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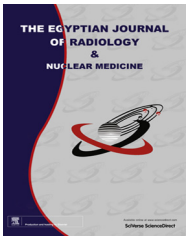

ORIGINAL ARTICLE

Sonohysterography for evaluation of endometrial abnormalities associated with tamoxifen therapy for breast cancer

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KEYWORDS

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Endometrial biopsy;
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Abstract *Objective:* To evaluate sonohysterography for the diagnosis of endometrial abnormalities in women treated with tamoxifen for breast cancer.
Patients and methods: We assessed 37 women treated with tamoxifen for breast cancer who underwent sonohysterography and correlative endometrial biopsy for evaluation of postmenopausal bleeding or thickened endometrium greater than 8 mm. In 14 patients, endometrial biopsy was followed by endovaginal sonography to ensure removal of endometrial pathology. Sonohysterography findings were compared with histopathology results.
Results: Sonohysterography findings coincided with histopathology results in 27 of 37 cases including 19 of 23 cases of endometrial polyps, 6 of 8 cases with thickened endometria and two cases had normal endometrium. Sonohysterography findings did not coincide with histopathology in 3 of the 14 cases who underwent endovaginal sonography after endometrial biopsy compared to 7 of the 23 cases who did not undergo such examination and 4 of these missed 7 cases were for endometrial polyps.
Conclusion: Sonohysterography is a useful procedure for the diagnosis of endometrial abnormalities in tamoxifen-treated women. Endometrial abnormalities are better diagnosed on sonohysterography than on endometrial biopsy which has the limitation of some missed endometrial polyps, a problem that may be minimized by performing endovaginal sonography after endometrial biopsy.

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1. Introduction

Tamoxifen citrate is a selective estrogen receptor modulator that is widely used for the treatment of breast cancer; it has also been used recently for the prevention of breast cancer in high-risk women (1–3). Large trials have shown that in women with estrogen receptor-positive breast cancer, tamoxifen treatment for 5 years reduces the annual breast cancer recurrence rate by 50%, reduces the annual death rate by 28%, and decreases the risk of contralateral breast cancer by 39% regardless of receptor status (1–3). The Breast Cancer Prevention Trial documented a 50% reduction in the rate of breast cancer among high-risk women who received tamoxifen treatment as compared with control subjects (2).

Tamoxifen inhibits estrogen-dependent tumor growth by competing with estrogen at receptor sites. This competition for receptor sites may result in either antiestrogenic or weakly estrogenic effects, depending on tissue site and receptor status. In the uterus, tamoxifen has an estrogenic effect that produces endometrial abnormalities such as endometrial polyps, hyperplasia and carcinoma (4–7).

The benefits of tamoxifen for breast cancer treatment far outweigh any potential endometrial abnormalities that may occur (2). However, because tamoxifen-treated women have an increased frequency of endometrial neoplasia and premalignant conditions such as atypical hyperplasia, it is important to develop adequate methods for diagnosing endometrial complications resulting from tamoxifen and there is interest in screening this population for endometrial abnormalities. The value of screening has not been established, and the optimum method of surveillance has not been determined (2,4–7). Several groups of investigators have shown the usefulness of sonohysterography for the diagnosis of endometrial abnormalities, particularly in women with abnormal uterine bleeding (8–12).

We designed this study to evaluate sonohysterography for the diagnosis of endometrial abnormalities in women who are undergoing tamoxifen treatment for breast cancer.

2. Patients and methods

This prospective study was conducted from April 2008 to October 2012 for 39 tamoxifen-treated women referred for sonohysterography. Thirty-seven sonohysterograms were completed and two studies were unsuccessful because of difficult cannulation of the cervix and were excluded from the study. All women had been undergoing tamoxifen therapy for a mean of 2.5 years (range, 1–4 years). The mean patient age was 48 years (range, 37–72 years). Women were referred for sonohysterography because of postmenopausal bleeding ($n = 6$) and endometrial thickening greater than 8 mm detected on preliminary transvaginal sonography ($n = 31$). Endometrial thickness measurements were obtained in the anteroposterior dimension on sagittal images, and any endometrial cystic spaces or polyps were also documented.

Sonohysterography was performed by an experienced radiologist using an endovaginal curved 4–9 MHz transducer (of Medison SONOACE 6000 °C unit). The procedure was explained to the patient in detail and informed consent had been obtained for all studies.

Sonohysterography was performed in a standard manner as previously described (13). All studies were performed with a 5 French or 7 French Zinnanti HS catheter (Thomas medical. Inc. Blomet, waterton industrial estate, Bridgend, CF13XA, UK). Briefly, after cleaning the cervix with povidone-iodine, a sterile 5 or 7-French occlusive balloon catheter that has been flushed with sterile saline to eliminate the air is then guided into the endocervical canal. The catheter is advanced past the external cervical os for a variable distance (usually 2–7 cm) and the catheter balloon was filled with fluid to avoid artifact. The speculum is then carefully removed, allowing the catheter to remain in place. Transvaginal scanning is then performed during the instillation of sterile saline solution. After assessment of the fundus and upper uterine segment, the balloon was decompressed while injecting more fluid to ensure adequate visualization of the lower uterine segment. The amount of saline solution required for the adequate distention of the endometrial cavity varied, ranging from approximately 10 to 40 ml depending on cervical leakage. The examination usually lasts 5–10 min.

The presence of endometrial thickening, polyps, subendometrial cysts and other abnormalities was recorded. Endometrial measurements were obtained in the sagittal plane. The anterior and posterior single thickness measurements were added together for a double-layer endometrial measurement. For tamoxifen-treated women, a double-layer thickness of 8 mm or less was considered normal (6,7,14).

On sonohysterography, polyps appear as echogenic, smooth, intracavitary masses outlined by fluid (15,16). Color Doppler images may show a single feeding artery at the base of attachment, a finding frequently seen with polyps (17).

All sonohysterograms were followed by endometrial biopsy with dilatation and curettage and the sonohysterography findings were compared with histopathology results. After performing sonohysterography for 23 patients and comparing their sonohysterography findings with histopathology results, we found that sonohysterographic findings did not coincide with histopathology results in 7 patients and 4 of them had characteristic sonohysterographic appearance for endometrial polyps but normal endometria were found at histopathology. We identified these 23 patients as group A.

We thought that performing endovaginal sonography in the operation room (OR) immediately after endometrial biopsy aiming to obtain normal endometrial thickness (less than 5 mm) on vaginal sonography may ensure removal of any missed endometrial pathology. Therefore, in the remaining 14 patients, endometrial biopsy was immediately followed by transvaginal sonography in the OR and the procedure was done by the same radiologist and the same US machine used in pre-operative assessment in the radiology department which was brought into the OR for each of the 14 patients. The sonographic findings were compared with those seen in the preliminary endovaginal sonography and sonohysterography and re-curettage were done for cases with residual thickened endometrium. We identified these 14 patients as group B.

Sonohysterography findings for each group and for all patients were compared with histopathology results after dilatation and curettage.

3. Results

All sonohysterography examinations were well tolerated by the patients and no complications were encountered. Sonohysterography revealed endometrial polyps in 23 cases (62%) and their mean dimension was 27 mm (range, 4–50 mm), thickened endometrium greater than 8 mm in 8 cases (21.5%), subendometrial cysts in 4 cases (11%) and normal endometrial in two cases (5.5%). Sonohysterography findings are presented in Table 1.

Sonohysterography findings coincided with histopathology results in 27 of the 37 cases including 19 of 23 cases of endometrial polyps, 6 of the 8 cases with thickened endometria (all had endometrial hyperplasia, two were simple and 4 were atypical hyperplasia) and two cases had normal endometrium both at sonohysterography and histopathology. No cases of endometrial carcinoma were seen. The sonohysterography findings are compared with histopathology results for all 37 patients in Table 2.

The 27 cases for whom sonohysterography coincided with histopathology were 16 cases in group A (23 patients who did not undergo intra-operative endovaginal sonography after endometrial biopsy) and 11 cases in group B (14 patients who underwent intra-operative endovaginal sonography after endometrial biopsy). In group A patients, 11 of 15 endometrial polyps shown on sonohysterography were confirmed on histopathology (Fig. 1A–C). Four of six patients with thickened endometria on sonohysterography had endometrial hyperplasia, one of which was simple and the other three were atypical hyperplasia (Fig. 3A and B). One patient had normal endometrium both at sonohysterography and histopathology. In group B patients, all eight endometrial polyps shown on sonohysterography were confirmed on histopathology and two of these patients underwent re-curettage due to residual thickened endometrium on intra-operative endovaginal sonography done after endometrial biopsy (Fig. 2A–C). The two patients with thickened endometria on sonohysterography had endometrial hyperplasia, one of which was simple and the other atypical hyperplasia. One patient had normal endometrium both at sonohysterography and histopathology.

The remaining 10 cases with discordant sonohysterography and histopathology were 7 cases in group A and 3 cases in group B. The missed 7 cases of group A were 4 cases of endometrial polyps on sonohysterograms but normal endometria were found at histopathology (Fig. 4), two cases with thickened endometria on sonohysterography but at histopathology, one case had an endometrial polyp and the other had normal endometrium, the last case had subendometrial cyst on sonohysterography, but histopathology revealed endometrial polyps. All three missed cases in group B had subendometrial cysts at sonohysterograms but at histopathology, two had endometrial polyps and the third had normal endometrium.

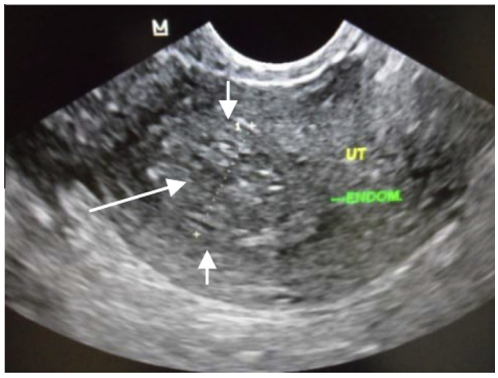

Fig. 1A. 46-Year-old woman undergoing tamoxifen treatment for 3 years. Preliminary sagittal transvaginal sonogram shows thickened endometrium with double-layer endometrial thickness measuring 12 mm (short arrows) and suspected mass within the endometrial cavity (long arrow).

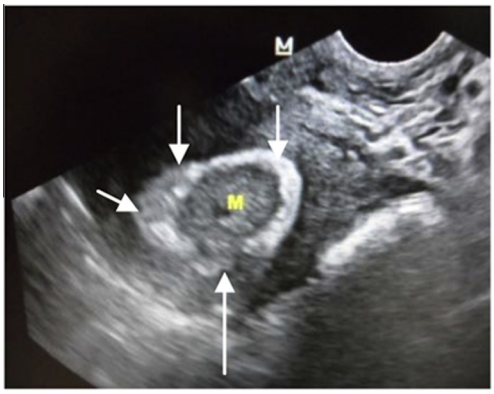

Fig. 1B. 46-Year-old woman undergoing tamoxifen treatment for 3 years. Sagittal sonohysterogram with image taken during instillation of saline into the uterine cavity shows delineation of endometrial polyp (M) with its pedicle at the posterior wall (long arrow). The injected fluid is seen as echogenic ring around the polyp (short arrows).

Table 1 Findings of sonohysterograms of 37 women treated with tamoxifen.

Finding	Number	Percentage (%)
Polyps	23	(62)
Thickened endometrium	8	(21.5)
Subendometrial cysts	4	(11)
Normal endometrium	2	(5.5)
Total	37	(100)

Table 2 Sonohysterography findings compared with histopathology in all 37 patients.

Histopathology	Polyp	Sonohysterography		
		Thickened endometrium	Subendometrial cysts	Normal
Polyp	19	1	3	0
Hyperplasia	0	6	0	0
Normal	4	1	1	2
Total	23	8	4	2

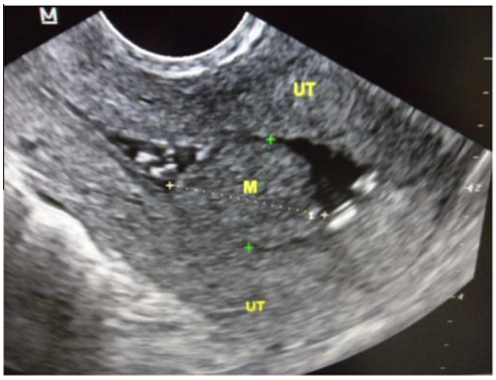

Fig. 1C. 46-Year-old woman undergoing tamoxifen treatment for 3 years. Sagittal sonohysterogram with image taken after instillation of saline into the uterine cavity shows large endometrial polyp (M) measured 25×20 mm. The polyp was seen as smooth echogenic mass projecting into the endometrial cavity outlined by fluid. The polyp was confirmed at histopathology.

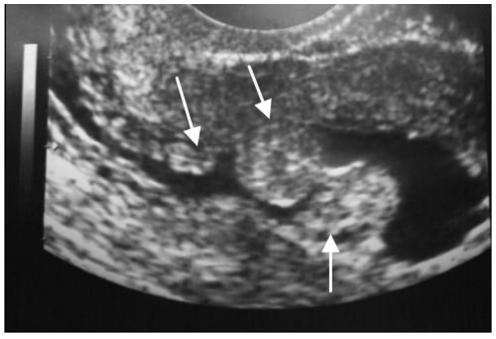

Fig. 2A. 52-Year-old woman undergoing tamoxifen treatment for 3 years. Sagittal sonohysterogram reveals three variable sized endometrial polyps (arrows) ranging from 5 to 20 mm. Polyps are seen as smooth echogenic masses projecting into the endometrial cavity outlined by fluid (two anterior and one posterior). Polyps were confirmed at histopathology.

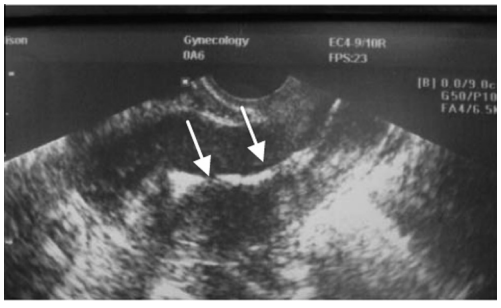

Fig. 2B. 52-Year-old woman undergoing tamoxifen treatment for 3 years. Intra-operative sagittal transvaginal sonogram after endometrial biopsy shows smooth endometrium (arrows) with normal thickness denoting successful removal of all polyps.

The sonohysterography findings are compared with histopathology results for group A and group B patients in Tables 3 and 4, respectively.

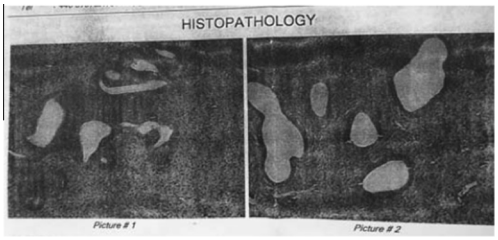

Fig. 2C. 52-Year-old woman undergoing tamoxifen treatment for 3 years. Histopathology reveals increased number of endometrial glands, columnar non-secretory cells and spinle stoma cells consistent with hyperplastic endometrial polyps.

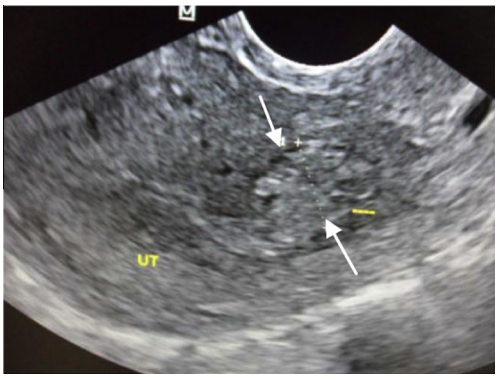

Fig. 3A. 47-Year-old woman undergoing tamoxifen treatment for 2 years. Preliminary sagittal transvaginal sonogram shows uneven thickening of the endometrium measuring 18 mm at the fundus (arrows).

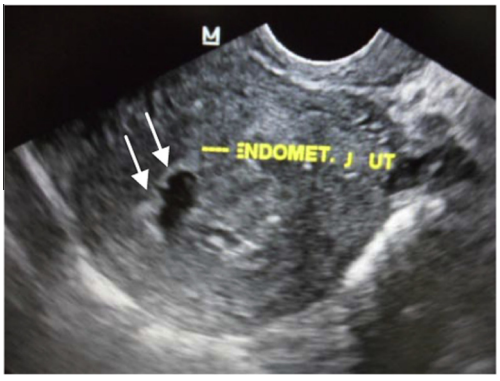

Fig. 3B. 47-Year-old woman undergoing tamoxifen treatment for 2 years. Sagittal sonohysterogram shows uneven thickening of the endometrium and irregularity of the anterior endometrial lining at the fundus (arrows). Histopathology shows atypical endometrial hyperplasia.

4. Discussion

The increased endometrial thickness observed in tamoxifen-treated women is caused by the estrogen agonist effect of tamoxifen, which is similar to hormone replacement therapy. Debate exists regarding the normal range of endometrial thickness for women treated with tamoxifen. An endometrial thickness of less than 5 mm essentially excludes the presence of

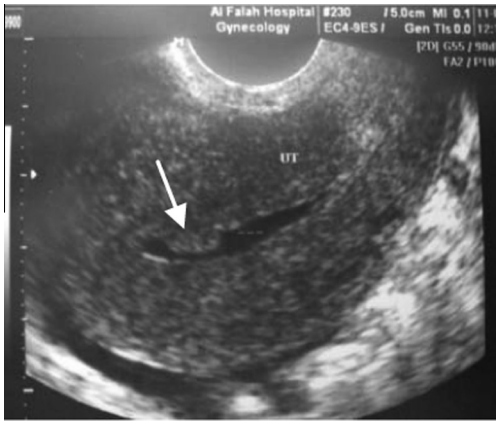

Fig. 4. 45-Year-old woman undergoing tamoxifen treatment for 3 years. Sagittal sonohysterogram reveals small anterior endometrial polyp (arrow) measured 5 mm. Histopathology shows negative finding (was negative for polyp).

endometrial abnormalities (18–20). Most asymptomatic women treated with tamoxifen have endometrial thickness exceeding 5 mm, and endometrial thickness in those women is greater than that in postmenopausal control subjects (6,21). Lin et al. (14) reported that 91 of 112 asymptomatic post-menopausal women undergoing hormone replacement therapy had endometrial thickness greater than 8 mm, and the authors recommended biopsy for asymptomatic women with endometrial thickness greater than 8 mm. Using the 8-mm cutoff value, approximately half of the women treated with tamoxifen will have transvaginal sonography endometrial measurements in the normal range (6,22). Our patient population included tamoxifen-treated women with postmenopausal bleeding and tamoxifen-treated women with endometrial thickening greater than 8 mm detected on preliminary transvaginal sonography but who were otherwise asymptomatic.

Endometrial polyps were the most frequent finding in our study. Using sonohysterography, we showed endometrial polyps in 62% of cases. Our results are similar to those of Timmerman et al. (22) and Lucy et al. (23) in studies comparing sonohysterography with hysteroscopy. Other investigators have reported a much lower prevalence of polyps, in the range of 33% (6,21). This discrepancy may be explained by sampling methods. Kedar et al. (21) suggested that the prevalence of endometrial polyps may be underestimated by reports that use endometrial biopsy as the standard of reference.

Previous studies have shown discrepancy between sonohysterography and hysteroscopy for the diagnosis of endometrial polyps raising the issue of gold standard (23,24). Lucy et al. (23) found that 5 of 31 endometrial polyps diagnosed using sonohysterography were not confirmed by operative hysteroscopy and histopathology despite their classic appearance. Similar results were shown by Schwarzler et al. (24) who reported that operative hysteroscopy missed two of 25 polyps detected using sonohysterography. Authors of these studies suggested that an endometrial polyp may be expelled spontaneously in the interval between sonohysterography and hysteroscopy. Alternatively, the discrepancy may be related to hysteroscopic technique. Although hysteroscopy has a wide field of view, visualization may be limited if the scope is advanced beyond a mobile polyp.

Similar limitations of endometrial biopsy for the diagnosis of endometrial abnormalities in tamoxifen-treated women mainly endometrial polyps have been reported by other studies (23,25). Lucy et al. (23) documented endometrial abnormalities on sonohysterography in 12 of 19 (63%) sonohysterograms that had negative correlative endometrial biopsy; 10 of these abnormalities were endometrial polyps. Similar results were reported by Dubinsky et al. (25). In our study, 4 of the 23 patients who had sonohysterographic appearance for endometrial polyps showed normal endometria at histopathology. We suggested that endometrial biopsy may obtain tissue from the adjacent endometrium and miss a mobile polyp or the polyp was small.

In our study, sonohysterography findings coincided with histopathology results in 27 of the 37 cases including 19 of 23 cases of endometrial polyps, 6 of 8 cases with thickened endometria (all had endometrial hyperplasia) and two cases had normal endometrium both at sonohysterography and histopathology. The remaining 10 cases with discordant sonohys-

Table 3 Sonohysterography findings compared with histopathology in group A patients (23 patients who did not undergo intra-operative endovaginal sonography after endometrial biopsy).

Histopathology	Polyp	Sonohysterography		
		Thickened endometrium	Subendometrial cysts	Normal
Polyp	11	1	1	0
Hyperplasia	0	4	0	0
Normal	4	1	0	1
Total	15	6	1	1

Table 4 Sonohysterography findings compared with histopathology in group B patients (14 patients who underwent intra-operative endovaginal sonography after endometrial biopsy).

Histopathology	Polyp	Sonohysterography		
		Thickened Endometrium	Subendometrial Cysts	Normal
Polyp	8	0	2	0
Hyperplasia	0	2	0	0
Normal	0	0	1	1
Total	8	2	3	1

terography and histopathology were 3 of the 14 cases who underwent endovaginal sonography after endometrial biopsy aiming to ensure removal of any missed endometrial pathology and 7 of the 23 cases who did not undergo such examination and 4 of these missed 7 cases were for the previously mentioned missed endometrial polyps. Among the 14 cases who underwent endovaginal sonography after endometrial biopsy, all 8 cases of endometrial polyps shown on sonohysterography were confirmed on histopathology, two of these patients underwent re-curettage due to residual thickened endometrium. Therefore, we thought that performing endovaginal sonography in the operation room after endometrial biopsy can minimize the limitation of endometrial biopsy for the diagnosis of endometrial abnormalities particularly endometrial polyps. Further prospective studies involving large groups of patients are still required to assess the added value of performing endovaginal sonography in the operation room after endometrial biopsy in tamoxifen-treated women.

We found four cases of premalignant condition (atypical endometrial hyperplasia) in our series but no cases of endometrial carcinoma. This conforms to Ascher et al., (7) and Lucy et al., (23) who reported that although estimates are that approximately 50% of tamoxifen-treated women will have endometrial abnormalities, most of these abnormalities are benign. Surveillance is done to exclude endometrial cancer, but the degree of risk should not be overestimated. The annual risk of endometrial carcinoma in tamoxifen-treated women is in the range of 1.6 in 1000 individuals (2). Endometrial carcinoma is more frequent with prolonged tamoxifen use (> 5 years), and patients generally present with vaginal bleeding (4,6). Many studies have shown that 80–88% of tamoxifen-associated endometrial cancers are early tumors (FIGO [International Federation of Gynecology and Obstetrics] stage 1) (2,4,26).

5. Conclusion

Sonohysterography is a useful procedure for the diagnosis of endometrial abnormalities in tamoxifen-treated women. Endometrial abnormalities mainly endometrial polyps are better diagnosed on sonohysterography than on endometrial biopsy which has the limitation of some missed endometrial polyps, the problem may be minimized by performing immediate intraoperative endovaginal sonography after endometrial biopsy.

Conflict of interest

The authors have no conflict of interest to declare.

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