INTRODUCTION

Ovarian cancer is an important health problem in women worldwide, constituting the seventh cause of death among female cancers and the second by gynaecological neoplasia. The disease is more frequently diagnosed in elderly women and generally recognized at an advanced stage, contributing to its high mortality rate. A high percentage (90%) of malignant ovarian tumours are epithelial in nature and display a wide heterogeneity in their histology, molecular features and clinical development.
The known risk factors in ovarian carcinomas are associated to reproductive events involving sexual steroid hormones, such as the use of oral contraceptive and pregnancy. In contrast, nulliparity and the use of hormonal replacement therapy increase the risk of developing this illness, as it has been proven that these hormones’ receptors often express themselves as borderline and malignant tumours, as well as ovarian cancer in its different histological subtypes.

Although evidence suggests that the exposure to steroid hormones could be linked to the appearance and progression of ovarian carcinomas, the currently available information is still insufficient to determine if the expression status of these receptors is associated to specific histological or molecular subtypes and their malignization grade or if it influences the specific clinical behaviour of each individual tumour. For this reason, we will analyse herein the role of the AR, ER and PR sexual steroid hormone receptors in the development and progression of ovarian carcinomas.

**EPIDEMIOLOGY**

Ovarian cancer constitutes the seventh cause of death by cancer in women and the second one by gynaecological neoplasia worldwide. The highest mortality rate being registered in Europe and the United States, while the lowest is found in Asian countries. It is estimated that by 2016 the United States will register 22,280 new cases and 14,240 women will die because of this illness, and 65,600 new cases were diagnosed in Europe in 2012, placing EOC as the first cause of death by gynaecological cancer in highest income countries [1,2].

Post-menopausal women have a higher risk of developing EOC, with the average age of diagnosis worldwide being 63, although varying in different countries; in Canada, the average detection age was 62 while in the UK 53% of the patients diagnosed with ovarian cancer were 65 years old or more. In Japan, the average age of diagnosis is 59 [3]. However, the median of the age of diagnosis in Chinese women was 51 [4] a similar age has been observed in mexican population.

The high mortality rate of the disease is attributed to its lack of specific biomarkers and scarce symptoms, difficulting its timely detection and treatment. Because of this, the illness is often detected only after reaching an advanced stage, when the tumour has already disseminated, with tumoral relapse and tumor resistance to chemotherapy being commonly reported.

Despite the efforts made both in basic and clinical investigation, very little has been achieved in the grounds of timely detection and design of specific treatments for each type of tumour allowing to diminish their mortality rate. However, during the last decades it has been possible to increase the overall survival rate to 5 years, as well as rise the patient survival percentage from 30% to 44%.

The most frequent histopathological presentations of EOC are of high serous carcinomas, endometrioid, mucinous, clear-cell and low grade serous ones, with the high-grade serous tumours being the most common (70%), followed by the endometrioid and mucinous ones, and
clear-cell tumours being the rarest [5]. Another way to classify them is by using the dualistic model based on their clinical behaviour and characteristic genic mutations, classifying these carcinomas in two broad categories designated as Type I and Type II; the first category includes low-grade serous and endometrioid tumours, as well as the mucinous and clear-cell ones, while the second group comprises high-grade serous and endometrioid tumours, undifferentiated carcinomas and malignant mixed mesodermal tumours [6].

As we have already mentioned, the risk and protection factors recognized for ovarian carcinomas are associated to reproductive events involving exposure to sexual steroids such as estrogens, androgens and progestins. On the other hand, the receptors to these specific hormones often expressing in borderline and malignant tumours of different histological types, even if their role in the progression of the illness remains unknown. However, it has been proven that the risk of suffering from ovarian cancer is age-related, with an increasing risk towards post-menopause, as post-menopausal women exhibit a doubled risk of acquiring EOC compared to women in reproductive age. Epithelial ovarian cancer appears mainly sporadically and less than 10% of the registered cases have a hereditary origin, being associated to mutations in the BRCA1/BRCA2 genes, as well as hereditary nonpolyposis colon cancer [5]. Other researchs report that up to 25% of all EOC have a heritable component [7,8].

The first tissues proposed as the possible origin of ovarian carcinomas were the ovarian surface epithelium and the cortical inclusion cysts, since they both express sexual steroid receptors, specifically to alpha and beta estrogen (ER\(_\alpha\) y ER\(_\beta\)), progesterone (PR-A and B) y androgens (AR). Additionally, the epithelial cells of the fallopian tubes fimbria have also been proposed as precursors of high grade serous carcinomas and express receptors to sexual steroids [9]. Studies carried out in our laboratory indicate that not all pre or post-menopausal women show these receptors in their ovarian epithelial cells, with 25% of them being positive for ER\(_\alpha\), while the remaining 46% are positive to AR [10]. Moreover, the frequency of these receptors increases in ovarian carcinomas, various reports can be found in literature coinciding in the fact that the AR is the most frequently expressed receptor in EOC [11] and it is interesting to note that the relationship between the \(\alpha\) and \(\beta\)-estrogen receptors in EOC differs to that of the normal superficial epithelium, as the expression rate of ER\(_\alpha\) and PRB increases in malignant ovarian tumours [12].

**ESTROGENS AND EPITHELIAL OVARIAN CANCER**

The steroid hormones estrogens, androgens, and progestins are steroids produced by the gonads, the adrenal and placenta steroids. They are liposoluble molecules that go through the plasmatic membrane and exert their biological effects through specific receptors that act as nuclear transcription factors by attaching themselves to response elements in their target genes.

Estrogens comprise 17 beta estradiol, estrone and estriol. The first of these is the most potent and is mainly produced by the ovaries during the reproductive stage. During their follicular
development, the theca internal cells are stimulated by the luteinizing hormone in order to transform cholesterol into pregnenolone and later achieve the androstenedione and testosterone synthesis, by aromatizing them to oestrone and estradiol in the granulose cells by means of the P450 arom induced by the follicle-stimulating hormone. Progesterone—a steroid hormone with 21 carbon atoms—is primarily synthesized by the corpus luteum during the second stage of the sexual cycle and is also produced by the placenta during the third month of pregnancy reaching levels up to ten times higher compared to those of the corpus luteum.

The risk factors in the development of epithelial ovarian tumours are associated to estradiol exposure: for example, in nulliparous women, the ovary experiences continuous ovulations, exposing the superficial epithelium to the follicular liquid, which contains high concentrations of 17β-estradiol, which could stimulate malignization; in contrast, the intraovarian estradiol levels are reduced during pregnancy. It has been demonstrated that the use of estradiol-based hormonal replacement therapy for more than five years increases the risk of developing EOC, diminishing when combined with progesterone. It has also been noted that patients suffering from EOC show higher estradiol levels and that some carcinomas display the capacity to metabolize estrogens [13,14].

Depletion of the ovarian follicles in post-menopausal women diminishes the serum levels of estrogens, although this effect is not observed in the androgen levels, which remain stable for many years after menopause [15].

Estrogens act through specific receptors known as ERα and ERβ, which, although sharing a similar affinity to 17β-estradiol, regulate different gene transcriptions. Several genes involved in the control of cell cycle and regulation of migration and invasion has been evaluated as target for estrogens [16]. Both ERα and ERβ are present in varying proportions in ovarian carcinomas, even if the role they play in the appearance and development of this neoplasia is not yet clear. However, the presence of ERα has been reported along with a wide 38-81% variation in ovarian tumours [17,18] is mostly expressed in borderline tumours and well-differentiated carcinomas associated to PR co-expression and could be a good prognosis biomarker in patients with EOC [19].

Hormonal therapy with tamoxifen, a Selective Estrogen Receptor Modulator (SERM), has been evaluated in ovarian cancer. A reduced percentage of patients responded to treatment, fewer than 20% in recurrent disease [20]. Based on the results in breast cancer and the evidence of estrogen metabolism in peripheral tissue (adipose tissue and skin) as well as its possible presence in the tumor tissue, it is estimated that treatments with aromatase inhibitors in ovarian cancer would be of clinical benefit. The results with aromatase inhibitors (Letrozole) seem to be more consistent in partial response and stable disease in ovarian cancer patients that present ER positive tumor tissue [21,22]. Another method used was a therapy with pure antiestrogen (Fulvestrant) obtaining similar result to those of previous treatments concerning estrogen antagonism. The effect of estrogens on tumor biology involves factors regulating cell proliferation, migration, invasion and
survival; as well changes in growth factors and its receptor and the presence of transcription coregulators proteins. Moreover, and considering epithelial ovarian cancer is at least five different diseases [5] the need of a personalized therapy is an even greater necessity.

PROGESTERONE AND EPITHELIAL OVARIAN CANCER

Progesterone has an anti-proliferative effect on the endometrium during the sexual cycle and the effects of this hormone in humans are mediated by two different isoforms of the progesterone receptor, PR-A and PR-B, which are codified by the same gene (11q22-23) and, although transcribed by two different promotors, they are identical in their sequencing with the only noticeable difference of PR-A’s lack of 164 amino acids in the terminal N region [23]. Both PR-A y PR-B are capable of regulating different genes depending on the cell on which they express themselves and it has been noted that whenever the expression rate of PR-A homodimers is high the transcription activity of PR-B is inhibited, thereby affecting the protective role of progesterone [24].

Progesterone’s relation to epithelial ovarian cancer has been asserted by epidemiological studies demonstrating a protective effect derived from the use of oral contraceptives containing progestins [25]. Likewise, parity is considered a protective factor on the development of ovarian cancer [26].

A recent multicentric study linking the presence of Progesterone (PR) and Estrogen Receptors (ER) with the overall survival rate in patients with epithelial ovarian cancer showed that the presence of PR is associated with improved progression-free survival in high grade serous carcinoma and in endometrioid ovarian carcinoma [19].

In epithelial ovarian cancer, there is a polymorphism in the G intron of the progesterone receptor known as PROGINS, which decreases the response to progesterone thereby increasing the risk of epithelial ovarian cancer, as can be observed in the invasive endometrioid subtype [27]: a multivariate analysis has shown that patients with epithelial ovarian cancer expressing both androgen and progesterone receptors have a higher progression-free survival and overall survival rate [11].

Recent studies suggest that progesterone induces apoptosis through the regulation of pro-apoptotic genes such as P53, Bax and the diminishment of Bcl-2 expression in ovarian cancer cells [28,29].

Progesterone has a regulating effect in the ADAMS family proteins (desintegrines and metalloproteinases with trombospondine motifs), which are secreted by various types of cells and take part in the scission of proteoglicans in the matrix as well as in angiogenesis. It has been reported that progesterone acts through its receptor in order to modulate both ADAMTS 1 and 4, which are involved in the migration and invasion processes of ovarian cancer cell lines [30].
The possibility of using progestins, such as medroxyprogesterone acetate, combined with chemotherapy in the treatment of epithelial ovarian cancer is currently being evaluated, as promising results showing that the combined treatment increases the effect and duration of its components, as well as the progression-free and overall survival of the patients [31]. However, and although there is still no conclusive evidence of this at the present time, new studies in the field will undoubtedly contribute new and relevant information. However, and in order to achieve this, these studies must take the presence of the two PR isoforms (A and B), as well as the nuclear and membrane receptors of the steroid into account, along with the consideration that epithelial ovarian cancer is a complex entity with different histologic types and gene expression, as well as diverse origins.

**ANDROGENS AND EPITHELIAL OVARIAN CANCER**

Androgens are male sexual hormones by definition and, although women produce them as well, they do so in a much smaller proportion than men. These hormones contribute to the normal physiology of the endometrium, the ovaries and the uterine tubes, as well as being precursors for estrogen synthesis [32].

The main androgens found in women are androstenedione and, to a lesser extent, testosterone, which reflects the synthesis of androgens by the ovary. The testosterone levels in young women vary between 20 and 50 ng/dL, increasing with polycystic ovary syndrome and diminishing with menopause. High concentrations of testosterone, reaching levels above 200 ng/dL could suggest the presence of ovarian neoplasias [33,34].

The biological function of androgens depends on their interaction with their specific receptors (AR), which belong to the super family of nuclear receptors acting as transcription factors. The presence of AR is associated to different types of malignant tumours, similar to those found in the prostate, breast and bladder, making its involvement in carcinogenesis processes evident, either individually or in collaboration with other coregulatory proteins and growth factors [35]. The androgen receptor is located in the surface epithelium of the ovary, the uterine tubes and the endometrium, as well as in the granulose cells of the ovarian follicles, modulating local or peripheral androgen-dependent functions. This receptor is also the most frequently expressed one in epithelial of ovarian inclusion cysts in postmenopausal women [10,36].

A recent study linked the serum levels of androgens to the risk factor of suffering from EOC in 565 patients, classifying the tumours either by their histological characteristics, grade and clinical stage or by following the dualistic model (Type I and Type II). In this study, the androgen levels, especially androstenedione, were associated to an increase or decrease of their risk depending on the characteristics of each individual tumour according to the work of Osey col. [37].

The mRNA levels in the AR are high in endometriosis, constituting a risk factor leading to the development of endometrioid and clear-cell carcinomas), for which reason the possibility that
both the AR and androgens themselves could be implicated in the appearance and development of these carcinomas in particular cannot be overlooked [36].

On the other hand, studies carried out in primary cell cultures extracted from high-grade serous tumoral tissue, the presence of Dihidrotestosterone (DHT) induced a significant increase in the percentage ratio of S phase cells positive for AR [38]. In in vitro studies, the treatment with DHT causes the dysregulation of genes related to the proliferation, survival and cellular migration in serous carcinomas and endometrial stromal cells. Furthermore, experiments in SKOV-3 and OVCAS-16 malignant ovary cell lines showed that DHT inhibited the effects of TGF-β (cytokine in charge of the regulation of cellular proliferation in epithelial cells) and altered the regulation of its receptors TGFβRI and TGFβRII [39].

It has been noted that polymorphisms of the androgen receptor could be linked to the risk of developing EOC. According to a case and control study carried out in a sample population of 2,800 Chinese women, the presence of a longer AR CAG repeat length is associated to a lower risk in patients with EOC [4]. Meanwhile, SKOV-3 ovarian cancer cell line cultures transfected with AR plasmids containing variable CAG repeat lengths showed that the length of a polymorphic Cytosine-Adenine-Guanine (CAG) repeat in the Androgen Receptor (AR) may inversely correlate with AR activity through modulation of Epidermal Growth Factor Receptor (EGFR) signaling that it could act in a deleterious manner in epithelial ovarian cancer [40].

Jönsson and col. [11] analysed the presence of proteins for ERα, ERβ, AR and PR by means of immune histochemistry in 118 malignant ovarian tumors of serous and endometrioid subtypes, finding that 82% of the samples were positive for ERβ and 44% for ERα and AR, while only 31% indicated positive for PR. The absence PR and AR was associated to high malignancy in contrast to ERβ in these same cases. It is important to point out that the co-expression of the AR and PR receptors was linked to a better prognosis both in progression-free survival and in overall survival rates.

Anti-androgenic treatments used successfully in positive AR prostate cancer cases have also been evaluated in EOC ones: Levine and col [41] report no changes in the progression of free survival after bicalutamide and goserelin treatment, discussing that the number of patients in the sample was limited (n=35) and only 58% expressed androgen receptor.

Although numerous investigation groups have tried to prove the participation of sexual steroids in ovarian carcinogenesis, none have been able to obtain conclusive evidence that allows to consider the expression profile of androgen receptors, estrogens and progesterone in the decision-making process in the treatment of this specific neoplasia, as is already being done in breast cancer cases.

Evidence of the involvement of sexual steroid hormones in ovarian cancer constitutes an important breakthrough, as it opens the possibility to improve the patients clinical status and
quality of life: for this reason, and although further research is still necessary, the therapeutic use of steroid hormones, used in combination with specific agents according to the biology of each specific tumor, should be implemented in future treatments (Figure 1).

**Figure1:** Steroids receptors are expressed in epithelial ovarian cancer. A) Androgen receptor in low grade serous carcinoma, B) Progesterone receptor in low grade serous carcinoma and C) Estrogen receptor alpha in endometrioid subtype.

**ACKNOWLEDGMENTS**

This work was supported by DGAPA-UNAM PAPIIT-IN224116, INsCan 080340MI.

We thank to Verónica Rodriguez-Mata, for technical assistance, Alejandro Garzon for reviewing the manuscript.

**References**


