Endometrium and steroids, a pathologic overview

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ABSTRACT
Normal endometrial function requires of cell proliferation and differentiation; therefore, disturbances in these processes could lead to pathological entities such as hyperplasia and endometrial adenocarcinoma, where cell proliferation is increased. The development of these pathologies is highly related to alterations in the levels and/or action of sexual steroids. In the present review, it has been analyzed how steroids, particularly estrogens, androgens and progestagens are involved in the etiopathogenesis of hyperplasia and endometrial endometrioid adenocarcinoma. The emphasis is given on pathological and pharmacological conditions that are presented as risk factors for endometrial pathologies, such as obesity, polycystic ovarian syndrome and hormone replacement postmenopausal women therapy, among others. Steroids alterations may promote changes at molecular level that enhance the development of hyperplasia and endometrioid cancer. In fact, there are solid data that indicate that estrogens stimulate cell-proliferation in this tissue; meanwhile, progestagens are able to stop cell proliferation and to increase differentiation. Nevertheless, the role of androgens is less clear, since there is contradictory information. It is most likely that the major contribution of steroids to the development of cell proliferation pathologies in endometria would be in early stages, where there is a high sensitivity to these molecules. This phenomenon is present even in stages previous to the occurrence of hyperplasia, like in the condition of polycystic ovarian syndrome, where the endometria have a greater sensitivity to steroids and high expression of cell cycle molecules. These abnormalities would contribute to the pathogenesis of hyperplasia and then in the progression to endometrioid adenocarcinoma.

1. Endometria and cellular proliferation pathologies

Changes in the plasma levels of steroids throughout the menstrual cycle, promote morphological and molecular modifications in endometrial cells, both in epithelial and stromal compartments. During the proliferative phase there is a predominance of estrogens, which increases endometrial cell cycle and mitosis. After ovulation, the high progesterone activity leads to cell differentiation and proliferation arrest; this stage is called the secretory phase [1–3]. Therefore, the endometrium is a steroid-sensitive tissue with a concomitant high proliferation rate in the first stage of the cycle. Under certain circumstances, the regulation of the cell cycle is disrupted, developing pathologies such as hyperplasia or endometrial adenocarcinoma [4,5].

The endometrial hyperplasia has been sub-classified as simple and complex [6]. Simple hyperplasia is characterized by a pseudostratified epithelium, normal stroma with small and uniformly spaced vessels, while the complex hyperplasia has a disordered architecture with irregular glands of different sizes, numerous papillae and normal stroma. In addition, the presence or absence of atypia should be determined in hyperplasia [6]. Depending on the type of hyperplasia, the probability of developing adenocarcinoma changes; indeed, a simple hyperplasia presents 4.3% of probability to generate cancer, complex hyperplasia 16.1%, when atypia is present in a simple hyperplasia the probability increases to 7.4% and in a complex hyperplasia with atypia the value reaches 47% [6].

The endometrial adenocarcinoma is the female reproductive oncological pathology with higher incidence in developed countries, the sixth most prevalent cancer in the world and its incidence is increasing [7–10]; about 142,000 women die annually from this cancer [11]. Endometrial cancer can be classified into two types: endometrioid (or type I) and papillary serous (or type II) [5,9,11,12]. Papillary serous endometrial cancer develops from atrophic endometria, presents a high degree of malignancy and is usually detected in advanced stages of the disease. On the other hand, endometrioid adenocarcinoma is the most common endometrial cancer (80% of the cases), it usually progresses from hyperplasia and has a better prognosis [11,12]. Genetic studies of
different mutations present in endometrial cancer, conclude that mutations of PTEN, PI3KCA, K-RAS and β-catenin are highly present in endometrial cancer [13,14]; while mutations of P53 are mainly present in non-endometrioid cancers [14]. In agreement, immunohistochemical studies have shown that papillary serous cancer has higher P53 protein levels than endometrioid cancer [12]. Additionally, several studies have shown that there is a greater expression of estrogen receptors (ERs) and progesterone receptors (PRs) in endometrioid compared to papillary serous cancer [12,15]. Therefore, the two types of endometrial cancer have different characteristics, with patterns of gene mutations that do not match and have distinct origins. Apparently, hyperplasia and endometrioid cancer would be closer in origin, with common risk factors and, in several cases, occurring as a continuous progression. In contrast, papillary serous cancer appears to be a separate pathological entity.

The role of steroids, particularly estrogens, in the development of these pathologies would be relevant considering that they regulate cell proliferation. Increased mitosis rates can trigger replication failures and increased mutations [7,16]. The aim of the present review is to analyze the link between steroids and the development of hyperplasia and endometrioid adenocarcinoma in human endometria, considering risk factors involved. The most important risk factors are associated to a predominance of estrogens without a progestagen opposition [7], including post-menopause hormone replacement therapy, obesity and ovarian dysfunction, such as polycystic ovarian syndrome (PCOS). Other risk factors have been described, as diabetes mellitus, infertility, nulliparity and tamoxifen treatment [7].

2. Steroids and its pathological role in endometrium

In the endocrine classical model, synthesis and metabolism of steroids occur in steroidogenic tissues such as adrenal or gonads. However, this is not the only source of these molecules. In an alternative model, steroid metabolism occurs in peripheral tissues (non-classical steroidogenic tissues), generating metabolites with androgenic or estrogenic activity from precursors like dehydroepiandrosterone sulphate (DHEAS) [17–21]. Indeed, in several pathologies, such as breast or prostate cancer, it has been described that the metabolism of steroids in tissues are involved in the etiopathogenesis of these processes [17,22–29]. Therefore, in the present review we analyze the role of estrogens, androgens and progestagens in the physiopathology of hyperplasia and/or endometrial endometrioid adenocarcinoma.

2.1. Estrogens and its relationship with hyperplasia/cancer risk factors

Estrogens increase cell proliferation in endometrial tissue during the proliferative stage of the menstrual cycle. When a high estrogen synthesis environment is generated, it can lead to an exacerbation of cell proliferation and development of pathologies [2,5]. This statement is supported by studies in post-menopausal women to whom were evaluated the polyp, hyperplasia and endometrial endometrioid adenocarcinoma frequency, and the presence of ovarian hyperthecosis. In the hyperthecosis condition an increment in the number of theca cells is observed, generating an increase production of androgen that is converted to estrogen in ovarian granulosa cells. The frequency of hyperthecosis in women with polyp, hyperplasia and endometrial endometrioid adenocarcinoma is higher than women with endometrial atrophy. Accordingly, the high estrogen levels generated by the hyperthecosis could exacerbate the development of pathologies with high cell proliferation [16].

It is noteworthy that the endometrium of post-menopausal women becomes more sensitive to estrogens [7], generating an increased risk of pathologies like cancer. In fact, the highest incidence of endometrial cancer occurs during the seventh decade of life [11]. Subsequent to menopause, estrogens such as estrone and estrone sulphate become relevant, since follicular activity and ovarian estradiol production decreases. These estrogens, although are less biologically active than estradiol, may favor cell proliferation of this tissue given the high steroid-sensitivity of endometria during post-menopause [7].

The use of hormone replacement therapy is highly controversial under the perspective that could be involved in the development of some cancers, including endometrial cancer. These therapies use compounds that have estrogenic activity to relieve the symptoms of menopause. In 1975, the peak incidence of endometrial cancer occurred in United States of America, which coincided with the peak of estrogen replacement hormone therapies sales in this country [7,30]. Therefore, based on clinical evidence, the recommendation is not to use opposed hormone replacement therapy in post-menopausal women without hysterectomy [11]. Besides, it is not only important that the therapy should have a progestagen opposition, but also the therapeutic planning. Thus, a recent systematic study has shown the risk of developing endometrial cancer with the use of different hormone replacement therapy protocols [31]. The authors found that estrogen increases the risk, as well as, tibolone (a drug with estrogenic, progestogenic and androgenic actions) and the use of combined estrogen plus progesterin therapy in a sequential regimen; however, the continuous combined therapy shows no increase in the risk of occurrence of this cancer [31].

One of the most documented endometrial cancer risk factors is obesity in both, pre-menopausal and in post-menopausal women. In fact, the rise of Body Mass Index (BMI) every 5 kg/m² generates a statistically significant increase in the risk of developing endometrial cancer [7,9,11,32,33]. Additionally, obesity increases the risk of mortality in women with endometrial adenocarcinoma, so the presence of severe obesity (BMI greater than or equal to 40 kg/m²) leads to an increase in the risk of death by 6.25 times compared to a woman with normal weight [32]. A recent meta-analysis indicated that odds ratios for endometrial cancer mortality were: 1.01, 1.17, 1.26 y 1.66, for BMI categories: 25–29.9, 30–34.9, 35–39.9 and 40-more, respectively [34].

At the molecular level, it has been determined that the endometrium of obese or overweight women without cancer, exhibit an increase in cell cycle and mitosis markers, such as Ki67 and phosphorylated Histone 3 (pH3) [35]. One mechanism proposed that the relationship between obesity and cancer may reside on the high circulation of estrogens, mainly estrone, originated from the aromatization of the androgen androstenedione in the adipose tissue [11]. In agreement, it has been documented that there is a positive correlation between the BMI and the levels of androstenedione, estradiol and estrone in plasma of post-menopausal women [7]. In addition, in pre-menopausal women, overweight increases anovulation periods; therefore, low progesterone levels could favor the occurrence of this cancer [11]. Other factors that could be involved are the high levels of insulin, glucose, insulin-like growth factor-1 (IGF-1), adipokines and cytokines promoting cancer initiation and development [32]. In this context, IGF-1 is capable of activating the transcriptional activity of ERs, even in the absence of the steroidoidal lignand [11,36]. Additionally, hyperinsulinemia is associated with increased synthesis of ovarian steroids, metabolism of androgens to estrogens and decreased sex hormone binding globulin (SHBG) levels, all of which would contribute to the development of endometrial cancer [7].

Other factor increasing the risk of endometrial cancer is the use of selective-estrogen receptor modulators (SERMs). In this regard, it has been identified that tamoxifen, as a treatment for breast cancer, triples the risk, whereas, raloxifene, a SERM used for osteoporosis treatment, does not increase the risk of developing endometrial adenocarcinoma [11].

2.2. Role of androgens

Considering that post-menopausal women have high risk of developing endometrial alterations and that estrogens decrease during menopause, it is important to consider androgens and its role in pathologies where cell proliferation is exacerbated. It is remarkable that levels
of bioactive androgens of cycling women are smaller (0.29–1.32 nM) than post-menopausal women (0.79–1.89 nM) [37].

The role of androgens in endometrial proliferation is less clear than that of estrogens. Studies in ovariecctomized mouse have allowed determining that non-aromatizable androgens such as dihydrotestosterone (DHT) promote the proliferation and formation of glands in the uterus. This androgen increases the weight and size of this organ, compared to the condition treated only with vehicle [38]. Additionally, in endometrial cancer some evidence indicates that androgens induce cell proliferation and that the use of anti-androgens such as enzalutamide, may inhibit the growth of endometrial cancer cells [39]. However, studies in an in vitro model of human endometrial cells stimulated with testosterone for 48 h indicate that this androgen decreases CYCLIN D1 and increases P27, being CYCLIN D1 a positive and P27 a negative regulator of the cell cycle [40]. In agreement, other in vitro assays confirm that testosterone decreases growth of endometrial cells [41,42]. The discordance of testosterone action would be associated with the role of androgens varying according to the stage of cancer [39]. Interestingly, data suggest that women with endometrial cancer have higher serum androgen levels than women without the pathology [7]. Nevertheless, it is not known if these androgens exert a direct role in the development of cancer, or whether its effect occurs through the metabolism of androgens to estrogens, being estrogens the modulators of the proliferation process.

2.3. Progestagens effect

As known, the action of progesterone is involved in the inhibition of proliferation and mitotic activity [43]. This has been demonstrated with the use of combined hormone replacement therapy (estrogen plus progesterin) that decreases the risk of developing a cancer compared to the administration of estrogen alone [7,31]. Women who have long periods of anovulation, as in the case of PCOS, exposure to estrogens without progestagen opposition or a decrease in the activity of PRs, have higher risk of developing endometrial hyperplasia or cancer [7,43].

The progestagens regulate factors that are involved in endometrial cancer development, one of these factors is the oncogene MYC that is downregulated by activated PRs. Additionally, activated PRs decrease the MYC transcriptional targets, SRD5A1, CDK2 and CCNB1 [44]. Likewise, progestagens are able to positively regulate the tumor suppressor gene FOXO1, which in turn is downregulated by PI3K/AKT. When AKT phosphorylates FOXO1, it is retained in the cytoplasm, avoiding its action as a transcriptional factor [45,46]. It has been determined that progestins are capable of inhibiting proliferation of endometrial cells via FOXO1 induction, being this transcriptional factor a pro-apoptosis protein [46,47]. In in vitro studies, AKT inhibition results in increased nuclear levels of FOXO1 [45] and increase of cellular apoptosis [47]. Likewise, the decrease in FOXO1 has been related to progression of endometrial cancer [46]. Other mechanisms in which progesterone would be involved are decreasing transcriptional activity of the AP-1 family, particularly C-JUN, which downregulates the recruitment of CYCLIN D1, and increases P21 and P53 genes promoters, favoring the arrest of the cellular cycle [48]. On the other hand, activated PRs inhibit NFKappaB, which has a tumorigenic and anti-apoptotic function, and increases the enzyme catecholestrogens (genotoxic) to methoxyestrogens (anti-cancerous) [48]. It is noteworthy, that the endometrium is a tissue composed of epithelial and stromal cells, compartments that present different roles in endometrial pathologies. In a murine model it has been determined that the paracrine epithelium-stroma interaction is fundamental in the regulation of epithelial cell growth. It has been determined that stroma through PRs activation would block the production of mitogenic mediators, generating inhibition of epithelial cell proliferation [49]. On the other hand, studies of co-culture of stromal and Ishikawa cells, a epithelial and cancerous origin cell line, determined that factors produced from stromal cells, via activation of PRs, generate changes that affect cancer cells, which respond by decreasing the activity of PI3K/AKT [49].

2.4. Sex hormone binding globulin (SHBG) role in endometrial pathologies

In order to evaluate the effect of steroids on sensitive tissues, not only serum or tissue levels of these molecules must be considered, it is also important to define the bioavailability of steroids, which is affected by binding molecules, such as SHBG. This globulin is a glycoprotein synthesized in the liver and is capable of binding to steroid hormones, presenting high affinity for androgens like testosterone. Being bound to SHBG, steroids become less bioavailable and increase its half-life [50]. The synthesis of the globulin is up-regulated by estrogens and down-regulated by androgens, insulin and by pro-inflammatory cytokines, the latter being associated with the BMI. In agreement, individuals with overweight or obesity present lower plasma levels of SHBG, with the consecutive greater steroids bioavailability [50]. In women with PCOS, between 60 and 70% of them are obese [51]; additionally, these women have a chronic pro-inflammatory environment [52]. Thus, it is most likely that high levels of pro-inflammatory cytokines associated with high BMI, decrease SHBG levels, favoring high levels of free serum androgens and estrogens and its bioavailability [7,50]. The pro-inflammatory environment in PCOS is not only systemic; it is also present in tissues like the endometrium, as recently reported [53]. Interestingly, the above could be related to the low levels of SHBG detected in circulation of these women and in tissues, as shown for endometria [50,54].

3. Alteration in endometrial cells proliferation in polycystic ovarian syndrome

PCOS is a particularly interesting condition due to its complex steroid panorama. This pathology affects between 5 and 18% of women of childbearing age [53,55–57]. The diagnosis is made when the woman presents hyperandrogenism (present even after menopause) and ovarian dysfunction, manifested by oligo/amenorrhea and/or polycystic ovaries at ultrasound [58–60]. Additionally, in this pathology a high activity of 5α-reductase is observed, evaluated by suppression of circulating steroids using dexamethasone and then an oral dehydroepiandrosterone (DHEA) challenge, detecting increases of DHT and its excretion metabolites [61]. Thus, in peripheral tissues the increase in enzymatic activity may promote the generation of molecules with high androgenic activity such as DHT [62].

Besides the abnormalities presented by women with PCOS in different tissues of the organism, the endometrium is one of the tissues particularly affected due to its dependence on steroid action. These abnormalities in the endometrium of PCOS women lead to failure in implantation, complicity during gestation and an increased risk for developing hyperplasia and endometrial cancer (probability increases 3–5 times in PCOS condition) [5,43,51,63,64]. Therefore, this pathology is characterized by high levels of androgens and unopposed estrogen action by progesterone, given the lack of ovulation proper of the syndrome. Furthermore, as it will be described later on, high concentrations of steroids with estrogenic activity are generated within the endometrial tissue. Undoubtedly, all together this steroidal panorama could be participating in the physiological alterations found in this tissue.

From the epidemiologically point of view, the endometrial cancer developed by women with PCOS presents a different behavior to that of women without the syndrome. For example, the peak of incidence of endometrial cancer in women with PCOS occurs before 50 years old, whereas in women without PCOS the peak is near the age of 70 years [5]. At the molecular level, it has also been shown high cell proliferation in endometria of women with PCOS compared to control.
Experimental evidence has shown alterations in the level and activity of some steroidogenic enzymes in endometria from women with PCOS that promote the synthesis of molecules with estrogenic activity [75–77]. Besides, an increase in the entry of DHEAS into endometrial cells of women with PCOS has been observed, concomitantly with the expression of high levels of transporters of sulphated steroids that belong to the OATPs family [75,78]. Subsequently, sulphated molecules must be desulphated, this step is augmented in pathological tissues due to an increase in sulphatase activity, whereas, sulfotransferase activity is decreased [76]. Furthermore, other enzymes of the steroidogenesis pathway are also affected, like the increased ratio between 17β-hydroxysteroid dehydrogenase type 1 vs. type 2 observed in endometria from PCOS women. Therefore, this could signify a major synthesis of molecules such as estradiol from estrone or androstenediol from DHEA [76,77].

By the other hand, androstenediol is increased in endometria of women with PCOS. This steroid has the ability to bind and activate ERα [40,79–81]. Probably, the source of this increased amount of androstenediol is the high metabolism of DHEA to androstenediol described in the PCOS tissue [75]. Moreover, the protein level of 3β-hydroxysteroid dehydrogenase, enzyme that catalyzes androstenediol-to-testosterone step is decreased, allowing the accumulation of androstenediol in these tissues [75]. Thus, the activation of ERs by androstenediol exerts several effects on endometrial cell cycle. In fact, the effects of androstenediol on endometrial cells, assessed on in vitro models, revealed an increase of cell proliferation, concomitantly with high levels of Ki67 and CYCLIN D1, and a decrease of P27 repressor cell cycle [40]. Besides, stimuli for 48 h with androstenediol increase the phosphorylation rate of molecules highly related with proliferation as AKT and ERK1/2. However, these changes are repressed when using a transcription inhibitor α-amanitin; therefore, one or more molecules could be acting as intermediary between the action of androstenediol and the activation of PI3K-AKT and MAPK-ERK1/2 pathways [82]. In this regard, VEGF is proposed as a potential candidate to be this intermediary molecule, mainly based on the high protein level of this growth factor found in endometria from women with PCOS, besides the estrogen response element present in its promoter. Therefore, androstenediol could be favoring transcription of this growth factor by steroids’ canonical pathway and, meanwhile, this growth factor could activate phosphorylation pathways related to proliferation, such as PI3K-AKT and MAPK-ERK1/2, acting in an autocrine/paracrine manner [83]. MAPK pathways may in turn phosphorylate nuclear receptors as ERα, enhancing its activity [83] (Fig. 1).

Despite the evidence showing the occurrence of steroidogenic activity in the endometrium, it has been shown that the addition of exogenous DHEA would not generate alterations in the proliferation of endometrial tissue in post-menopausal women, remaining atrophic independent of treatment [17,84,85]. Therefore, it is likely that not only the excess of DHEA or DHEAS as precursors is sufficient to trigger steroid metabolism in endometrial tissue, but also requires an increase of activity of key enzymes that allow the synthesis of steroids with estrogenic or androgenic activity, as occurs in PCOS.

4. Steroid receptors and co-regulators

Steroid activity not only depends on the ligands levels present in target tissues, but also with level and activity of the receptors and co-regulators (co-activators or co-repressors) expressed in the tissues. The classical steroid receptors are members of the superfamily of nuclear receptors, which act as transcriptional factors [86]. For estrogens there are two subtypes of ERs: ERα and ERβ, each presenting many isoforms [87]. It seems that when both subtypes are co-expressed, ERβ would negatively regulate the activity of ERα [87]. On the other hand, a single isoform for AR has been reported, whereas, for progesterone two isoforms have been described, PRA and PRB [13,86].

In the endometrium from women with PCOS it has been determined...
high levels of ERα, in secretory and proliferative phases of the menstrual cycle [5,43,68,88–91]. Additionally, AR is also highly expressed in endometria from women with PCOS with or without hyperplasia [5,57,62,43,89,90]. Moreover, it has been reported that phosphorylated ERα levels are increased in endometria with hyperplasia, which indicates an increased activity of this receptor [83]. Accordingly, the endometria of women with PCOS would have high sensitivity to estrogens and androgens that could be importantly involved in the pathologic process of cancer [88].

It is relevant to point out that in endometria the levels of AR, ERα and PRs decrease as the tissue becomes dedifferentiated as in the progression of endometrial cancer; particularly in the case of ERα; the loss of this receptor is associated with a more aggressive course of the disease and a lower survival rate of patients [12,39,92]. Furthermore, high levels of AR in primary tumor tissue are associated with increased patient survival. Likewise, in endometrial hyperplasia, AR expression is high compared to control endometria [39]. However, in advanced cancers with metastasis, there is a discordance respect AR protein levels, which are highly expressed in metastatic foci and poorly expressed in primary lesion [39].

In patients with endometrial pathology (hyperplasia and adenocarcinoma) treated with progesterone, the ligand down regulates PRs levels [48]. This decrease would be explained by the fact that progesterone favors the phosphorylation of receptors, increasing the ubiquitination and subsequent action of the proteasome, enhancing the protein degradation [46]. This reduction of PRs expression is one of the possible causes that explain the limited therapeutics success of treatment with progestagens in proliferative endometria pathologies [48,49,93]. While progesterone decreases PRs levels, estrogens increase them. This regulation favors the decrease of ERs levels in advanced tumors, diminished the protein levels of PRs and of its target gene, FOXO1 [44]. Therefore, it is most likely that in cancer development steroids would have a preponderant role in the earlier stages, since when cancer becomes more undifferentiated, there is a decrease of receptor levels, becoming independent of these hormones.

Regarding co-activators, these molecules allow the coordination of the transcription of target genes in its different stages; Initiation, elongation, termination and renewal of transcription modulators. They are required for the recruitment of chromatin remodelers, allowing transcription [36]. In endometria from women with PCOS, the co-activators AIB1, the intermediary factor-2, p160 and ARA70 are highly expressed [88–90]. Meanwhile, in endometrial cancer samples prior to and after treatment with medroxyprogesterone acetate, it has been determined that the co-repressor NCoR is increased by 158% after treatment, coinciding with a decrease in the Ki67 cell cycle marker. In vitro assays determined that NCoR would be acting suppressing ERs activity and decreasing cell proliferation [94]. Additionally, data indicate that AIB1 and P72 co-activators decrease their mRNA levels in endometrial cancer while the samples lose its histological differentiation [95], this in agreement with the diminution of receptor levels, as has been mentioned above.

In conclusion, steroids as estrogens, androgens and progesterone would have a role in the pathophysiology of endometrial hyperplasia and endometrial endometrioid adenocarcinoma, considering these two pathologies as a continuum. The pathophysiologic role of steroids would be particularly relevant during the early stages of the disease, in the hyperplasia and differentiated cancer, or even previously, as has been observed in studies in PCOS and obese women, when the endometria is highly sensitive to steroids and express high levels of receptors and co-activators. It is during these early pathology stages that some preventive measurement can be taken to control or regulate the activity of steroid molecules in order to avoid the developing of endometrial cancer.

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