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REVIEW ARTICLE

Uterine Function: From Normal to Polycystic Ovarian Syndrome Alterations

Silvana Rocío Ferreira and Alicia Beatriz Motta*

Laboratory of Ovarian Physio-pathology, Center of Pharmacological and Botanical Studies, School of Medicine, University of Buenos Aires, Argentina

Abstract: ***Background*:** The endometrium is one of the most important female reproductive organs. Polycystic ovarian syndrome (PCOS) is a reproductive and endocrine pathology that affect women of reproductive age. PCOS negatively affects the endometrium, leading to implantation failure and proliferative aberrations.

***Methods*:** We conducted a search at the http://www.ncbi.nlm.nhi.gov/pubmed/electronic database using the following key words: endometrial steroid receptors, endometrium, uterine function, endometrium and PCOS, implantation window, implantation and PCOS, implantation markers, inflammation, oxidative stress. We selected the articles based on their titles and abstracts, then we analyzed the full text and classified the articles depending on the information provided according to the sections of the present review.

***Results*:** The endocrine and metabolic abnormalities displayed in women with PCOS promote complex effects on the endometrium, leading to a low rate of implantation and even infertility. Women with PCOS show alterations in the Hypothalamic-Pituitary-Ovarian axis, which results in constant circulating levels of estrogen, similar to those at the early follicular phase, and a deficiency in the withdrawal of estrogen and progesterone. Besides this deficiency in the withdrawal of estrogen and progesterone, the insulin/glucose pathway, adhesion molecules, cytokines and the inflammatory cascade, together with the establishment of a pro-oxidative status, lead to an imbalance in the uterine function, which in turn leads to implantation failure or even endometrial cancer.

***Conclusion*:** Women with PCOS display a dysregulation of the Hypothalamic-Pituitary-Ovarian axis, which alters the steroid pathway. In addition, the deficiency in the withdrawal of estrogen and progesterone in the endometrium results in abnormal endometrial cellular proliferation. The imbalance in adipose tissue observed in PCOS patients reinforces the increase in circulating hormones. The present review describes the role of hormones, metabolites, cytokines, adhesion molecules and the insulin/glucose pathway related to the uterine endometrium in women with PCOS and their role in implantation failure and development of endometrial cancer.

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1. INTRODUCTION

The uterus is a muscular organ of the female reproductive system that is responsible for several reproductive functions, including menses, implantation, gestation, labor and delivery. It consists of three distinct tissue layers: the endometrium, the myometrium and the perimetrium. The endometrium is considered one of the most complex tissues in the body. It is made up of simple columnar epithelial tissue with exocrine glands and a highly vascular connective tissue which supports the developing embryo and fetus during pregnancy.

The present review discusses some aspects of endometrial uterine tissue functions, focusing on the dif-

*Address correspondence to this author at the Center of Pharmacological and Botanical Studies, School of Medicine, University of Buenos Aires, Paraguay 2155 (1121), Buenos Aires, Argentina; Tel: 005411 45083680; Fax: 00541145083680;
E-mail: aliciabmotta@yahoo.com.ar

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ferences between healthy and PCOS endometrial tissues. It also analyzes the response of the women's endometrium PCOS during the implantation process and the contribution of PCOS animal models which study the endometrium particularly.

Our search in *Pubmed* had the aim to collect and analyze articles from different PCOS studies in human or PCOS models in animals or endometrial cultured cells.

PCOS is a reproductive endocrinopathy that affects 5 to 10% of women in their reproductive ages [1] PCOS is characterized by clinical or biochemical hyperandrogenism, oligo/anovulation and/orovarian cysts [2]. Although insulin resistance is not considered in the diagnosis of PCOS, its presence aggravates the symptoms [3]. PCOS is more than a reproductive endocrinopathy commonly because it is associated with other pathologies such as metabolic syndrome, non-alcoholic fatty liver, type 2 diabetes and endometrial cancer [1, 4, 5]. Although the ovulatory disorders in PCOS patients can be corrected, the pregnancy rates remain low and the spontaneous pregnancy loss rates are high [6]. This suggests that uterine dysfunction might also contribute to adverse reproductive outcomes in PCOS [7].

The endometrium of women with PCOS has not been extensively studied but several evidences support abnormal gene expression, which leads to implantation failure, miscarriage and even endometrial cancer [8, 9].

2. PHYSIOLOGICAL ENDOMETRIUM

The uterine endometrium includes epithelial cells, stromal cells, immune cells, and blood vessels [10]. Both epithelial and stromal cells are sensitive to the stimulation of steroid hormones during the menstrual cycle [11]. Estradiol modulates epithelial cell proliferation, whereas progesterone inhibits estradiol - stimulated epithelial cell proliferation [12].

2.1. Endometrial Function During Menstrual Cycle

The human endometrium is exposed to the regulation of steroid hormones, which modulate uterine growth. During the ovulatory cycle, ovarian follicular growth (follicular phase) and circulating estradiol increase, promoting the proliferation and growth of the endometrium, from 2 mm after the postmenstrual phase to 10-12 mm in the peri-ovulatory period [13]. During the follicular phase, the DNA replicates, thus inducing cell proliferation and tissue remodeling [14]. After ovulation, by the influence of progesterone, DNA synthesis is inhibited together with mitotic activity and cellular differentiation. All these changes are necessary to prepare the endometrium for the implantation of the conceptus. By modulating specific genes, progesterone down- regulates estrogen receptors, induces estrogen metabolization in the epithelium [13, 15] and down-regulates the androgen receptor in both the epithelium and stroma [16].

During the "window of implantation", 7 to 10 days after ovulation, the endometrium turns receptive to embryonic implantation. Progesterone induces the decidualization of endometrial stromal cells, triggers or up-regulates prolactin, insulin- like growth factors (IGFs), insulin-like growth factor binding proteins (IGFBPs), and insulin and relaxin receptors [15]. The main task of decidualization is to facilitate trophoblast invasion. If embryonic implantation does not occur, the withdrawal of estradiol and progesterone triggers a set of events that result in menstruation [17]. In addition, the withdrawal of estradiol and progesterone develops a pro-inflammatory state that involves cellular apoptosis and increases the production of prostaglandins and metalloproteinases [14, 18].

To be receptive, the endometrium has to acquire adhesion ligands associated with inhibitory components, which could put a barrier to the implantation process.

2.2. Endometrial Steroid Receptors

The regulation of the endometrium also depends on the spatial and temporal expression of steroid receptors. Estrogen receptors (ERs) and progesterone receptors (PRs) are expressed in the human endometrium and respond to estrogen and progesterone via autocrine or paracrine processes. The pattern of distribution and expression of these receptors are important for the endometrial function. Two isoforms of ERs: alpha and beta are present in the endometrium. From proliferative to late secretory phase ER-alpha, ER-beta and PR decreased its expression in the glandular epithelia [19]

In the normal women, androgen receptors (ARs) have a cyclic action during the menstrual cycle and androgen levels regulate the expression of ERs. AR expression is present in the epithelium and stroma of the endometrium and decreases during secretory phase of the cycle. AR in the decidualizing endometrium controls a network of genes that regulate cell cycle regulation and cytoskeletal organization. Androgen levels increase from proliferative to secretory phase and still rise during early pregnancy because they play an important role in decidual-trophoblast interaction [20, 21]. Recently, Xu *et al.* [22] reported that both the decidualization process and progesterone significantly inhibit AR protein expression *in vivo*, whereas estradiol in-

creases AR protein levels in the stromal cells of mouse uteri. By regulating AR expression, estradiol and progesterone modulate the proliferation and differentiation of uterine stroma and embryo implantation during early pregnancy.

The responsiveness of uterine tissue to the action of progesterone depends on nuclear PRs, which are members of the superfamily of steroid receptors that control transcription of target genes [23, 24]. There are two predominant isoforms of PRs: PRA and PRB, which encode the same PR gene but using alternative promoters and translation start sites [25]. Although PRC, PRM and PRS have been described in human myometrial cells *in vitro* [26, 27], their *in vivo* function remains unknown. PRA and PRB are not functionally equivalent and when PRA and PRB are co- expressed, PRA displays a transcriptional inhibition of PRB [28]. These data suggest that not only the expression of individual PR isoforms but also their ratio are important in the functionality of the endometrium.

It is important to point out that *in vivo* PRA knockout studies in mice have demonstrated that the progesterone-induced inhibition of proliferation (induced by estradiol) disappears, resulting in uterine dysfunction and infertility [29]. These findings suggest that PRA has a central role in uterine function. PRs are able to modulate both genomic and non-genomic responses but also independent mechanisms of nuclear PR activation have been reported in mouse uterine tissue [30].

In the normal human endometrium, non-genomic activities are regulated in a cycle- dependent way [31]; however, the exact mechanisms of each membrane PR in endometrial cells remain to be elucidated. During the proliferative phase, in epithelial cells, the expression of PRA and PRB increases in a similar way, whereas, in stromal cells, PRA expression is greater than PRB expression [32, 33]. During the secretory phase, PRA expression in epithelial cells is decreased whereas that in stromal cells is minimal or shows no changes [32]. These findings suggest that PRA and PRB expressions are differentially regulated.

2.3. Cell Adhesion Molecules and Implantation in the Normal Endometrium

Cell adhesion molecules (CAMs) are intimately related to implantation. CAMs are surface ligands, usually glycoproteins that mediate cell-cell adhesion. CAMs are composed of integrins, cadherins, selectins and immunoglobulins.

Integrins: Integrins participate in both cell-cell and cell-substratum interactions and are present in essentially all human cells. The distribution and expression of integrins are regulated within the cycling endometrium and the disruption of their expressions is associated with decreased uterine receptivity and infertility [34]. Three specific integrins are co-expressed during thehuman menstrual cycle: $\alpha1\beta1$, $\alpha4\beta1$, and $\alpha V\beta3$, but only the $\beta3$ mRNA subunit expression has been shown to increase after day 19 and is not detected before.

Cadherins: Cadherins are responsible for the calcium-dependent cell-to-cell adhesion mechanism. The family of cadherins is formed by three subclasses: E-, P-, and N-. Considering that E-cadherin is located in the adherens junctions and that its suppression results in the dysfunction of cell-cell adhesion, E-cadherin is considered as the most important during the implantation period in different species [8, 35]. During the menstrual cycle E-cadherin shows a dual function. In the preliminary phase, E-cadherin expression is increased on the cell surface because it is required to ensure adhesiveness while in the mid-secretory phase, low levels of E-cadherin are necessary to allow epithelial cells dissociation and blastocyst invasion [8]. Progesterone via calcitonin modulates E-cadherin levels, regulating implantation [36, 37].

Selectins: Selectins are a family of glycoproteins that include P-selectin, L-selectin and E-selectin. They have an important role in leukocyte transendothelial trafficking [38]. Human L-selectin plays a fundamental role during the implantation process [39]. L-selectins are expressed in leukocytes and are able to interact with their carbohydrate-based ligands on the endothelium [8], a step essential for optimal L-selectin-mediated adhesion of leukocytes to the vasculature.

The selectin adhesion system has been well established at the maternal-fetal interface (Achache and Revel, 2006). Over the entire embryo surface, strong staining of L-selectin has been observed [40]. On the maternal side, the expression of selectin oligosaccharide-based ligands, such as MECA-79, is up-regulated during the implantation window [40]. Moreover, pinopode, a progesterone-dependent endometrial projection which appears during the uterine receptivity window, participates in blastocyst implantation. Blastocyst loosely attaches to pinopode via L-selectin ligand (MECA-79). It has been reported that testosterone decreases both uterine pinopodes and MECA-79 expressions during uterine receptivity, leading to the failure of blastocyst implantation [41].

Immunoglobulins: They are the most extensive among adhesion molecules and, among them, ICAM-1 not only is the one that mediates cell-cell adhesion,

constituting a ligand for β2 integrin, but also plays a fundamental role in the transendothelial migration of leukocytes and other immunological functions [42]. The endometrium expresses a wide population of leukocytes such as macrophages, T lymphocytes and granulocytes, which are significant in differentphysiological functions, including decidualization [43], menstruation [44] and parturition [45]. Those leukocytes express ICAM-1 within the endometrium.ICAM-1 seems to play a role in recurrent pregnancy loss and its endometrial release is lower than that in the control group [46]. In summary, ICAM-1 indirectly participates in the interaction between the blastocyst and the endometrium by interacting with the immune system.

2.4. Cytokines and Chemokines

Cytokines encompass a group of proteins that modulate extensive cellular functions such as cellular proliferation and differentiation in the endometrium. Cytokines play a major role in both reparative and inflammatory processes during the menstrual cycle in ovulation, implantation and human endometrial function. Cytokines and chemokines are secreted by endometrial epithelial cells, stromal fibroblasts and immune cells. They are fundamental for the dialog between maternal and embryonic tissues as well as between epithelial and stromal compartments [30, 47]. During the implantation window and the process of decidualization, cytokines, including glycoprotein 130, leukemia inhibitory factor (LIF) and IL-6, facilitate implantation, whereas, the chemokines IL-8, MCP-1 and RANTES recruit leukocyte cohorts to the implantation site [48] Disturbances in cytokine and chemokine expression lead to implantation failure and abnormal placental formation in mice and humans [30, 49].

LIF is a pleiotropic cytokine that belongs to the interleukin (IL)-6 family [50]. Due to its ability to induce macrophage differentiation, LIF was initially described as a hemotopoietic factor [51] but then, autocrine and paracrine effects of LIF, such as proliferation, differentiation and cell survival led to investigate its role in blastocyst development and implantation [52]. Although mRNA expression of LIF has been described in a variety of mammals, its expression during the menstrual cycle are controversial, particularly in the proliferative to early secretory phase. At the time of implantation, LIF peaks in the human endometrium and the blastocyst contains mRNA for LIF receptor [53]. Other authors have found LIF mRNA transcript only in the mid- and late-secretory phases of the cycle [54]. Fertile patients display a 2.2-fold increase in LIF secretion between the proliferative and secretory phase [55]. Moreover, LIF has been proposed as a possible cause of the unexplained infertility and failures of implantation [55].

3. MENSTRUAL CYCLE IN WOMEN WITH PCOS

The endocrinological and metabolic abnormalities displayed in women with PCOS have complex effects on the endometrium, leading to a low rate of implantation and even infertility. In PCOS patients who show anovulatory cycles, the dysregulation of the Hypothalamic-Pituitary-Ovarian axis leads to constant circulating levels of estradiol comparable to those in the early follicular phase [56]. This results in a deficient regulatory withdrawal of estradiol and progesterone in the endometrium, causing abnormal endometrial cellular proliferation, differentiation and tissue desquamation [56].

It is not clear whether the lower receptivity of women with PCOS is due to an altered effect of progesterone or excessive androgen (and/or insulin) signaling. In a murine PCOS model, it has been reported that hyperandrogenism is able to alter the immune, oxidative, apoptotic, and inflammatory states of mice whose endometrial tissue remain in the proliferative phase [57, 58, 59, 60].

The imbalance in adipose tissue displayed in PCOS patients [61] reinforces the increase in the circulating levels of estradiol and testosterone. All these changes result in an accumulation of follicles between 10-12 mm in the cortex of ovaries of women with PCOS, which do not develop a dominant follicle [62]. In addition, hyperinsulinemia, a feature of anovulatory women with PCOS, down-regulates sex-hormone-binding globulin (SHBG), which increases free testosterone levels [63, 64]. Women with PCOS also show increased levels of serum insulin concentration and testosterone/SHBG ratio. These findings and the fact that women with PCOS display lower IGFBP levels as compared with healthy controls [65] contribute to an increase in the concentration of free IGF and testosterone leading to a super stimulation of endometrial uterine tissue losing cyclic desquamation. The absence of normal ovulation also induces the stimulatory and mitogenic effects of estradiol, leading to endometrial overgrowth, unpredictable bleeding patterns, hyperplasia and even endometrial cancer [66].

4. ENDOMETRIAL FUNCTION IN WOMEN WITH PCOS

Women with PCOS often show an abnormal menstrual cycle and anovulation, which result in minimal

or lack of progesterone production and thus in an endometrium thicker than that of healthy controls [67].

It is known that women with PCOS have a decreased endometrial responsiveness to progesterone [4, 68] and that the endometrial PR expression in anovulatory women with PCOS is higher than that in ovulatory PCOS patients [69]. Therefore, women with PCOS show higher PR expression in epithelial cells than in stromal cells [70]. These findings and the fact that animal studies indicate that functional stromal cells are required for epithelial cell proliferation and differentiation in the uterus [10] might explain why PCOS patients display enhanced epithelial proliferation. It is important to point out that in stromal cells from PCOS patients, the increased total PR expression is associated with decreased expression of Ki-67 [10, 71]. Cell proliferation is increased in stromal compartment but not in epithelial compartment [71]. Taken together, these findings allow hypothesizing that the lack of progesterone-induced PR-mediated stromal cell proliferation might be a consequence of the progesterone resistance displayed in women with PCOS but that does not affect the increased proliferation of epithelial cells.

The presence of P450 in the endometrium is controversial. Some groups reported that the endometrium of PCOS patients displays increased expression of aromatase P450, the enzyme that converts testosterone to estradiol [25], and androgen stimulation enhances the synthesis of aromatase P450 mRNA and the production of estradiol in endometrial cells *in vitro* [25]. On the other hand, Bacallao *et al.* did not detect gene or protein expression of P450 aromatase in the endometrium concluding that this enzyme could not be relevant to the pathophysiology of the endometrium.

In women with PCOS, endometrial AR expression remains higher than that of normal fertile controls [72].

It is important to consider what happens to women with "progesterone resistance". Progesterone resistance is defined as the presence of decreased responsiveness of target tissues to bioavailable progesterone [73]. Impaired progesterone response has been described in the endometrium of women with PCOS [68, 74], but little is known about the molecular mechanisms underlying endometrial progesterone resistance.

4.1. PCOS and Endometrial Cancer

The risk of developing endometrial cancer is three times higher in women with PCOS endometrial cancer than healthy women. This means a 9% risk of endometrial cancer in Caucasian women with PCOS compared with 3% in healthy women [7].

Cyclin-dependent kinases (CDKs) regulate the cell cycle and are involved in the possible development of endometrial cancer observed in women with PCOS. In this context, the expression of cyclin D1 is critical in cycle progression through the G1 phase and is associated with CDK4 [75]. Over-expression of cyclin D1 has been described in cancer [76, 77]. In addition, the G1/S transition also requires the action of cyclin E, which is associated with CDK2. It has been reported that p27 negatively regulates the cyclin E/CDK2 complex and that p27 is decreased in women with PCOS [78]. Recently, Plaza-Parrochia *et al.* [79] found that the endometrial tissue from women with PCOS displays high levels of cyclin D1, low levels of p27, and high levels of Ki67, a molecular marker of the cell cycle, all of which lead to increased endometrial proliferation as compared to control tissue. These authors also demonstrated that androstenediol enhances cell proliferation by increasing the levels of cyclin D1 and decreasing those of p27 and that testosterone has a repressor role in the cell cycle. In summary, the estrogenic and androgenic balance could play a fundamental role in endometrial proliferation found in women with PCOS.

4.2. Insulin/Glucose Pathway and Endometrial PCOS Function

Besides progesterone and estradiol, human uterine fluid contains blood-derived glucose that is necessary for synthesis of ATP [80, 81]. There is a close relationship between glucose metabolism, implantation, embryonic development, and pregnancy [82, 83]. Glucose transporters (GLUTs) are responsible for the transport of glucose across the cell membrane, thus regulating glucose utilization [83]. GLUTs have different localization, expression, and regulation in different tissues in both human and rodents [83]. Among them, GLUT4 (SLC2A4) represents an important modulator of glucose homeostasis and the dysfunction of GLUT4 leads to insulin resistance and type 2 diabetes [84]. GLUT4 mRNA and protein have been reported in human and rodent endometrium and uterine stromal cells [82, 85, 86]; however, the exact mechanism of GLUT4 action remains unknown. Data about the mechanisms that regulate GLUT4 expression in the endometrial tissue are limited. Recently, Li *et al.* [86] reported that GLUT4 is down-regulated under conditions of hyperandrogenemia in tissues from PCOS patients and in an induced PCOS-like rat model.

They also reported that changes in endometrial GLUT4 expression in PCOS patients involve the androgen-dependent alteration of AR expression and

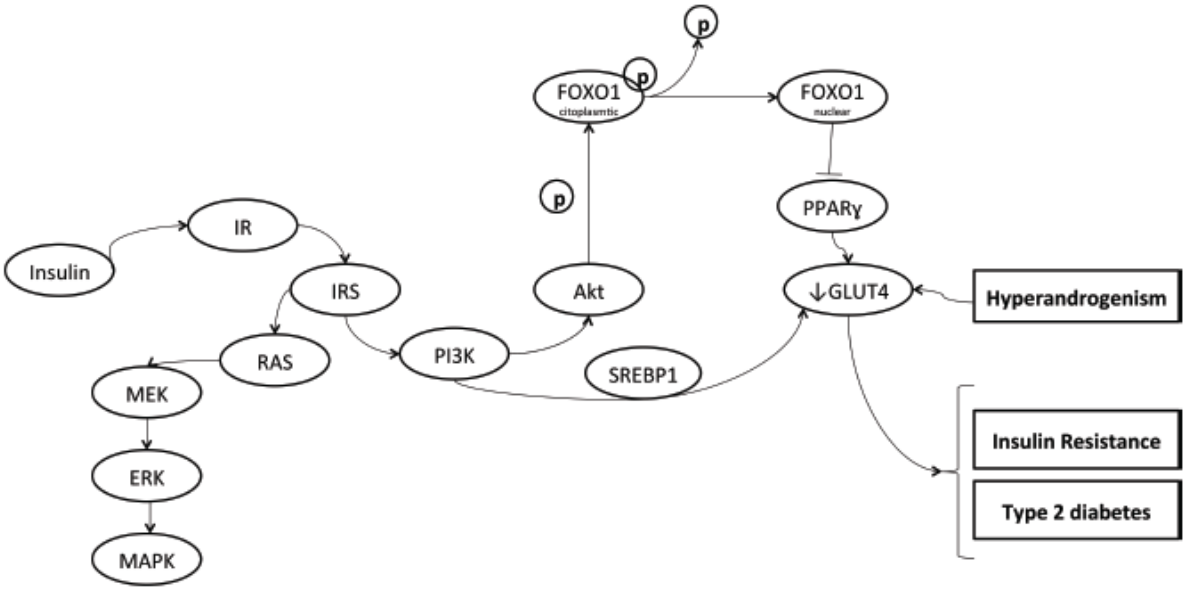

Fig. (1). This figure shows the insulin/glucose pathways in endometrial tissue in women with Polycystic Ovary Syndrome. It must be started that much of the cascade down-stream of the insulin receptor. It is not known whether any of the members of these cascades is limiting.

changes in the insulin receptor/PI3K/Akt/mTOR signaling network.

After the insulin-insulin receptor binding, it follows the activation of the insulin receptor substrate-1 (IRS-1). In that context, it has been reported that hyperandrogenic women with PCOS present diminished expression of GLUT4 as well as lower levels of IRS-1, suggesting a disruption in the translocation of vesicles with GLUT4 to the cell surface in these patients [88]. In addition, the phosphorylation of Akt at Ser473, a pathway that follows IRS-1 activation, is increased in the endometrium of women with PCOS [78, 89]. Besides the mechanisms described above, the decreased levels of GLUT4 are due to its genetic modulation.

In this context, it is known that the peroxisome proliferator- activated receptor (PPAR) and the so-called forkhead box class (FOXO) transcription factors are able to regulate glucose homeostasis [90].

PPARs are members of a superfamily of nuclear receptors [91]. Particularly, PPAR gamma (PPARɣ) is expressed mainly in insulin-sensitive tissues, thus having a fundamental role in regulating glucose intake [92]. As mentioned, FOXO proteins form a family of forkhead-winged helix box transcription factors [90]. FOXO1 is the most abundant in insulin-sensitive tissues [93]. When FOXO1 is located in the cytoplasm, it is inactivated by phosphorylation by Akt [94], but, on its basal state, FOXO1 molecules are detected in the nucleus, where they bind directly to the promoter of PPARɣ. This results in the suppression of PPARɣ transcription [90] and, as described above, PPARɣ modulates the expression of GLUT4 gene [95]. These findings suggest that the negative effect of FOXO1 over PPARɣ transcription disappears when FOXO1 is phosphorylated and excluded from the nucleus.

In this context, Kohan *et al.* [96] reported that when PPARɣ transcription is depressed by FOXO1, it leads to lower levels of GLUT4 in hyperandrogenic women with PCOS than in healthy controls [96], which result in the alteration of the endometrial function in these patients.

On the other hand, it has recently been reported that the PPARɣ coactivator-1alpha (PGC-1alpha) has a synergistic action with estrogen by regulating mitochondrial function since the knockdown of PGC-1alpha attenuates the survival of endometrial cancer by inducing cell apoptosis [97] (Fig. **1**).

5. ADHESION MOLECULES AND IMPLANTATION IN PCOS

Particularly, Apparao *et al.* [72] reported that the endometrium of PCOS patients displays a delay or absence of αVβ3. By using an *in vitro* cell-culture model, these authors reported the up-regulation of epithelial ARs by estradiol and androgens and the inhibition of ARs by both progestins and epidermal growth factor (EGF). The authors also demonstrated that EGF induces the expression of αVβ3, whereas estradiol and androgen treatment inhibits αVβ3 expression.

Taken together, these data suggest that the poor reproductive performance observed in women with PCOS might be due, in part, to the concomitant increase in both serum androgen and endometrial ARs. This combination reduces endometrial receptivity as judged by the down-regulation of αVβ3.

In PCOS patients, the expression of E-cadherin is higher, while the expression of intercellular adhesion molecule-1 (ICAM-1) is lower, during the secretory and proliferative phases, respectively. Also, there is a negative correlation with the expression of MECA-79 (a selectin oligosaccharide-based ligand) and integrin and body mass index. Conventional doses of progesterone may not be enough to correct the changes of endometrial histomorphology and the receptive markers of PCOS women. These data suggest that obesity may be a factor that interferes with this response [98].

It has been recently reported that an increase in the inflammation in PCOS patients induces leukocyte-endothelium interactions and a simultaneous increase in E-selectin. This effect is accentuated in women showing insulin resistance [99]. Moreover, it has been reported that the anti-hyperglycemic drug metformin induces beneficial effects on PCOS patients by decreasing polymorphonuclear rolling flux and adhesion by decreasing levels of E-selectin [18]. However, little is known about the involvement of selectins in embryo implantation.

Moreover, non- insulin-resistant women with PCOS have higher soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble ICAM -1 levels than insulin-resistant women with PCOS [99, 100]. In addition, metformin generates beneficial effects on PCOS patients by decreasing polymorphonuclear ICAM-1 levels [101]. On the other hand, ICAM1 K469E polymorphisms have been associated with PCOS and metabolic comorbidities in obese women [102]. [104]

6. CYTOKINES AND CHEMOKINES IN ENDOMETRIAL PCOS FUNCTION

It has been reported that progesterone down-regulates genes encoding for LIF in the endometrium of PCOS patients and that progesterone resistance resulting in increased estradiol activity leads to reduced endometrial receptivity and increased risk for hyperplasia and cancer [74, 103].

IL-6 is a pleiotropic cytokine, originally identified as a factor inducing immunoglobulin production, but then found to have a wide range of biologicalactivities. IL-6 is expressed in endometrial stromal cells and decidual cells, with a fundamental role in placental morphogenesis and trophoblast invasion [43, 104]. Women displaying recurrent miscarriage show decreased endometrial IL-6 levels [105], whereas women with pre-eclampsia have increasedIL-6 expression in the decidua [106]. In addition, in a recent report, Piltonen *et al.* [107] demonstrated that when endometrial stromal fibroblasts (both decidualized controls and non-decidualized cells from PCOS patients) were stimulated *in vitro* with estradiol and progesterone, the levels of IL-6 decreased. These authors suggested that these data demonstrated that endometrial stromal fibroblasts with failure in the process of decidualization are able to respond to steroid stimuli. They also demonstrated that even in decidualized PCOS cells, the levels ofIL-6 were decreased as compared with controls. In addition, they demonstrated that chemoattractants (Monocyte chemoattractant protein-1, MCP-1, and Regulated on Activation, Normal T Cell Expressed, RANTES) were increasedin non-decidualized endometrial stromal fibroblasts as compared with both decidualized controls and PCOS endometrial stromal fibroblasts [108].

MCP-1 and RANTES regulate the implantation process and their action is linked to the inflammatory cascade and the activity of the transcription factor NF-kB [110].

6.1. Inflammation and Oxidative Stress in PCOS

Inflammation is a key contributor to the pathogenesis of PCOS. Low-grade chronic inflammation is commonly displayed in patients with PCOS who have hyperandrogenism or hyperandrogenemia [111]. Until now, it is not clear whether increased androgen levels in PCOS induce inflammation or, in contrast, whether inflammation triggers the production of androgens, which subsequently results in hyperandrogenism [112]. The presence of chronic low-grade inflammation in PCOS is related to an increased risk of type 2 diabetes and cardiovascular disease [113]. It has been suggested that low-grade chronic inflammation is initiated and controlled by adipose tissue as weight loss is able to significantly alleviate low-grade chronic inflammation [114].

NF-kB has been implicated in acute inflammation and in low-grade chronic inflammation. The production of proinflammatory mediators, including inflammatory cytokines and chemokines, is controlled by the activity of transcription factors, such as NF-κB and ERK ½ [112].

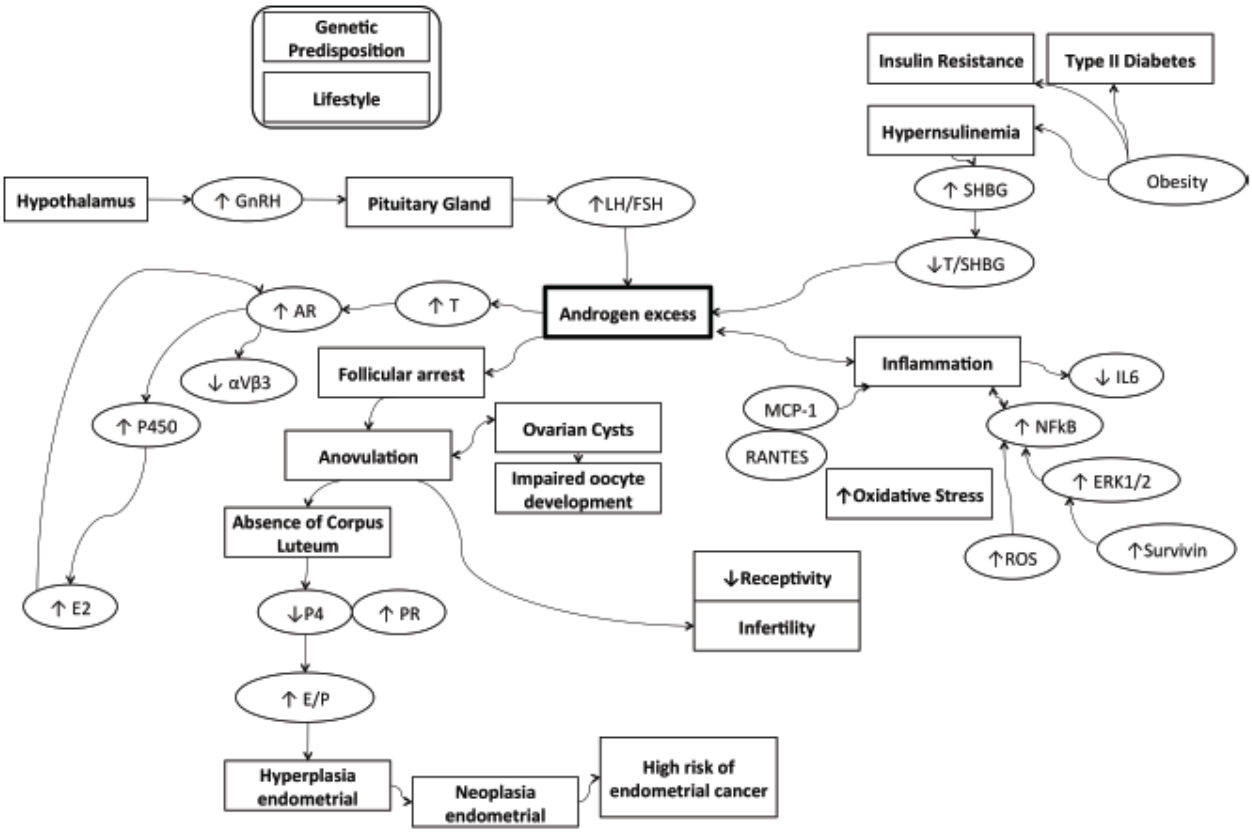

Fig. (2). Molecular mechanism involved in the physiopathology of Polycystic Ovary Syndrome.

Clinical studies have confirmed that ERK1/2 and NF-κB activation in plasma is higher in patients with PCOS than in healthy subjects [115].

Reactive oxygen species (ROS)-induced oxidative stress is a known activator of NFκB and impairs cells and tissue properties related to human fertility. These free radicals, together with the oxidized molecules, may have a cytotoxic or deleterious effect on the endometrium. Autoantibodies or increased ROS in serum are often associated with the inflammatory response. Palacio *et al.* [116] showed that patients with PCOS have significantly increased anti-endometrial antibodies levels and anti- human serum albumin -MDA, as well as oxidized proteins (protein-MDA) in serum than control patients, and thus concluded that oxidative stress could be one of the major reasons for altered endometrial functioning with impaired embryo attachment in PCOS patients [117].

Piltonen *et al.* [105] showed that up-regulated inflammatory genes in stromal and epithelial cells of the endometrium may contribute to the increased risk of endometrial cancer in women with PCOS. They also demonstrated that chemokine (C-C motif) ligand 2 increases the expression of survivin, an apoptosis inhibitor which stimulates tumor cell proliferation, migration, and invasiveness by activating the PI3K/Akt and MAPK/ERK1/2 signaling pathways, which are also activated in endometrial cancer [118] (Fig. **2**).

6.2. Metformin as a Treatment of PCOS: Impact on Endometrium

Metformin is an insulin sensitizer commonly used for the treatment of PCOS in women. Several studies have been focused on the effect of the metformin in improving endocrine and metabolic parameters. It is well known that metformin also re-establishes ovulation, improving the menstrual cycle. In particular, the effect of metformin seems to reduce miscarriage levels by increasing the receptivity of the endometrium facilitating embryo implantation.

Li *et al.* [86] reported that metformin reverses the alterations found in the endometrial AR expression and the insulin receptor/PI3K/Akt/mTOR signaling network. Other authors have demonstrated that the effect of metformin is directed at the endometrial level and decreases insulin resistance condition by increasing the expression of GLUT4. In this way, metformin indirectly restores endometrial function, promoting better reproductive outcomes [87].

CONCLUSION

In summary, the present review describes the role of hormones, steroid receptors, metabolites, adhesion molecules and cytokines in womens' endometrium and the relevance of the molecular pathways in the normal functioning of this organ. As we observed, the endometrium is strictly regulated by hormones during the menstrual cycle, implantation and pregnancy. Endocrine-reproductive alterations such as PCOS has a lot of short and long term consequences in women at reproductive age. Also PCOS is linked with several disorders such as obesity, type 2 diabetes mellitus, endometrial cancer and cardiovascular disease. The high percentage of spontaneous miscarriage, implantation failure and infertility in women with PCOS is due to several impaired molecular pathways that impedes its normal function. Nowadays, PCOS treatments are mainly focused on improving the metabolic and reproductive function in order to re-establish fertility or maintain a safe pregnancy. Metformin is one of the mainly treatments for PCOS patients, but changes in lifestyle are also recommended for these patients. Despite all the investigations about PCOS, its etiology remains unknown and further investigations are need to elucidate what is the cause of this syndrome.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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