Rev Esp Patol 1999; Vol. 32, N~ 3: 414-419

Short Course 6

Pathology of the endometrium

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Endometrial changes in modern hormonal treatment

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Postmenopausal hormone therapy is used to relieve climacteric symptoms. Estrogen therapy also reduces the risk of cardiovascular disease and offers protection from osteoporosis in postmenopausal women. Originally, estrogen replacement therapy was widely used and its use is still required by the Food and Drug Administration in North American trials as a group for comparison with estrogen combined with progestagen therapy. It is well known that estrogens play an important role in regulating endometrial proliferation. Estrogens, if given alone and for a long period of time, may induce a whole spectrum of proliferative aspects, ranging from persistent proliferative endometrium to hyperplasia and adenocarcinoma. Many epidemiological studies have clearly shown that the use of unopposed estrogens in postmenopausal women increases the risk of developing endometrial carcinoma. In the metaanalysis by Grady *etal.* (1), the overall relative risk of endometrial cancer in estrogen users compared with nonhormone users is 2.3. The risk increases with the duration of use but is already high even in the group receiving estrogens for less than 12 months and at a low dose (2). Moreover, the risk higher after 5 years of discontinuation of the treatment is still two-fold higher in estrogen users than in nonestrogen users. This explains why estrogen alone is no longer used in Europe, even in hormone replacement therapy (HRT) trials.

The current HATs developed in Europe include the use of a progestational agent, which is given either continuously with estrogen or sequentially for at least 10 days in the latter half of the cycle. When combined with estrogen therapy, progestins can prevent the development of endometrial hyperplasia. The risk of endometrial cancer in women receiving estrogen plus progestin in a correct regimen should be the same as in the general population. A normal woman not receiving HRT has a very low (approximately 1%) risk of developing endometrial hyperplasia in the perimenopause and postmenopause; consequently, the goal of an adequate regimen of HAT is to obtain no more than 1% of endometrial alterations. Two crucial issues regarding endometrial safety of HRT are dose and duration of progestin association. The optimal progestin association is influenced by the amount of estrogen taken. As far as the duration is concerned, we know that progestin association for less than 10 days per cycle does not protect the endometrium, as the relative risk of endometrial cancer is around 2, even for treatments shorter than 5 years. Furthermore, recent data suggest that among long-term current HRT users, an increased risk of endometrial cancer exists even if the progestin is taken for more than 10 days per month in sequential regimens (3). The second variable is the dose of progestin, taken either according to cyclic sequential or to continuous combined regimens. Comerci *et al.* (4) reported insufficient safety in terms of endometrial protection with a continuous combined regimen with low doses of both estrogens and progestins (2.5 mg/day). These authors found eight cases of endometrial carcinoma in women using this regimen for more than 3 years. If low-dose estrogens and low-dose progestins are to be prescribed continuously, these women must be followed up very carefully.

The antiestrogenic action of the progestagens is based on the endometrial changes observed in the biopsy. A wide variety of changes in varying combination can be encountered depending on the dosage, the duration of use, whether a continuous or sequential administration is used and the time in the cycle when the biopsy is obtained. There is an adequate progestational response when there is a disparition of mitoses in the glandular component and a secretory transformation of the mucosa or an atrophic aspect. The secretory transformation is observed only if the mucosa has been primed with estrogens that allow the synthesis of progesterone receptors. The secretory transformation is subsequently visible mainly in the sequential treatment. The first modifications induced by the progestagens are visible in the glandular component. After 2 or 3 days of treatment, the glands become irregular and convoluted and accumulate intracytoplasmic glycogen. After 6 days of treatment, apical secretion is present in the glandular lumen and edema is present in the stroma. After 10 days of treatment, coiling of spiral arteries is visible, surrounded by large, round predecidual cells. Predecidual transformation of all the stromal cells appears in the further course. These modifications are very similar to the one observed during the menstrual cycle. A specific morphological aspect is seen with high doses of progestational treatment. It is characterized by a complete decidualization of the stroma associated with small atrophic glands. With high doses of progestagens or with continuous treatment, the mucosa may also appear atrophic with a fibrous stroma and a small atrophic gland.

The utility of uterine sampling prior to beginning the treatment is questionable. When a patient is receiving continuous therapy, any episode of uterine bleeding after a period of amenorrhea or spotting after 1 year of treatment requires histological sampling of the endometrium. When a patient is receiving sequential therapy, an endometrial biopsy is indicated for two main reasons: firstly, if the patient is suffering from heavy withdrawal hemorrhaging and secondly, if the patient is experiencing intermittent hemorrhaging. Microscopic examination of the endometrial biopsy generally reveals a secretory transformation or an atrophic aspect that in itself does not explain the hemorrhaging. Abnormal maturation (also termed luteal phase defect), in which there is a difference in maturation between the glands and the stroma or between different parts of the mucosa, explains why the patient is bleeding in the middle of the treatment as the glands are at different stages of maturation throughout the cycle. The most common lesions which hemorrhage are polyps. Ulceration on the surface of the polyp and

very small vessels resulting from neovascularization explain why the patient experiences hemorrhaging. Neovascularization is an essential part of the definition of a poiyp. Polyps in themselves do not present a risk for the patient but they result in a decrease in compliance to treatment as a result of the hemorrhaging. Hyperplasia without atypia generally occurs in patients who do not comply with treatment or in patients who have not taken the treatment for a sufficient number of days. Hyperplasia without atypia is associated with vascular thrombosis and explains why the patient is hemorrhaging. Endometrial carcinoma is sometimes diagnosed at biopsy as an incident case but in most cases the carcinoma is probably present prior to treatment and has not been discovered before because the patient was asymptomatic and no baseline was performed. Alternatively, the biopsy may have been done blindly and it could therefore have missed a small carcinoma. In the case of carcinoma, it is usually the invasion of the stroma that causes the bleeding.

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Endometrial pathology of tamoxifen

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Tamoxifen is a widely used long-term treatment for breast cancer. Although initially developed as a contraceptive, it was seen to have antiestrogenic actions beneficial to breast cancer sufferers, reducing recurrences or metastases by 50% and the appearance of tumors in the contralateral breast. Furthermore, a recent study has shown that the preventive administration of tamoxifen to women with a high risk of developing breast cancer reduces the incidence of malignant tumors by 45%.

The antiestrogenic effect of tamofixen seems to be target site specific because it behaves as a mildly estrogenic substance at bone level (preventing osteoporosis) and also, less advantageously, at endometrial level. Thus, rather than being a pure antiestrogen, it is better called a selective estrogen receptor modulator. The mechanism of its estrogenic action at endometrial level is unknown although several theories have been considered.

We have been able to demonstrate a substantially higher rate of proliferation markers in apparent atrophic endometria of control curettages in patients subjected to long-term tamoxifen treatment (LTTT). LTTT causes a marked decrease in estrogen receptors and a substantial increase in progestogen receptors, which explains the marked decidual change of endometria in LTTT patients when progestogen is administered simultaneously.

Clinically, LTTT uteri are large and a substantial increase in thickness is seen with ultrasonography. Diffuse cystic change is also frequently seen in as many as a third of all cases.

Benign changes

A quarter of all cases develop endometrial polyps that are different form the usual ones in that they have a wide base of implantation, are multicystic and exhibit a wide range of metaplasias in the glandular and stromal components. In these polyps we have also demonstrated an evident increase of proliferation markers.

Malignant changes

In the early 1980s it was noted that endometrial carcinoma was higher in LTTT patients. This is not surprising as higher doses (40 mg/day) were used in that era~. Experimentally, an enhancement of endometrial cancer was noted. The risk of developing an endometrial cancer was double after an accumulative treatment of 9-15 g, triple after 15 g and quadruple after concurrent irradiation. Latency period was approximately 2 years.

The clinicopathological types of tumor developing in LTTT situations have given rise to much controversy. While population controlled studies showed that most tumors corresponded to well-differentiated endometrial cancers in low stages, other studies from referral centers showed a predominance of unusual, high-grade; aggressive tumors, such as papillary serous carcinoma. Our study comprising more than 175 cases of control biopsies of LTTT patients and 150 studies of material from symptomatic patients showed 35 cases of endometrial cancer with a predominance of low-grade endometrioid adenocarcinoma, opposed to four cases of papillary serous carcinoma, one clear cell carcinoma, five cardnosarcomas and four sarcomas. An interesting feature of the three cases of carcinosarcoma was a unusual botryoid pattern, reminiscent of the morphology of chorionic villi. Additionally, three cases of atypical polypoid adenomyoma associated with LTTT were found for the first time.

Due to the high incidence of endometrial polyps in LTTT, a special interest was taken in the malignant tumors developing in them. Papillary serous carcinomas associated with polyps were seen in only two cases, while in the three other cases, two endometriold carcinomas and one carcinosarcoma were found.

Despite the obvious possibility of developing an endometrial carcinoma with LTTT, the improvement in the survival and quality of life in breast cancer patients is clearly worth the risk. In numerical terms, 30 times more lives are saved by tamoxifen than are lost by its side effects. However, a LTTT patient needs a close follow-up with ultrasonography and biopsy if changes are detected. Alternative selective estrogen receptor modulators such as raloxifen may prove to be an answer to this problem in the near future.

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