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Review

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

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different mutations present in endometrial cancer, conclude that mutations of PTEN, PI3KCA, K-RAS and β-catenin are highly present in endometrioid 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 estrogens 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 metabolization 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 unopposed 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, progestagenic and androgenic actions) and the use of combined estrogen plus progestin 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/m^2 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/m^2) 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 steroidal ligand [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