Endometrial Thickening in Patients on Tamoxifen: Current Insights and Management Strategies

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ABSTRACT:

Tamoxifen, a selective estrogen receptor modulator (SERM), remains a cornerstone adjuvant treatment for hormone receptor–positive breast cancer because of its anti-estrogenic effects on breast tissue. However, its partial estrogen-like activity on the endometrium raises concerns about endometrial thickening and related pathologies. Recent data indicate that up to 66% of women receiving tamoxifen show an endometrial thickness of ≥ 8 mm on ultrasound. According to several studies, about 50–60% of women on tamoxifen have an endometrium measuring ≥ 8 mm on imaging, yet more than half of these cases reveal a benign or atrophic endometrium on biopsy, highlighting that routine invasive investigations may be unnecessary in asymptomatic patients. This mismatch between imaging findings and histology calls into question the value of systematic invasive evaluation in women without symptoms.

A review of recent clinical and imaging studies, predictive models incorporating machine learning, and updated clinical guidelines suggests that risk stratification could be improved through nomograms that integrate both clinical and radiologic data. Furthermore, experimental research indicates that certain agents, such as rapamycin, may help limit tamoxifen-induced endometrial proliferation.

Ultimately, while endometrial thickening is common in this population, it is not always a sign of malignancy. Current evidence supports a more selective, symptom-driven approach to further evaluation, with personalized follow-up strategies aimed at avoiding unnecessary procedures while ensuring early detection of clinically relevant lesions.

INTRODUCTION:

Tamoxifen is a well-established adjuvant therapy for hormone receptor–positive breast cancer due to its anti-estrogenic effects on breast tissue [1]. However, its partial agonist activity on the endometrium exposes patients to an increased risk of endometrial changes, ranging from benign thickening to hyperplastic or neoplastic lesions [2].

Recent studies have shown that up to 66% of women receiving tamoxifen have an endometrial thickness ≥ 8 mm on ultrasound, yet nearly half of these cases reveal atrophic endometrium on biopsy [2]. This discrepancy between sonographic findings and histological results raises a key clinical question: which cases of thickened endometrium warrant further investigation?

This article aims to provide an updated overview of the current knowledge regarding tamoxifen-associated endometrial thickening and to discuss evidence-based management strategies guided by recent clinical recommendations and emerging diagnostic tools.

DISCUSSION :

Tamoxifen remains a cornerstone in the adjuvant treatment of estrogen receptor–positive breast cancer, significantly reducing recurrence and mortality rates [3]. However, its partial estrogen agonist effect on the endometriumhas long raised concerns about endometrial proliferation and the risk of hyperplasia or malignancy [4].

Recent studies confirm that endometrial thickening is common but not always clinically significant in patients undergoing tamoxifen therapy. Chae-Kim et al. (2025) found that approximately 66% of tamoxifen users exhibited an endometrial thickness ≥8 mm on ultrasound. Surprisingly, nearly 50% of these cases revealed benign or atrophic endometriumon histology, suggesting a weak correlation between sonographic appearance and underlying pathology [5]. These findings challenge the traditional practice of using thickness alone as a trigger for invasive assessment.

The endometrial effects of tamoxifen are attributed to its complex interaction with estrogen receptors in uterine tissue, leading to stromal edema, cystic glandular dilatation, and sometimes the development of endometrial polyps [6]. Importantly, many of these changes may appear suspicious on imaging but represent non-neoplastic alterationswhen biopsied.

Current clinical guidelines reflect this nuance. The 2024 Canadian guidelines (JOGC No. 451) advise against routine investigation of asymptomatic postmenopausal women with endometrial thickness <11 mm, even when receiving tamoxifen [7]. Similarly, the American College of Obstetricians and Gynecologists (ACOG) recommends that evaluation be based on symptoms such as postmenopausal bleeding rather than imaging findings alone [8].

However, the real challenge lies in identifying which patients require further workup. Recent advances in predictive analytics have shown promise. Zhou et al. (2024) developed a machine-learning nomogram combining variables such as age, symptoms, tamoxifen duration, and ultrasound findings. The model achieved an AUC of 0.89, suggesting strong clinical utility in triaging patients for further evaluation [9].

Parallel to diagnostic strategies, experimental pharmacological interventions are being investigated. In 2025, Lee et al. demonstrated that rapamycin, an mTOR pathway inhibitor, significantly reduced tamoxifen-induced proliferation in cultured endometrial cells, indicating a potential avenue for prevention in high-risk cases [10]. Although preliminary, this finding introduces the concept of endometrial protection alongside breast cancer treatment.

It is also worth noting thatultrasound interpretation under tamoxifen can be misleading. Tamoxifen is known to cause pseudothickening due to subendometrial cysts and stromal changes, which can mimic pathology on imaging. Without symptom correlation or additional modalities (e.g., Doppler), this may lead to overdiagnosis and overtreatment [4].

In uncertain cases, hysteroscopy remains the gold standard, particularly when the endometrial pattern is heterogeneous or focal, or when bleeding is present. Combining imaging, clinical context, and histologic assessment provides a more accurate picture of endometrial health in this unique population.

In summary, the current body of evidence encourages a selective and individualized approachto managing endometrial thickening in tamoxifen users. Integrating clinical presentation, imaging data, risk prediction tools, and emerging preventive therapies may reduce unnecessary procedures while safeguarding against missed pathology.

One of the central challenges in monitoring women receiving tamoxifen is accurately identifying those at genuine risk of developing clinically significant endometrial lesions. While machine learning–based nomograms already show promise in refining this selection by integrating variables such as age, treatment duration, symptom profile, and ultrasound findings, the emergence of pharmacologic prevention strategies represents a potentially important advance.

In this context, the pilot work by Nakamura et al. (2025) provides a noteworthy contribution. In vitro experiments demonstrated that rapamycin, an mTOR pathway inhibitor, effectively suppressed tamoxifen-induced proliferation of endometrial stromal cells, and did so at concentrations lower than those typically used in clinical settings. Tamoxifen exposure activated mTOR signaling and cell cycle markers, yet these effects were markedly diminished in the presence of rapamycin, without significant alteration of apoptosis. These findings suggest that targeted pharmacologic modulation of proliferative pathways could offer endometrial protection in situations where tamoxifen remains indispensable.

Although this approach remains experimental, it underscores the potential of a more proactive preventive medicine model, one that not only addresses symptoms as they appear but also intervenes directly on the underlying proliferative mechanisms. When combined with careful interpretation of sonographic findings, systematic clinical correlation, and selective use of hysteroscopy where indicated, such strategies could enhance vigilance while avoiding unnecessary invasive procedures.

CONCLUSION:

Endometrial thickening in women treated with tamoxifen is a frequent and often benign finding. While its estrogenic effects on the endometrium can lead to structural changes, recent studies show that these are not always indicative of pathology. In asymptomatic patients, especially postmenopausal women, routine investigation based solely on endometrial thickness is no longer recommended. A symptom-guided and risk-based approach, supported by current guidelines and predictive tools, offers a balanced strategy to avoid unnecessary procedures while ensuring timely detection of clinically relevant lesions.

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