Value of sonographic endometrial findings in patients with breast cancer under tamoxifen therapy

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Tamoxifen is utilized as adjuvant therapy in women diagnosed with breast cancer. In these patients, despite its positive risk/benefit ratio, tamoxifen may cause secondary effects on the endometrium, with increased risk of malignant diseases\(^1\).

So, the first question to be answered is: “Does tamoxifen increase the incidence of endometrial abnormalities?”

The literature presents two meta-analysis-studies that have been developed with this objective\(^2,3\). Both have demonstrated that long-term use of tamoxifen in patients with breast cancer is associated with a higher incidence of uterine diseases: the studies developed by Tabor et al.\(^2\) and Cohen\(^3\) – 48 papers and 106 papers, respectively. The first one has demonstrated 330 women with endometrial cancer, and other 3,483 without cancer.

Tamoxifen may lead to a range of histological alterations in the endometrium, including cystic atrophy, endometrial polyp, hyperplasia, atypical hyperplasia, endometrial adenocarcinoma, and, also, sarcoma\(^4,5\) and uterine serous carcinoma\(^6\) in a pre-existing polyp. The increase in the risk for endometrial cancer developed in polyps is estimated between 2.5% and 10%\(^5\), although, according to other authors, it is a little lower\(^9\). Aggressive endometrial carcinoma\(^7\) and uterine metastasis from infiltrating ductal carcinoma of the breast\(^8\) also have been described.

Other authors have not found alterations in the endometrial thickness\(^9,10\) or increase in the rate of polyps\(^11,12\) and hyperplasia\(^12,13\). The rate of active endometrium pre- and post-tamoxifen therapy has been estimated in 10%\(^11\). Estrogenic effect on the endometrium has been observed in a minority of patients, without the development of hyperplasia or malignancy\(^14\).

The second question is: “Is the ultrasound screening of asymptomatic patients mandatory?”

For answering this question, it is necessary to know the endometrial thickness (ET) cut-off value considered as ideal in the screening for endometrial diseases in postmenopausal women. The higher is the ET cut-off value, the lower will be the sensitivity (higher number of false-negative cases), and specificity (lower number of false-positive cases).

At the Clinic of Gynecology of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, ET ≤ 4 mm is considered as normal in postmenopausal women. The same value is adopted by the Department of Gynecology at Escola Paulista de Medicina da Universidade Federal de São Paulo\(^11\).

By means of a questionnaire applied in the United Kingdom, 23.6% of the physicians have considered as normal an ET ≤ 4 mm, and 47.8%, an ET ≤ 5 mm\(^15\). Garuti et al.\(^16\) have adopted ET = 4 mm in the follow-up of these patients, with safe outcomes, without increasing the number of hysteroscopies, highlighting that 2.7% of patients present pre-tamoxifen-therapy endometrial atypias. Therefore, it is necessary to perform an ultrasound study before initiating the therapy, as well as to treat each and every pre-existing uterine disease\(^16\). Transvaginal ultrasound (TVUS) is useful in the screening for endometrial diseases in asymptomatic patients with ET > 4 mm\(^17\), although the screening of these patients is not universally accepted because of the high number of false-positive results\(^11\). An ET 15 mm-cut-off value has been proposed for women under tamoxifen therapy for increasing the specificity (87.2%), in spite of the low sensitivity (37.9%)\(^18\). TVUS seems to be insufficient in the screening for endometrial alter-
ations, particularly hyperplasia in patients under tamoxifen therapy. Combined TVUS and hysterosonography (HSG) and color Doppler may be utilized to improve the specificity of the method, and reduce the number of unnecessary interventions. However, the rate of failures is high because of cervical canal stenosis (39.3%) or patient’s intolerance (6%). HSG has presented 85.5% sensitivity, 83.3% specificity, 93.7% positive predictive value, and 66% negative predictive value for differentiation between normal and pathological endometrium, lower values when compared with hysteroscopy that has presented 100% sensitivity, 94.1% specificity, 97.8% positive predictive value, and 100% negative predictive value. HSG improves the sensitivity for the diagnosis of endometrial polyps, when compared with endometrial biopsy. In postmenopausal patients under tamoxifen therapy, with bleeding, the ET cut-off value ≤ 5 mm has shown 97% sensitivity and 35% specificity. A higher cut-off value (≤ 10 mm) has not improved the overall accuracy in the diagnosis of endometrial pathological involvement.

According to Garuti et al., hysteroscopy would be indicated in the following situations: a) ET > 4 mm; b) increase of at least 50% in the ET measured by hysteroscopy; c) metrorrhagia; d) previous findings of endometrial hyperplasia.

A detailed investigation of the endometrium by means of endometrial cytology and hysteroscopy with directed biopsy have been proposed for asymptomatic patients under tamoxifen therapy. Hysteroscopy seems to be more accurate in the detection of polyps, hyperplasia and neoplasia, so many authors postulate that asymptomatic patients under tamoxifen therapy should be evaluated as if they were symptomatic.

Postmenopausal bleeding in patients under tamoxifen therapy increases the risk for endometrial diseases.

Other aspects regarding ET and use of tamoxifen that should be taken into consideration are: a) the therapy duration seems not affecting the lesions severity; b) the ET increases with the therapy duration, at a rate of 0.75 mm/years, with a mean ET of 12 mm (6–21 mm) after five years, and decreases at a rate of 1.27 mm/year.

A secondary increase of > 50% in the ET measured by TVUS in postmenopausal women under tamoxifen therapy is associated with high rates of endometrial diseases, including endometrial cancer.

Future studies should be focused on the different etiologies of endometrial carcinomas associated with the use of tamoxifen and development of new selective estrogen receptor modulator (SERM).

Patients with breast cancer are predisposed to the development of endometrial diseases. The significant role of genetics and patient’s predisposition to develop diseases like cancer is unquestionable.

References


