implantation window. Since the development of gene microarrays, a detailed analysis of many thousands of genes in one go, or gene profiling, has become possible. Attempts to study the genetic profile of the endometrium allowed us first to determine the changes occurring during different phases of the menstrual cycle, including the window of implantation [38]. Then, there was a description of differences between genetic make-up of endometria coming from women with normal fertility potential and those with reproductive failures [39]. It showed that many genes during the implantation window are up-regulated, while others were down-regulated, to produce a perfect receptive environment. This allowed us to pinpoint candidate genes that showed the most promise in detection of non-receptive vs. receptive endometrium. However, already at that stage, it became apparent that different teams of scientist obtained varying results. For example, the works of Kao et al., and later papers by Rijsjewik and Haouzi, revealed that only a small amount of up- and down-regulated genes were similarly expressed in all studies [40, 41]. Furthermore, some studies aimed to detect gene profiles in the same menstrual cycle, in the same patient. The studies failed to acknowledge the ever important role of inflammation arising from endometrial biopsy on the result of second biopsy performed a few days later in the same woman. Does it matter? There is cumulating evidence, both anecdotal and research-based, that inflammation caused by endometrial injury (as in biopsy procedures) could influence implantation [42].

Nevertheless, the emergence of genomics have allowed some researchers to offer commercial kits to assess endometrial receptivity, especially suited to patients undergoing IVF procedures with recurrent implantation failures. Apparently, Endometrial Receptivity Array (ERA), consisting of 238 genes that label the endometrium as receptive or non-receptive, allows for the prediction of the overall success rate of pregnancy (62.8%) and implantation (37.9%) in patients with previous recurrent implantation failures [43]. These results are comparable to controls, which have not experienced implantation failures. There is however a need for larger studies to confirm that positive effect.

It is vital to bear in mind that gene regulation is not the end of the endometrial receptivity. For the gene to take its effect it has to be transcribed into mRNA and then translated into amino acids that make up the final protein or other substances. Therefore, in the "-omics" era, there is a growing trend to describe the results of gene up- or down-regulation on the synthesis of proteins, lipids and metabolic effects. As with the genomics, there have been numerous studies attempting to detect changes in the protein content between the receptive and non-receptive endometrium. Some of them detected that up to 50% of proteins with markedly different expression during the window of implantation showed little or no change in corresponding mRNA levels [44]. This alone shows how the posttranscriptional, translational, or posttranslational changes affect the final product and, consequently, endometrial receptivity. To further add to the complexity of endometrial changes, there is a growing trend to use laser capture microdissection to analyze various components of the endometrium (glands, stroma, luminal epithelium and immunologic cells) separately, to better understand changes occurring during the acquisition of the receptive status [45].

The role of metabolic products, endometrial secretions and, as of recently, lipid analysis, has yielded some interesting insights into endometrial receptivity. The role of the endometrium as a histiotroph has been well connected with the "quiet embryo" hypothesis [46, 47]. The less damage in the genes, transcript and proteins in the embryo, the better the prognosis for viability and less metabolic changes detected in the embryo. Since it is the endometrium that provides nutrients to the developing embryo, more research focused on that subject. Interesting lessons from the nutritional status of an early pregnancy have been implicated in long-term health outcomes, confirming that the phrase "you are what you eat" might apply to the earliest stages of human life

[48, 49].

Lipid profiles during embryo implantation have also shown interesting results. Some molecules as lysophosphatidic acid (LPA), prostaglandins (PGs) and endocannabinoids have turned out to be strong predictors of implantation success or failure [50]. Studies in mice have provided some interesting hypotheses regarding the role of prostaglandins and LPA in the establishment of receptive endometrium. Since drugs like NSAIDs influence the level of prostaglandins, they might have an adverse effect on the implantation also in humans [51]. A relative noninvasiveness of collection of the uterine fluid, and subsequent description of the metabolic, protein and lipid content, makes it an ideal candidate to study endometrial receptivity.

Comorbidities

Apart from molecular and genetic changes in the endometrium, there are also other numerous comorbidities that need to be addressed in women trying to achieve pregnancy. Endometrial polyps, submucous myomas, and adhesions do influence the fecundability. They present not only a physical barrier for embryo implantation, but there is also ample evidence that the presence of myomas or polyps does indeed change endometrial receptivity at the molecular level [52, 53].

Also, endometriosis is a disease that is associated with decreased ability to achieve pregnancy. Apart from poorer results in ovulation induction, formation of adhesions that block the Fallopian tubes, alterations of the pelvic hormonal and immunological status that affect the fertility, endometriosis also affects the eutopic endometrium [54, 55]. It may explain why in some women with minimal endometriosis a markedly decreased fertility potential is observed [56].

Treatment

"Do no harm". This could be the key element regarding receptivity treatments. When talking about receptivity, we are predominantly concerned with IVF implantation results. There is no doubt that controlled ovarian hyperstimulation used in ART cycles damages the endometrium causing not only changes in the histologic aspect of the endometrium, but also when viewed from the molecular point of view [57]. There are papers showing that transfer of frozen embryos gives better results than transferring fresh embryos to the endometrium primed by ovulation induction drugs [58]. Unfortunately, since we do not fully understand receptivity of the endometrium, there is presently little we can do to help improve it. The Granulocyte colony-stimulating factor is among the factors currently under investigation. Preliminary work has shown some improvement after uterine perfusion with G-CSF in the increase of thickness of the endometrium in poor responders [59]. However, other papers question these results [60].

It is important to remember that no gene, no molecule, no protein or secretion could be viewed as a standalone marker for endometrial receptivity. It is often found that some substances work in concert with each other to produce the desired effect, while a lack of a certain protein can be successfully ameliorated by the presence of another. We now know that the endometrium is not an inert tissue. Rather, it is an active host that, through an intensive dialogue with the embryo, recognizes its proper viable potential, allows the implantation, controls its extent, and provides the developing embryo with nutrients for a large portion of the first trimester of pregnancy. Insight into the processes that occur within the period of maximal receptivity, i.e. the implantation window, one day might allow us to control the implantation, resulting in markedly improved fertility potential for the human race.

Oświadczenie autorów

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