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Chapter 4

Secretory Phase and Implantation

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Abstract

This chapter will explore the latter phase of the menstrual cycle focusing on the secretory phase of the endometrium. In particular, focus will be on the mid-secretory endometrium and appropriate markers and hormonal environment for successful implantation. This will be put in the context of the luteal phase of ovulation and the hormonal support that progesterone provides. We will also review pathologic states, such as endometriosis and related progesterone resistance, which affect mid-secretory phase and implantation. Finally, we will provide a detailed review of the literature on what the current state of knowledge is regarding receptivity and the microenvironment of the mid-secretory endometrium which is essential to implantation.

Keywords: secretory, implantation

1. Introduction

The female reproductive system prepares women for conception and pregnancy through two distinct, but highly integrated, cycles, the ovarian cycle and the endometrial cycle. The human endometrium, under the influence of complex biological signals, undergoes cyclic changes in preparation for implantation and the initiation of pregnancy. An array of molecular activity, still poorly understood, gives rise to relatively consistent morphologic changes of the endometrium during each cycle. In an era of assisted reproductive technologies (ART), there exists an ever-increasing demand to delineate these pathways in order to improve pregnancy rates. Ultimately, success in the field of reproduction and fertility requires an understanding of these complex processes, from molecular to cellular to tissue, in both the healthy patient as well as in the setting of various pathologic states.

This chapter will discuss the endometrial cycle with an emphasis on the secretory phase, including the molecular and biochemical components of endometrial receptivity and implantation. Markers and techniques for assessment of receptivity will be reviewed, as well as pathologic states that alter fertility.

2. The menstrual cycle and the endometrium

The endometrium is comprised of two anatomic layers, the functionalis and the basalis. The functionalis is made up of a compact zone, including stroma underneath the luminal epithelium, and a spongy zone which lies above the basalis layer [1, 2]. It is the functionalis layer that is shed in the monthly menses. The basalis layer lies on the myometrium; it undergoes fewer cyclic changes compared to the functionalis layer and is responsible for regenerating the functionalis after menstruation (**Figure 1**).

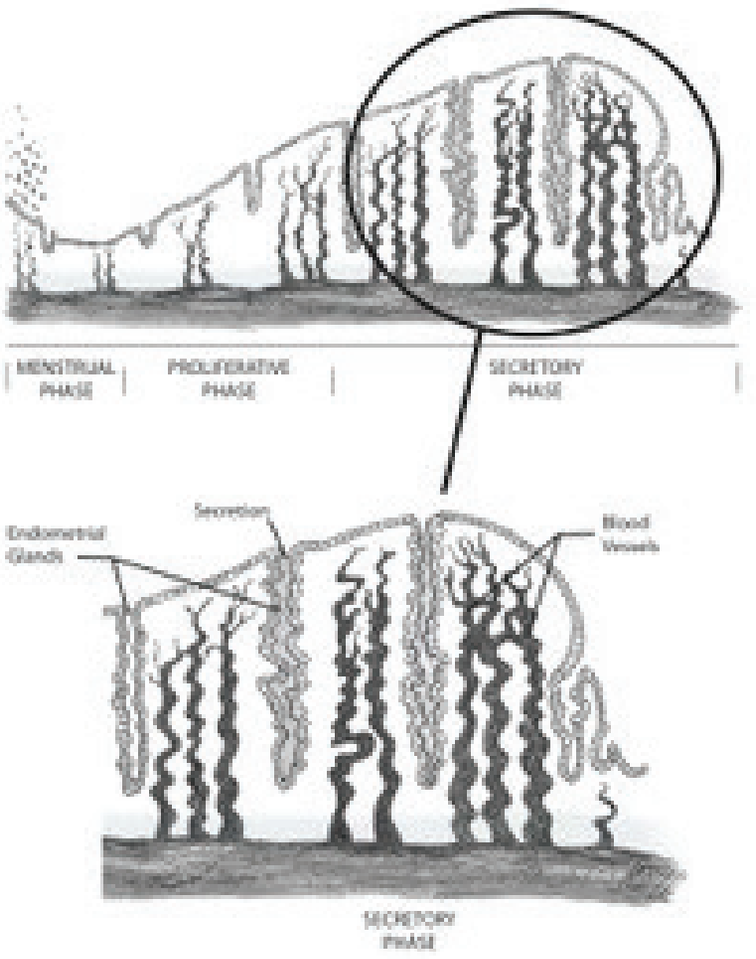

Figure 1. Functional anatomy of the human endometrium during the secretory phase.

The endometrial cycle consists of three sequential phases—the proliferative phase, secretory phase, and menstruation. Each phase is marked by physiologic changes that are controlled by circulating levels of estrogen and progesterone, which are synthesized and secreted from the ovary. The ovarian cycle is characterized by follicular development mediated by FSH (follicular phase), oocyte release mediated by the LH surge (ovulation), and development of the corpus luteum and production of progesterone (luteal phase). In the idealized 28-day cycle, ovulation occurs on day 14. After ovulation, the remnant of the dominant follicle becomes the corpus luteum, a temporary endocrine structure which produces progesterone (**Figure 1**) [1–4]. The corpus luteum becomes atretic on day 28 and menses begins the next day, establishing day 1 of the subsequent cycle.

During the proliferative phase, estradiol derived from the growing follicles drives the restoration of the functionalis layer with re-epithelialization by approximately day 5 of the menstrual cycle. This phase is characterized by hypertrophy and proliferation of glands, increase in stromal matrix, and elongation of terminal arterioles to the endometrial lumen. A gradient of angiogenic factors, particularly VEGF, is released from the endometrial epithelium by estradiol [5]. Estrogen also upregulates the progesterone receptors that orchestrate the environment during the secretory phase, which will be covered in more detail in the next section [2, 4]. In the absence of fertilization, progesterone levels decline due to atresia of the corpus luteum. This leads to vasospasm, ischemia, subsequent tissue death and endometrial shedding, or menses.

3. The secretory phase

For decades, endometrial dating has been assessed histologically [4, 6]. After ovulation, there is an increase in superficial stromal edema that becomes generalized by day 21. Stromal cells near terminal spiral arteries show an increase in cytoplasmic volume and surrounding extracellular matrix, a process termed predecidualization, which eventually encompasses the majority of the superficial endometrium by day 25. This transformation appears to represent a form of mesenchymal-to-epithelial transition (MET) [7]. By day 27, the superficial stromal cells are nearly indistinguishable from decidual cells of pregnancy. The increasing edema during the secretory phase results in the global endometrial thickening that is readily apparent with ultrasonography. Throughout the secretory phase, there are also distinct changes in spiral arteries. They rapidly lengthen, outpacing endometrial thickening, and become increasingly coiled [4, 6, 8, 9].

During the proliferative phase, there is an increase in glandular epithelium mitotic activity and pseudostratification of nuclei. There is a parallel increase in the proliferation of stromal components as well during this phase. After ovulation, this process is replaced by secretory transformation of glands and a slowing of stromal proliferation. At the cellular level, the early-secretory phase glands are characterized by abundant endoplasmic reticulum, accumulation of glycogen-rich vacuoles, and displacement of nuclei centrally. Six days after ovulation, loss of vacuoles from the cytoplasm corresponds with maximal glandular secretory activity [4, 9].

A complex interplay between mesenchymal cells and immune cells highlights the secretory phase of the superficial endometrial stroma. A substantial portion of the uterine leukocyte population is made up of CD56–/CD16+ uterine natural killer (uNK) cells, which are believed to play a tolerizing role in maternal allorecognition of fetal trophoblasts, rather than cytotoxicity. This cell population increases dramatically after ovulation and vanishes before menses in the absence of pregnancy. When conception occurs, the uNK cells are largely found in proximity to spiral arteries and extravillous trophoblasts in early pregnancy. The activity of uNK cells have been shown to be controlled by steroid hormones as well as local chemokines, including those containing the (C-X-C motif) and various interleukins [1, 4].

Macrophages (CD68+ and CD163+) are also found in the superficial endometrium, rapidly accumulating in the stroma after ovulation and declining in the absence of progesterone. T cells are found scattered throughout the endometrium with little to no menstrual-cycle change in concentration, as well as uterine dendritic cells (uDCs) which are most prominent in decidua of pregnancy [4].

The end of the secretory phase and beginning of the premenstrual phase is characterized by degradation of the stromal network, infiltration of the stroma by leukocytes, and cessation of glandular activity in the absence of the appropriate signals, such as hCG from developing trophectoderm. The degradation of the stromal network is catalyzed by matrix metalloproteinases (MMP), which become activated in the setting of falling progesterone levels. Evidence of apoptosis is evident throughout the tissue, and the ultrastructurally electron-dense contents of glandular cells characteristic of secretion vanish. These structures include the well-developed rough endoplasmic reticulum, Golgi apparatus, and glycogen-secreting cytoplasmic projections [1, 4].

4. Microarchitecture and implantation

The implantation of the blastocyst is a highly organized, selective process that, with some variations, is preserved among mammals. In women, nonhuman primates and other hemochorial placental species a narrow "window of implantation" (WOI) exists, during which the endometrium is capable of "receiving" the trophectoderm of the blastocyst. The interaction is orchestrated by a variety of molecules and is overall regulated by steroid hormones [4, 9]. Recent research suggests the WOI only lasts between 12 and 48 h, and is often shifted in patients with infertility [3]. In 1999, Wilcox et al. narrowed the timing of implantation to between 8 and 10 days after ovulation, with increased embryonic losses correlated with later implantation [10].

The process of implantation follows four well-described steps, which is coordinated with endometrial preparation by changes in steroid hormones. The focus here starts with apposition and transient adhesion of syncytial trophoblast cells to the endometrial epithelium, which is followed by firm attachment and finally, trophoblast invasion. As the blastocyst enters the uterine cavity, the zona pellucida is shed allowing for exposure of the trophectoderm [9, 11]. Driven by progesterone, the secretory phase endometrial epithelial cells enter a hypersecretory state, with characteristic features described as the *Arias-Stella reaction*. This

hypersecretory state of the tissue provides the necessary histiotrophic nutrition essential for embryo and placental survival, as vascular remodeling occurs later [12, 13].

The molecular basis of blastocyst invasion is of active interest in the field, as failure of these mechanisms is associated with pregnancy loss. Current research suggests that mucin (MUC)1, a large transmembrane mucin and a barrier to implantation is downregulated and/or removed through the action of surface proteases and decreased expression of progesterone receptors. The loss of MUC1 allows for appropriate apposition, adhesion, and attachment of the embryo to the endometrium. Initial transient adhesion is mediated by selectins and galectins. More firm attachment is mediated by integrins, including $\alpha\nu\beta3$ and $\alpha4\beta1$, and CD44 and their shared ligand, osteopontin (OPN). Other attachment-associated molecules include trophinin, HB-EGF, fibronectin, vitronectin, laminin, IGFBP1, and the latency associated peptide linked to TGFβ [2–4, 9, 11].

Specialized surface macromolecules have also been implicated in blastocyst adhesion and invasion. Endometrial epithelium consists of both ciliated and nonciliated, secretory cells, the proportions of which are regulated by estrogen levels. The secretory cells develop transient surface structures in response to progesterone levels, called pinopodes, during the time of maximal receptivity [14]. These structures are involved in pinocytosis and contain various adhesion molecules, including $\alpha\nu\beta3$, glycodelin, and OPN [15]. The development of pinopodes is dependent upon HOXA-10, a homeobox gene whose expression is vital for endometrial receptivity, regulating both endometrial stromal cell proliferation and epithelial cell morphogenesis [16]. Blocking the expression of HOXA-10 results in a significant reduction in the number of pinopodes. Although some evidence points to pinopodes role in adhesion and invasion of the embryo, their precise function and overall importance is still debated [2, 3].

Adhesion via these molecules is static dynamic process. Extracellular contact with appropriate ligands transmits signals, through a variety of pathways, into intracellular cascades that results in gene transcription and protein expression that mediate migration, proliferation, and cytoskeletal remodeling. The overall result is the successful invasion of the embryo into a primed endometrium, where it has the potential for growth and development [2–4].

5. Receptivity markers and clinical applications

The assessment of endometrial receptivity has drastically changed since the establishment of the Noyes' criteria for histologic dating in 1950 [6]. Once the clinical significance of the pathological criteria was questioned, a more detailed understanding of the biochemical pathways influenced by steroid hormones during the menstrual cycle led to new targets to identify endometrial receptivity [17]. Initially, single molecules were analyzed. With the advent of microarray technology and massively parallel, next generation RNA sequencing, vast amounts of molecules can be analyzed at the same time to give a much more complete picture of the endometrial environment [1, 3, 4].

Cytokines are involved in many processes of the ovarian and endometrial cycles and have been shown to play a critical role in implantation. Leukemia inhibitory factor (LIF) is an IL-6 family member and its expression has been demonstrated in the human endometrial

epithelium during the mid- to late-secretory phase [16]. In women of proven fertility, endometrial biopsies demonstrated LIF mRNA expression increased from day 18 to 28, with a peak at day 20, and showed a corresponding 2.2-fold increase in LIF protein secretion between the proliferative and secretory phase [18]. IL-6, another cytokine expressed in the endometrium shows a regulated temporal pattern throughout the menstrual cycle with the highest detected levels during the luteal phase. IL-6 mRNA levels increase progressively during the mid- to late-secretory phase and IL-6 protein was strongly expressed in luminal and glandular epithelial cells during the window of implantation. The protein is strongly pronounced. Bone morphogenic protein 2 (BMP2), a member of the TGF-β superfamily, is first detected in the stroma surrounding the site of blastocyst attachment during the mid-secretory phase. BMP2 is considered a critical regulator of decidualization due to its role in regulating proliferation and differentiation, as well as its expression during the implantation period [19, 20].

Amniotic fluid contains very high concentrations (~5 μg/ml) of prolactin (PRL), which is produced by the decidua. It has been determined that endometrial PRL production begins around cycle day 22, and levels rise throughout pregnancy. Similarly, high levels of IGFBP-1 and LEFTY2 are produced by secretory phase endometrium in response to progesterone and expression of these can be recapitulated in vitro. Given their abundance and production during the menstrual cycle, these proteins serve as potential markers for endometrial receptivity, although clinic utility is not yet clear [1–4, 11].

Prostaglandins (PGs) have been shown to play a crucial role for successful embryo implantation due to their vasoactive properties. The generation of PGs from membrane-bound arachidonic acid is achieved by cytosolic phospholipase A_2 (cPLA_2) and cyclooxygenase (COX). Studies in female mice lacking cPLA_2 or COX-2 enzymes have demonstrated the vital role of PGs in implantation. PGE_2 and PG$F_{2\alpha}$ expression was detected in human endometrium throughout all stages of the menstrual cycle but was downregulated during the late-secretory phase [16].

Several integrins have been identified as possible markers of uterine receptivity and have been noted to undergo alterations in the epithelium and decidua during implantation. The co-expression of α1β1, αvβ3, and α4β1 heterodimers marks the period of endometrial receptivity by mediating firm attachment between the embryo and endometrium. The regulated expression of secretory phase integrins suggests that steroid hormones likely play a role in their presence; for example, α1β1/laminin receptor (VLA-1) expression on secretory phase endometrial epithelium is suggestive of progesterone-induced upregulation. The firm attachment mediated by integrins also generates other integrin-associated ligands. OPN, a ligand for αvβ3, is significantly upregulation in endometrial epithelial cells and mediates cellular adhesion and migration during embryo implantation. Calcitonin, a known upregulator of αvβ3, is transiently produced in the uterine epithelia during the period of implantation. It downregulates E-cadherin expression and promotes the outgrowth of trophoblasts into the uterus [16, 21].

Another critical endometrial glycoprotein, MUC1, is a factor that interferes with cellular adhesion. MUC1 is likely the first uterine molecule that the blastocyst encounters during the apposition phase, where it is thought to repel the embryo until the time and place is ideal

for firm attachment. This is confirmed by the apparent local downregulation of MUC1 by progesterone before implantation in the receptive endometrium of mice. The reduced expression facilitates embryo-epithelial interactions by unmasking cell adhesion molecules on the endometrial surface [16]. When measured in humans, MUC1 showed increased generalized expression during the peri-implantation period, somewhat contradicting the studies in other species.

Two cytoskeleton-related proteins, stathmin 1 and annexin A2, have opposing regulation in the receptive versus pre-receptive endometrium. Stathmin 1 is a phosphoprotein that regulates microtubule dynamics during cell cycle progression, specifically at the embryo implantation site. In receptive human endometrium, downregulation of stathmin 1 supports decidualization. Annexin A2, an apical surface molecule in receptive human endometrium, is involved in cellular differentiation, regulation of prolactin secretion, and prostaglandin formation. Annexin A2 expression is highest in the mid- to late-secretory phase and decreased in the pre-receptive phase. This pattern of expression, along with in vitro effects on embryo adhesiveness, suggests annexin A2 plays a role in implantation [22].

BCL6, a transcriptional repressor mutated in some lymphomas, is associated with inflammation and significantly elevated values are seen in the secretory phase of patients with endometriosis and otherwise unexplained infertility. Data suggest that BCL6 is associated with progesterone resistance, leading to implantation defects and increased IVF failures [23, 24]. It is being developed as a diagnostic biomarker for endometriosis.

Ion channels and gap junctions in the endometrium have recently demonstrated a role in regulating endometrial receptivity and embryo implantation. The volume of electrolyte-containing fluid in the uterine lumen fluctuates throughout the menstrual cycle under the influence of ovarian hormones and is significantly reduced in the mid-secretory phase, encouraging blastocyst-endometrial apposition. This is suggestive of a net fluid absorption across the endometrium during the receptive phase. Cystic fibrosis transmembrane conductance regulator (CFTR) mediates Cl^- efflux, which is essential for epithelial fluid secretion. The endometrial epithelium is known to contain CFTR, playing an active role in endometrial Cl^- and fluid secretion. Downregulation of CFTR by progesterone during the secretory phase contributes to the decrease in fluid volume, which aids embryo implantation. The epithelial sodium channel (ENaC) also is present in the endometrium establishing a sodium gradient and providing a driving force for water absorption. CFTR has an inhibitory effect on ENaC, so the downregulation of CFTR during the secretory phase enhances the absorptive activity of the endometrial epithelium. ENaC is upregulated by progesterone, furthering the absorptive properties of the endometrial epithelium during the secretory phase. Other ion channels such as K^+ and Ca^{2+} and ion transporters, SLC4 and SLC26, are emerging as important players in regulating certain processes of embryo implantation [19]. Connexin 43 gap junctions also appear to mediate water and small molecule (<1.2 nm Stokes radius) transport and decidual differentiation [7, 25].

Microarray analysis of endometrial tissue allows for assessment of hundreds to thousands of molecules at once. Genomic and proteomic analyses have identified varying levels of genes and proteins implicated in a wide array of activities during decidualization. Receptivity

markers are measured in clinical settings to avoid implantation failure and to hopefully provide a more favorable outcome for patients utilizing ART. Although some of the mentioned biomarkers have only recently been discovered as key players in the human receptive endometrium, these discoveries show promise in better understanding the complex interactions throughout the secretory phase and window of implantation.

Aspiration and assessment of secreted uterine fluids, called secretomics, which largely looks at protein and lipid levels, allows for high-throughput analysis of endometrial secretions during the secretory phase without the need for biopsies. Although our understanding of microarray technology as it related to infertility is still evolving, current and future products on the market will likely find clinical utility and are discussed in more detail later in the chapter [3, 26, 27].

6. Pathologic states and the secretory phase

Given the complex nature of endometrial receptivity, it is very vulnerable to perturbation. Local factors that can negatively impact receptivity and implantation can be broadly grouped into mechanical and inflammatory factors. Mechanical abnormalities encompass both congenital anomalies and acquired conditions. Local inflammatory factors include endometriosis, adenomyosis, hydrosalpinges, and endometritis [2, 28, 29].

Mechanical abnormalities of the uterus such as uterine septa, fibroids, polyps, and adhesions result in physical barriers to successful fertilization and implantation. These conditions are linked with recurrent pregnancy loss and infertility and substantial evidence exists that shows surgical correction of these abnormalities can improve outcomes [2, 29].

Given the delicate regulation of the menstrual cycle and the narrow implantation window, inflammatory factors that affect signaling pathways can effectively derail normal physiologic processes. In the setting of local inflammation, progesterone resistance and estrogen receptor dominance can result in impaired implantation. With endometriosis, for instance, there is an increase in inflammatory cytokines including TNFα, INFγ, IL-1, and IL-17. This leads to downstream effects such as phosphorylated STAT3, which in turn leads to an estrogen dominant and progesterone resistant state, shown through microarray analysis [2, 28]. Decreased expression of IL-11 and CCL4, which are associated with embryo receptivity, is found in chronic endometritis and is believed to be related to infertility associated with this condition [30]. Low integrin levels have been associated with inflammatory conditions and reduced $\alpha\nu\beta3$ expression, which can be caused by increased estrogen levels, and have been tied to IVF failure. Conversely, aromatase overexpression is seen in inflammatory states, and is linked with predicting failure in ART cycles. Other chemokines and cytokines, such as interleukins, are similarly linked to inflammation and pregnancy failure [2].

Although there still exist many gaps in our understanding of endometrial receptivity and implantation at the level of the uterus, pregnancy and ART failure cannot be fully explained by local factors. There exist several systemic disorders that can impact the uterine

environment and the embryo's ability to implant. These diseases include thyroid dysfunction, vitamin D deficiency, hyperprolactinemia, inflammatory bowel disease, obesity, and smoking. There exists significant evidence relating hypothyroidism and poor fertility/IVF success rates, prompting levothyroxine treatment in patients with TSH < 2.5 mIU/L [2]. Obesity has similarly been linked to infertility, with evidence demonstrating that even modest weight loss improves pregnancy rates [2, 31]. However, our understanding of how these systemic states affect fertility is still limited, and further research is warranted to fully evaluate these relationships.

7. Future directions

Historically, dating of the receptive endometrium was based on morphologic criteria [6]. Shortcomings in the sensitivity and specificity of this method, fueled by significant advances in our molecular understanding of the endometrial cycle, have led to new approaches [17]. Although utilization of single molecular markers has not yielded satisfactory results, high-throughput analysis has been more promising [3]. The recent application of the "-omics" technologies, that utilize high-throughput techniques with sophisticated large data analysis to generate far more detailed patterns of molecular and biochemical processes, has revolutionized our understanding of the receptive endometrium and promises to yield clinically useful tools [3, 4, 26, 27].

The analysis of the endometrial cycle using transcriptomics has been actively investigated for over a decade [3]. Using gene expression microarray techniques, researchers have been able to study the expression of thousands of genes simultaneously during different phases of the endometrial cycle. They have identified unique gene profiles during the window of implantation, which includes important factors previously identified, such as LIF, OPN, CXCL14, glycodelin, IL15, L-selectin ligands, and various antioxidants [3]. One example of a commercially successful diagnostic test based on a transcription signature is the endometrial receptivity array (ERA). In controlled trials, use of this tool identified shifted windows of implantation in women with implantation failure. Using the test to adjust the timing of embryo transfer yielded pregnancy and implantation rates similar to control groups [32].

Although the current transcriptomics method has yielded impressive results, it relies on a tissue biopsy. An alternative matrix that researchers have analyzed since the 1970s is endometrial fluid [16]. More recently, high-throughput analysis of vaginal secretions, coined secretomics, has been utilized [26, 33]. As it focuses on sampling extracellular fluid, the analytes of interest are mainly proteins and lipids, with mass spectroscopy and chromatography used as the analytical methods. Analysis of lipid levels has revealed elevated levels of PGE2 and PGF2α during the WOI. Although preliminary information from endometrial secretions is intriguing, further investigation is required [26, 33].

Our understanding of infertility and endometrial receptivity has come a long way over the past several decades. However, many questions remain unanswered. New molecular and

biochemical markers during the endometrial cycle continue to be discovered and they are likely to inform even better diagnostic algorithms. These include potential targets for pharmaceuticals and predictors of therapeutic success. Discoveries in this arena are fueled by advances in research technologies. High-throughput analysis, in particular, has revolutionized the field. Massively parallel sequencing will allow an even more detailed look at the unique genomic and transcriptomic signatures of the receptive endometrium. Translation of this research into clinical trials, and then clinical practice, is expected to have a major impact on the field of reproductive endocrinology and infertility.

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