Endometrium in women with polycystic ovary syndrome during the window of implantation

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Summary

The human endometrium undergoes to a complex series of proliferative and secretory changes in each menstrual cycle and displays only a short period of receptivity, known as the "window of implantation", necessary for the implantation of the blastocyst in the uterus. The implantation process occurs in a sequential manner, leading to the establishment of pregnancy. Morphofunctional changes during this period may prevent or hinder the implantation. For this reason, the study of the endometrium at this stage is important for the improvement of therapies that may interfere with the mechanisms involved in maternal-embryonic interaction. Several gynecological disorders, including polycystic ovary syndrome (PCOS), are associated with decreased fertility and uterine receptivity. In spite of recent advances in assisted reproduction techniques, allowing the selection of high quality embryos, the implantation rate remains low and has not increased enough in recent decades. This article aims at reviewing the endometrial aspects of the "window of implantation" in women with polycystic ovary syndrome, focusing mainly on adhesion molecules. For that purpose, we analyzed 105 articles published in journals indexed in PubMed in the last 50 years (up to May 2011). In conclusion, the endometrial receptivity seems to be the major limiting factor for the establishment of pregnancy in a large number of gynecological diseases, including PCOS, and treatment to improve implantation rates is likely to be taken towards this direction.

Keywords: Endometrium; embryo implantation; cell adhesion molecules; infertility, female.

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Introduction

The polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935, characterized by the association between polycystic ovaries and amenorrhea, infertility, hirsutism and obesity[1]. It is estimated to affect approximately 5% to 7% of women of reproductive age, representing the most frequent cause of anovulatory infertility[2,3].

The diversity of PCOS clinical features has led to the creation of three consensuses to establish diagnostic criteria for this syndrome. The first was the meeting of the National Institutes of Health (1990), which defined as PCOS diagnostic criteria the presence of clinical or laboratory hyperandrogenism and spaniomenorrheic cycles or amenorrhea (fewer than six menstrual cycles per year), provided that other alterations such as Cushing's syndrome, hyperprolactinemia, adrenal enzyme deficiency and thyroid disorders had been ruled out[4].

The second was the consensus of Rotterdam (2003), carried out by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), which established as diagnostic criteria: spaniomenorrheic cycles or amenorrhea (chronic anovulation), clinical or biochemical signs of hyperandrogenism and the presence of polycystic ovaries (identified by ultrasonography), with at least two of three criteria being necessary to define the diagnosis of PCOS[5].

The third consensus was proposed by the Androgen Excess and PCOS Society (AE-PCOS) in 2006, which established as diagnostic requirements: hyperandrogenism (hirsutism and/or hyperandrogenemia), ovarian dysfunction (oligo-/anovulation and/or polycystic ovaries), while ruling out other causes of androgen excess[6,7]. Thus, based on the ESHRE/ASRM (2003) and AE-PCOS Society[6] criteria, the wide spectrum of signs and symptoms that are observed in these patients can be identified[8].

The pathophysiology of PCOS has puzzled gynecologists and endocrinologists for many years and is very difficult to be defined. The clinical features of PCOS demonstrate a disorder of follicular development resulting in chronic anovulation, where the endocrine environment is characterized by a state of equilibrium in which the concentrations of gonadotropins and sex steroids have little variation in comparison with the cyclic pattern of hormone concentrations that occurs during the normal cycles[9].

PCOS usually displays increased serum concentrations of luteinizing hormone (LH) in 60% of cases, low levels of follicle stimulating hormone (FSH) and increased LH/FSH ratio. The decrease in FSH levels results from increased frequency of GnRH pulses and chronic elevation of estrone (peripheral aromatization of androstenedione) and normal or slightly increased levels of inhibin B, derived from small ovarian follicles[10].

PCOS has been considered as a complex disorder, with interaction of genetic variants and environmental factors that can interact, combine and contribute to its pathophysiology[6]. Studies have been developed to identify genetic variants involving the regulation of gonadotropin secretion and action, insulin, energy and weight regulation, in addition to androgen synthesis and action[1].

An association between glucose intolerance and hyperandrogenism was first recognized by Archard and Thiers in 1921, when they described the case of a diabetic woman with a beard[1]. Insulin resistance with compensatory hyperinsulinemia is now recognized as one of the key factors in this syndrome[11,12]. Approximately 35% of women with PCOS also have impaired glucose tolerance and 7% to 10% meet the criteria for type 2 diabetes. The excess insulin action would be exerted by a direct action on ovarian theca cells via IGF-1 receptor or insulin itself, or by decrease in the hepatic production of IGF-binding protein (IGFBP), increasing the bioavailability of IGF-1 and IGF-2, in addition to stimulating cytochrome P450c17α, which increases ovarian and adrenal androgen production[13].

Insulin and LH act synergistically, stimulating ovarian androgen production. Obesity is a common feature in PCOS, representing another mechanism for the development of insulin resistance[14,15].

Insulin resistance and hyperinsulinemia are important in the pathophysiology of PCOS, but about 25% to 50% of these women do not exhibit these alterations, leading to the conclusion that insulin resistance and hyperinsulinemia are not primary causes or a pathogenic factor of all women with PCOS[1].

Ovarian dysfunction (anovulation or low progesterone production) in women with PCOS may increase the risk of miscarriage[16]. While anovulation is an obvious cause of infertility in PCOS, emerging data suggest that endometrial receptivity also contribute to infertility[3].

The occurrence of spontaneous ovulation in spaniomenorrheic women with PCOS does not necessarily lead to an increase in endometrial receptivity, especially in cases of fertilization programs[17]. On the other hand, infertility treatment with ovulation induction agents such as clomiphene citrate has shown disappointing results, with low pregnancy rates[16]. This fact is perhaps best illustrated with *in vitro* fertilization (IVF), where success rates also remain low in spite of the excellent quality of transferred embryos. This suggests that anovulation is not the only cause of infertility[18], implying that endometrial receptivity might have a crucial role in the establishment and development of pregnancy in women with PCOS.

This article aims at reviewing the endometrial aspects of the "window of implantation" in normal endometrium and in women with polycystic ovary syndrome, focusing mainly on adhesion molecules.

Methods

We conducted a search at http://www.ncbi.nlm.nih.gov/pubmed/ electronic database using the following keywords: (I) "implantation", (II) "implantation AND PCOS", (III) "implantation markers", (IV) "endometrium", (V) "polycystic ovarian syndrome AND endometrium", (VI) "implantation window".

The initial selection of articles was based on their titles and abstracts, analyzing the full texts of those related to the subject. A total of 105 publications were retrieved from this search, excluding repetitions, and we selected for analysis the ones considered more relevant by the authors of this review.

Results

Normal endometrial morphology

The endometrium is the mucous membrane lining the uterine cavity, with an embryonic origin of the fusion of the Mullerian ducts, around the 20th week of gestation. The surface is covered with simple columnar epithelium, which is in deep contact with endometrial stroma and glandular system. It has an essential role in reproduction and is considered one of the most complex tissues in the body, responding to cyclical changes in estrogen and progesterone in the ovarian menstrual cycle, as well as the complex interaction between autocrine and paracrine factors[1].

The description of menstrual physiology is developed based on specific anatomical and functional changes in the glands, blood vessels and endometrial stroma. This distribution occurs in a simplified form in the phases: proliferative (early, middle and late) and luteal or secretory phase (early, middle and late)[19]. The whole process constitutes an integrated evolution cycle of endometrial growth and regression, which is repeated throughout the female reproductive life[20,21].

The proliferative phase is associated with follicular growth and increased estrogen secretion, leading to endometrial reconstruction. Mitoses become prominent and pseudostratification is observed. All tissue components (glands, stromal and endothelial cells) show proliferation, with DNA nuclear and RNA cytoplasmic syntheses, which peak on days 8-10 of the cycle, reflecting maximum concentration of estrogen receptors in the endometrium[22]. An important characteristic of this phase is the increase in ciliated cells and cells with microvilli, necessary for the mobilization and distribution of endometrial secretions. The microvilli are cytoplasmic extensions of endometrial epithelial cells in response to estradiol and have the function to increase the active cell surface[23].

The first morphological sign that ovulation has occurred is the appearance of intracytoplasmic glycogen vacuoles in the glandular epithelium, around the 18th day of the menstrual cycle. The glandular cells become tortuous and exhibit a nucleolar channel system within them, due to progesterone. The vessels become more spiraled; then the active secretion of glycoproteins and peptides occurs in the endometrial cavity. Plasma transudation and circulation immunoglobulins are also sent to the region, through binding proteins produced by epithelial cells. The secretory peak is reached seven days after the peak of gonadotropins through the cycle, coinciding with the time of blastocyst implantation. The proliferation ceases three days after ovulation, with a decline in mitosis and DNA synthesis due to progesterone interference with the estrogen receptor expression[24].

The secretory phase shows signs of the combined reaction of estrogen and progesterone activity on the endometrium. Progesterone stimulates the 17-β-hydroxysteroid dehydrogenase and sulfotransferase, which converts estradiol to estrone sulfate, and this is rapidly excreted from the cell[1]. Progesterone can inhibit specific genes that undergo cyclical changes during the menstrual cycle and also antagonize the stimulatory action of many oncogenes that are likely to mediate estrogen-induced growth. The end result is the stability of the endometrial lining and, consequently, the prevention of hyperplastic states[1,25].

The luteal phase is the most widely studied and the histological changes are of clinical importance, serving as a guideline for the diagnosis of imperfect ovulation, unsuitable for the process of implantation. The early luteal phase (day 15) is characterized by the presence of glycogen-rich secretory vacuoles below the nucleus. In the middle secretory phase, the vacuoles are located near the lumen of the glands and the nuclei are located in the basal position and there is secretion in the glandular lumen as well as stromal edema. The endometrial thickness reaches 6-8 mm. In the late luteal phase, alterations occur in the stroma with prominent and dilated arterioles, reaching up to the surface layer and the endometrium is called pre-deciduous. The absence of pregnancy determines the involution of the corpus luteum with decreasing levels of estrogen and progesterone and the onset of a menstrual period[1].

Adequate levels of these hormones are important for the harmonic endometrial development, both glandular and stromal, enabling receptivity for the blastocyst implantation. In the absence of adequate endometrial preparation, there will be several infertility possibilities[26].

Noyes et al.[27] examined the histological characteristics of endometrial biopsies performed during 8,000 spontaneous cycles in 300 women and established the criteria for endometrial dating, which were accepted as the gold standard for endometrial receptivity, detecting abnormalities in the latter. This classic study is still much used for the chronological analysis of endometrial alterations; however, deficiencies have been identified. The dating is more specific in the early and late luteal phases, but not during

the period of the "window of implantation", demonstrating few histological parameters and great inter-observer variability, especially in infertile women in this cycle phase[28].

Recent gene expression studies in endometrial tissue have shown that some genes present in the proliferative phase of the menstrual cycle are essentially related to DNA replication, leading to cell proliferation and remodeling. After ovulation, with the production of progesterone, the endometrium undergoes a series of changes, including inhibition of cell proliferation, DNA synthesis and mitotic activity, initiating cellular differentiation, which is related to the preparation of the endometrium for potential embryo implantation. The epithelial tissue proliferation inhibition is related to genes regulated by progesterone, including the down-regulation of estrogen receptor and up-regulation of the estrogen-metabolizing enzymes such as 17-β-hydroxysteroid dehydrogenase, which effectively minimizes estrogen action on this cell type. Moreover, progesterone is related with the regulation of androgen receptor (AR) in the epithelium and in the stroma, seven to ten days after ovulation, where the endometrium becomes receptive to embryo implantation during the period called the "window of implantation"[9].

Window of implantation

The embryo implantation represents the most critical step in the reproductive process in many species. It consists in a biological phenomenon, in which the blastocyst binds closely to the endometrial surface to form the placenta, which provides an interface between fetal and maternal circulation[29,30]. The implantation requires a receptive endometrium and an embryo at the blastocyst stage, as well as an interaction between both[31]. The existing literature data are still scarce on the endometrium and the initial implantation mechanisms[18].

The process of implantation occurs in a sequential manner, where each step occurs to ensure the next one, leading to the establishment of pregnancy. It can be classified into three stages: apposition, adhesion and invasion. In the apposition phase, the embryo leaves the *zona pellucida* overlying the endometrium and the trophoblast cells unsteadily attach to the surface of the receptive endometrial epithelium[32,33]. The blastocyst then closely attaches itself to the endometrial epithelium, at the endometrial basal lamina and stromal extracellular matrix. At this point, the connection between the endometrium and the embryo is sufficiently close to resist displacement by uterine flow, i.e., the L-selectins present in the mucins (glycoprotein 1 - MUC1) of the endometrium surface epithelium cells, which express receptive epitopes that help with blastocyst attachment[34].

The first sign of this reaction occurs around the 21st day of the menstrual cycle in humans and coincides with an increase in vascular permeability at the site of blastocyst attachment. Subsequently, the blastocyst penetration occurs, invading the stroma to establish a relationship with the maternal vasculature, and although this activity is mainly controlled by the trophoblast, the decidua also limits the extent of invasion[3,35].

Implantation occurs during a limited period between the 20th and 24th days of the menstrual cycle, known as "window of implantation"[36]. This process involves a complex sequence of events that is crucial to establish pregnancy. Many molecular mediators, under the influence of ovarian hormones, have been postulated to be involved in this fetal-maternal interaction[26]. Morphofunctional alterations during this period may prevent or hinder the implantation. For this reason, the study of the endometrium at this phase is important to improve the mechanisms involved in the maternal-embryonic interaction[3].

During the window of implantation, endometrial stromal cells undergo a decidualization process due to progesterone, a process that is characterized by changes in the cytoskeleton (down-regulation of smooth muscle actin) and up-regulation of prolactin, of the insulin-like growth factors (IGF), IGF-binding proteins (IGFBPs), insulin and relaxin receptors, among others. The decidualization process is important to regulate trophoblast invasion and establish a suitable environment of cytokines and immunomodulators in the stroma during implantation. In the absence of embryo implantation, withdrawal of estrogen and progesterone initiates important endometrial events, like vasomotor reactions, cell apoptosis and increased metalloproteinase and prostaglandin production, resulting in the shedding of the endometrial tissue and menstruation[3,37].

Many molecules have been characterized on the endometrial or embryo surface, but the precise function of each one remains unknown. Researchers have explored several signaling proteins such as interleukins, receptors and ligands, cytokines and growth factors to determine how the embryo implants in the endometrium. A better understanding of the molecular involvement in implantation will allow the knowledge of blastocyst implantation failures in the endometrium[18,26].

The endometrium receptivity consists in the acquisition of adhesion ligands associated with fewer inhibitory components, which could form a barrier to implantation[29].

The family of cell adhesion molecules is comprised of four members: the integrins, cadherins, selectins and immunoglobulins. The surface ligand, usually glycoproteins, mediates cell-to-cell adhesion and has as classical function the maintenance of tissue integration, wound healing, cell migration and tumor metastasis[26]. A model shown in the literature is the possibility that the embryo expresses L-selectin on its surface and the endometrium

expresses appropriate ligands and integrins. This mechanism mimics the attack of other cells, including leukocytes to sites of inflamed endothelium[18].

The integrins, cell adhesion molecules (CAMs) are considered good markers of endometrial receptivity and vital to cell communication. They constitute a family of glycoproteins, formed by the two different non-covalent bonds: α and β subunits. Integrins participate in cell matrix and cell-to-cell adhesion in many physiological processes, such as embryological development, hemostasis, thrombosis, wound healing, immune and non-immune defense mechanisms and oncogenic transformation. A variety of integrins has been demonstrated in the lumen of glandular endometrial epithelium[38].

An increase in integrins α1 β1, α4 β1 and αVβ3 has been described in the endometrium in the midluteal phase (20th -24th day of the menstrual cycle), and the expression of subunit β3 showed no increase before the 19th day, which has been proposed as an endometrial blastocyst receptor[25]. They undergo hormonal influences, where high estrogen levels inhibit the expression of integrins and increases progesterone. Integrins have been expressed by the trophoblast at the time of implantation[39], showing the possibility of a sandwich model in embryonic adherence[26].

Cadherins constitute a group of cell surface transmembrane glycoproteins responsible for the calcium-dependent cell-to-cell adhesion mechanism. They are divided into sub-classes E, P and N-cadherins. Regarding implantation, subunit E-cadherin is the most studied and is located in the lateral plasma cell membrane, important for the junction between epithelial cells[40]. Studies in mouse embryos have shown that E-cadherin gene mutations result in pre-implantation defects[41]. The role of this protein in human implantation is not known, but its levels have been shown to be increased in the luteal phase[42], although no variations have been demonstrated in the menstrual cycle by immunohistochemistry studies[43].

In vitro studies with Ishikawa cell cultures have shown a transient increase in intracellular calcium triggered by calcitonin, suppressing the expression of E-cadherin at the cell contact site[44]. Progesterone induces calcitonin expression in the endometrial epithelium in the middle secretory phase of the menstrual cycle[45], probably by regulating the expression of E-cadherin. It is possible that E-cadherin has a dual role: in the initial phase, it is required for cell adhesion and at the time of implantation, it decreases to allow blastocyst invasion[26].

Selectins are glycoproteins that also belong to the CAM family and include P-selectins, L-selectins and E-selectins. L-selectin is important for the process of human implantation and consists of a large glycosylated extracellular domain and a small cytoplasmic tail[46]. They are known to play a role in transendothelial leukocyte migration[47]. The adhesion system of selectins is well established in the maternal-fetal interface. On the side of the blastocyst, L-selectin has been observed and on the maternal side, the expression of selectin ligands such as MECA-79 or Heca-452 is increased during the window of implantation[48]. The immunoreactivity of the L-selectin ligand MECA-79 seems to be stronger in the epithelial lumen than in glandular epithelium[49]. The physiological importance of the interaction between L-selectin and its oligosaccharide ligands was investigated in the endometrium[48] and trophoblastic cells, suggesting that this process could constitute the initial step in blastocyst implantation[50]. The role of L-selectin is regulated by a variety of mechanisms including gene transcription and associations acting on the cytoskeleton, in addition to its topographic distribution by increasing or decreasing the free cell surface. Despite research advances, little is known about the involvement of selectins in embryonic implantation, suggesting that its participation occurs at the initial stages, by signaling the best place for blastocyst implantation into the uterine wall[26].

Among the components of the CAM family, immunoglobulins are the most extensive. The intercellular adhesion molecule-1 (ICAM-1 or CD54) is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily and is expressed on the surface of various cell types such as fibroblasts, leukocytes, endothelial and epithelial cells. This molecule is regulated by inflammatory and noninflammatory cytokines. The interaction of ICAM-1 is essential for the transendothelial migration of leukocytes and several immunological functions[51]. It has been well established that the endometrium, under normal circumstances, contains a large population of leukocytes, including macrophages, T-lymphocytes and granulocytes, which is important in many physiological mechanisms such as decidualization[52], menstruation and childbirth[53]. This population of leukocytes expresses ICAM-1 in the endometrium and was found in both epithelial and stroma cells, suggesting that this protein may play a role in the pathophysiology of the endometrium[54].

The relationship between the expression of ICAM-1 and recurrent pregnancy loss has been investigated, having been identified in endometrial cells in the luteal phase of patients with and without unexplained pregnancy loss[55].

Although ICAM-1 has not been shown to be indispensable in the initial steps of the interaction between the blastocyst and the endometrium, it can participate indirectly in this process by interacting with the immune system[56].

HOX genes are essential for the proliferation, differentiation and endometrial receptivity by mediating some sex steroid functions during each reproductive cycle. The mRNA of the HOXA-10 and HOXA-11 are expressed in epithelial and endometrial stroma cells, especially in the middle and late secretory phases, remaining at high levels

after embryonic implantation[3]. Some morphological and molecular markers, which are specific to the window of implantation are regulated by HOX genes, such as pinopods, β3-integrin and IGFBP-I[57].

Several benign diseases, including PCOS, are associated with decreased cyclical fertility and uterine receptivity[3,18]. In spite of technological advances in assisted reproduction techniques, allowing the selection of top-quality embryos, the implantation rate is still low and has not increased enough in recent decades[3,58]. Uterine receptivity plays a key role in establishing the success of pregnancy and when altered, it may limit the success of assisted reproduction techniques and contribute to infertility in certain gynecological diseases, such as PCOS[18].

Endometrium in polycystic ovary syndrome during the window of implantation

In women with PCOS who are oligo- or anovulatory, the regulatory role of progesterone is suboptimal or absent, and this results in constant non-opposition of estrogen action on the endometrium[3,9]. Thus, endometrial growth and differentiation in women with PCOS are influenced by androgens, insulin and estrogen without progesterone opposition. In the absence of ovulation and the effects of progesterone regulation, the endometrium does not undergo a secretory transformation and is constantly exposed to the stimulating and mitogenic effects of estradiol, which may lead to endometrium overgrowth, unpredictable bleeding patterns, hyperplasia and cancer.

The endometrium of women with PCOS is considered a model of dysfunctional endometrium, demonstrating overexpression of androgen receptors and failing to regulate estrogen receptors (ERs), when compared to normal women[59]. Studies carried out in PCOS have shown differences in complements of steroid receptors and coactivators, when compared to fertile women. The endometrium, in this case, overexpresses androgen receptors and fails to regulate the ER-α (estrogen receptor, α) in the window of implantation[59-61].

PCOS has other common features in addition to hyperandrogenism and ovulatory dysfunction that are not included in the diagnostic criteria already established, such as abnormal secretion of gonadotropins, insulin resistance and metabolic abnormalities (dyslipidemia). Increased expression of AIBI coactivators (nuclear receptor coactivator 3) of the estrogen receptor and TIF2 (transcriptional intermediary factor 2) may enhance the estrogen activity in endometrial cells in PCOS[59].

The existing literature data are not very clear whether there is an endometrial dysfunction in PCOS, regardless of progesterone action. Some studies indicate that the endometrial process, including cell proliferation, differentiation and response to biological stimulus, could be affected by other factors such as cytokines and growth factors, explaining in part the poor reproductive outcomes in this group of women[18].

There is an obvious increase in the deregulated expression of uterine receptivity markers in the endometrium of women with PCOS. Studies show that in ovulatory patients with PCOS, the αvβ3-integrin, HOXA-10, HOXA-11 and the expression of insulin-like growth factor (IGFBP-I) binding protein is decreased during the secretory phase[3,60,62,63]. Literature considerations on the expression and regulation of αVβ3-integrin show that this protein may represent a marker for the human implantation process.

The expression of HOXA-10 *in vitro* has shown to be directly decreased by testosterone, suggesting that androgen decrease could improve endometrial responsiveness[3]. Studies have shown decreased expression of αvβ3-integrin and overexpression of estrogen activity markers (Cyr61) in the window of implantation[64].

Another study also showed that the dysfunction in the implantation would be related to dysfunctional endometrial alterations in women with PCOS[18,37].

Final considerations

The endometrial modifications that occur during the window of implantation require subtle collaboration of a large number of different factors and although some have been described, their individual role in the development of the endometrium is not yet fully understood. Studies in humans have been mostly developed in cycles outside of the pregnancy and genetic suppression experiments (animal or *in vitro*) provide indirect evidence.

The exact mechanism of implantation failure is still poorly understood, particularly in diseases such as PCOS. Although the quality of embryos is an important determinant, the endometrium, through a temporary and coordinated receptivity mechanism, synchronized between its cells and those of the embryo, has an unquestionable contribution to the success of pregnancy.

The reduced expression of uterine receptivity markers and lack of regulation of the expression and activity of steroid receptors can contribute to the low pregnancy rate observed in women with PCOS; however, whether these alterations are due to inadequate progesterone action or increased insulin and androgen action remains to be clarified.

Conclusion

Endometrial receptivity seems to be the main limiting factor for the establishment of pregnancy in a large number of gynecological disorders, including PCOS and treatment to improve implantation rates is likely to be taken towards that direction.

The perspectives consist in the development of tools, such as regulation of transcription factors of endometrial proteins or gene therapy to improve uterine receptivity in infertile women with PCOS and thus, increase implantation rates in this population.

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