

REVIEW

The effect of tamoxifen on the genital tract

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Abstract

Tamoxifen is a selective estrogen receptor modulator (SERM) that is widely used in the treatment of patients with breast cancer and for chemoprophylaxis in high risk women. Tamoxifen results in a spectrum of abnormalities involving the genital tract, the most significant being an increased incidence of endometrial cancer and uterine sarcoma. This article reviews the effects of tamoxifen on the genital tract and the strengths and weaknesses of various imaging modalities for evaluating the endometrium.

Keywords: Endometrial polyp; adenomyosis; endometrial cystic atrophy; endometrial hyperplasia; ultrasound; hysterosonography; MRI.

Introduction

Tamoxifen, a selective estrogen receptor modulator, is one of the most commonly prescribed antineoplastic drugs in the world. Tamoxifen has a complex mechanism of action including anti-estrogenic activity in the breast and estrogenic effects in other tissues, including the endometrium. It is widely used for the treatment of breast cancer and for chemoprevention in high risk pre- and postmenopausal women. Tamoxifen has been shown to cause adverse effects at the uterine level, of which endometrial carcinoma and uterine sarcoma are the most significant.

Controversy exists regarding appropriate surveillance for endometrial cancer in these patients^[1]. Currently, the American College of Obstetricians and Gynecologists (ACOG) does not recommend screening by endometrial biopsy or transvaginal ultrasound for asymptomatic women treated with tamoxifen^[2]. The ACOG recommends a baseline gynecologic evaluation prior to the initiation of tamoxifen followed by routine annual gynecologic evaluation. Women should be informed about the risks of endometrial hyperplasia, endometrial cancer, and uterine sarcoma and should promptly report any abnormal vaginal symptoms. Any abnormal vaginal bleeding should be investigated. However, surveys have indicated that some physicians favor surveillance of asymptomatic

breast cancer patients treated with tamoxifen. One community-based study of breast cancer patients treated with tamoxifen found half of the patients reported regular surveillance, by either transvaginal ultrasound or endometrial biopsy, for uterine abnormalities^[3]. Therefore, radiologists must become familiar with the imaging features of the uterus in women receiving tamoxifen and the relative strengths and weaknesses of the various imaging modalities with respect to evaluation of the uterus.

Effect of tamoxifen on the uterus

Tamoxifen results in a spectrum of uterine abnormalities including benign alterations such as endometrial polyps, endometrial hyperplasia, endometrial cystic atrophy, adenomyosis, and uterine fibroid growth as well as malignant transformation into endometrial carcinoma and uterine sarcoma^[4–8].

Endometrial polyps

Endometrial polyps are the most common endometrial pathology reported in association with tamoxifen exposure^[11]. The incidence in women treated with tamoxifen is between 8 and 36% versus 0–10% in untreated women^[6,9–14]. Tamoxifen-related polyps are different

from polyps in the general population. They tend to be larger with a mean diameter of 5 cm versus 0.5–3.0 cm in the general population. Microscopically, tamoxifen-related polyps contain a combination of proliferative activity, aberrant epithelial differentiation, and focal periglandular stromal condensation. It has been postulated that the periglandular stromal condensation may be associated with a form of Mullerian adenocarcinoma and may also account for difficulties in resecting tamoxifen-related polyps at hysteroscopy^[15,16]. Tamoxifen-related polyps are reported to have an increased rate of malignant change ranging from 3 to 10.7% compared with 0.48% in the general population^[14,17].

Endometrial hyperplasia

The incidence of endometrial hyperplasia in postmenopausal women with breast cancer treated with tamoxifen is increased. The incidence is 1.3–20% in these patients, compared to the 0–10% incidence in postmenopausal breast cancer patients who are not receiving tamoxifen^[6,10–13,18–22]. The diagnosis of endometrial hyperplasia is based on microscopic findings of a morphologically abnormal proliferative-type endometrium, with some authors insisting that there must also be an abnormal increase in endometrial volume^[22]. Endometrial hyperplasia can be divided into two broad categories: hyperplasia without cytologic atypia and hyperplasia with cytologic atypia. The categories can be further subdivided into simple or complex depending on the extent of glandular complexity and crowding. The nomenclature has prognostic significance: in patients with atypical hyperplasia, 23% progress to carcinoma, whereas in patients without atypia, only 2% progress to carcinoma^[22].

Endometrial carcinoma

Tamoxifen increases the relative risk of developing endometrial cancer. Various studies have reported a 1.3–7.5-fold increase in the relative risk of developing endometrial cancer with data from major clinical studies indicating tamoxifen use results in an approximately two-fold increase in the incidence rate of endometrial cancer^[13,15,23–28]. The risk of developing endometrial cancer increases with duration of treatment and cumulative tamoxifen dose as well as prior estrogen replacement therapy, obesity, and the presence of pre-existing endometrial pathologic conditions^[13,15,19,23,25,26]. The Early Breast Cancer Trialists' Collaborative Group reported the incidence of endometrial cancer in patients treated with tamoxifen approximately doubled in trials of 1–2 years and approximately quadrupled in trials of 5 years^[13,15,19,23,25,26,29].

Many studies found that most cases of endometrial cancers occurring in tamoxifen-treated patients were of low grade and stage, with no differences in stage,

grade, or histologic subtype compared to non-treated patients^[24,26,30–32]. However, other studies have found endometrial cancers in postmenopausal patients treated with tamoxifen to be more advanced with poorer prognoses than in non-treated patients^[33–37]. Additionally, these studies have shown an increase in unfavorable histologies including carcinosarcoma, adenocarcinoma and Mullerian mixed tumors, resulting in more advanced stage at diagnosis and worse survival^[33,35,37–41]. In light of these findings, additional studies may be warranted to determine if there may be a benefit to screening asymptomatic women treated with tamoxifen.

Endometrial cystic atrophy/adenomyosis

The paradoxical development of endometrial cystic atrophy, also known as 'tamoxifen mucosa', in patients treated with tamoxifen may be accounted for by the complex mechanism of action of tamoxifen which includes both agonist and antagonist effects on the endometrium as well as mechanisms unrelated to the estrogen receptor^[41,42]. Endometrial cystic atrophy is diagnosed histologically when multiple cystic spaces lined by atrophic endometrium are present within a dense fibrous stroma^[43]. At hysteroscopy, endometrial cystic atrophy is described as smooth, white, hypervascularized, and atrophic, with scattered protuberances^[5]. 'Tamoxifen mucosa' differs from the atrophic mucosa in postmenopausal women who are not treated with tamoxifen as their mucosa is characterized as pale, thin, and without protuberances^[44]. There is controversy regarding the exact location of the cysts in patients treated with tamoxifen. Some investigators report the cysts reside in the endometrium and others have placed the cysts in the subendometrial location^[17,43,45,46]. This is complicated by the fact that endometrial glands that extend into the myometrium are also called adenomyosis. The incidence of adenomyosis is increased 3–4 times in women treated with tamoxifen than in the general population^[7]. Therefore, it is unclear if the apparent increased incidence of adenomyosis in women treated with tamoxifen is a true phenomenon or represents a spectrum of tamoxifen-associated cysts (adenomyosis-like changes)^[16]. Regardless of their location, the cysts seen in women treated with tamoxifen do not appear to be premalignant^[43].

Leiomyomas

Estrogen receptors are located both in the endometrium and uterine stroma^[41]. Several studies have demonstrated a growth of uterine fibroids in postmenopausal patients treated with tamoxifen^[4]. However, the leiomyomas in women treated with tamoxifen do not appear to differ histologically from those in untreated women^[4,47,48].

Effect of tamoxifen on the ovaries

Tamoxifen was initially synthesized as a contraceptive in the 1960s but was found to induce ovulation in anovulatory infertile women in 1971^[49]. Tamoxifen induces estrogen production in the premenopausal ovary without a significant subsequent rise in FSH and LH^[42]. Pre- and postmenopausal women treated with tamoxifen have an increased risk of developing ovarian cysts^[12,50,51]. Asymptomatic unilocular cysts in these patients should be followed conservatively and discontinuation of tamoxifen usually leads to the reduction and disappearance of these cysts^[50]. One study found women taking tamoxifen for less than 2 years were not at increased risk of ovarian cancer^[52]. Of particular concern is the negative effect of tamoxifen-induced ovulation and the risk of ovarian carcinoma in patients with BRCA1 and BRCA2 gene mutations. Annual sonographic monitoring of the ovaries in this population has been recommended although its efficacy is still unproven^[42].

Effect of tamoxifen on the cervix

Tamoxifen has estrogen agonist effects on the cervix of postmenopausal women. In one study, 89% of tamoxifen-treated postmenopausal breast cancer patients developed estrogenized cervical smears rather than atrophic smears^[53]. Women treated with tamoxifen have a higher incidence of benign reactive atypia or atypical squamous cells of undetermined significance, without an increase in dysplasia or cervical cancer^[54].

Effect of tamoxifen on the vagina

Tamoxifen has been shown to have both estrogen agonist and antagonist effects on the vaginal epithelium^[42,55,56]. In one study, an estrogen agonist effect was seen on the vaginal smears in 34 of 49 postmenopausal breast cancer patients treated with tamoxifen and was more common in older patients^[57]. Another study showed that there appears to be an anti-estrogenic effect of tamoxifen on the vaginal epithelium in an estrogen-rich environment. The maturation index is a measure of hormonal stimulation on the endometrium and is used to describe the estrogenic status of the vaginal epithelium. When postmenopausal breast cancer patients were primed with estradiol valerate to provide them with an estrogen-rich vaginal epithelium prior to the administration of tamoxifen, the maturation index and estrogenic status of the vaginal epithelium was found to decrease^[58]. Despite its mechanism of action, vaginal dryness and dyspareunia have been reported in both pre- and postmenopausal patients treated with tamoxifen^[57,59].

Imaging review

Endovaginal ultrasound

Ultrasound is the first-line imaging modality for evaluation of the uterus and ovaries. Ultrasound is sensitive, but not specific, for evaluating endometrial abnormalities. The normal postmenopausal endometrium appears as a single echogenic line and should not exceed 5 mm as a bilayer thickness^[60,61]. Most women undergoing tamoxifen treatment have a thicker endometrium compared with control subjects (9–13 mm versus 4.0–5.4 mm)^[10–12,62]. In postmenopausal women undergoing estrogen replacement therapy, the normal endometrium may measure up to 8 mm in thickness.

The upper limit for normal endometrial thickness on transvaginal US in asymptomatic women receiving tamoxifen remains controversial^[63,64]. Various authors have recommended endometrial thickness cut-off values ranging from 4 to 10 mm with sensitivity of positive histologic findings ranging from 85 to 100% and specificity ranging from 56 to 96%^[12,63,65–69]. Increased endometrial thickness correlates with increased incidence of endometrial pathology^[70]. However, positive histologic findings, such as endometrial proliferation and simple hyperplasia, may be clinically unimportant. Additionally, a thicker endometrium on the US image does not necessarily correlate with specific pathologic endometrial findings^[66].

Regardless of the cutoff value for detecting endometrial abnormalities, the most common endometrial transvaginal US pattern seen in women treated with tamoxifen is a thickened endometrium with cystic spaces described as a 'Swiss cheese' pattern^[10–12,27,71–76] (Fig. 1). The findings of a thickened endometrial complex, with or without cystic changes, is often non-specific and may be caused by endometrial polyps, submucosal leiomyoma, cystic atrophy, endometrial hyperplasia, or carcinoma^[63].

Hysterosonography

Hysterosonography has increasingly been used to improve the ability to diagnose intrauterine pathologic conditions and to resolve discrepancies between endometrial thickening on transvaginal US images and insufficient material or non-diagnostic results at endometrial biopsy^[66,77–82]. Hysterosonography is an attractive adjunct to transvaginal US because it more clearly defines endoluminal lesions that are pedunculated or sessile and can be used to better determine whether an abnormality is endometrial or subendometrial (Fig. 2).

The potential utility of hysterosonography in imaging tamoxifen-related changes was noted in a 1994 case report in which a patient treated with tamoxifen was described as having an atrophic endometrium at endometrial biopsy despite a thickened endometrium (1.9 cm) on endovaginal US images^[83]. Hysterosonography

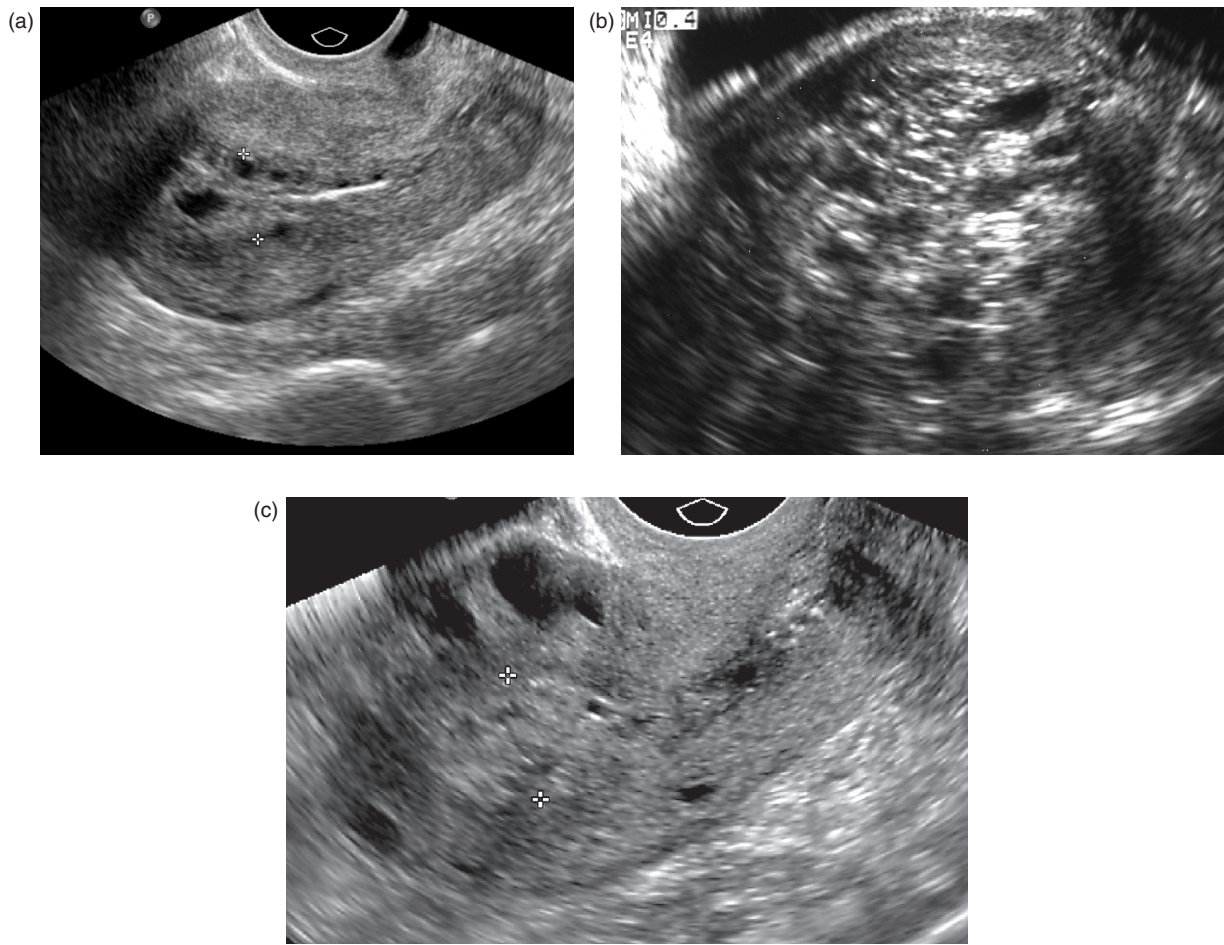


Figure 1 (a,b,c) Sagittal transvaginal ultrasound images from three different patients show the most common endometrial finding in women undergoing tamoxifen treatment: a thickened endometrium with cystic spaces. Calipers in (a) and (c) denote the endometrial thickness. (b) Reprinted with permission from Ascher *et al.*^[16].

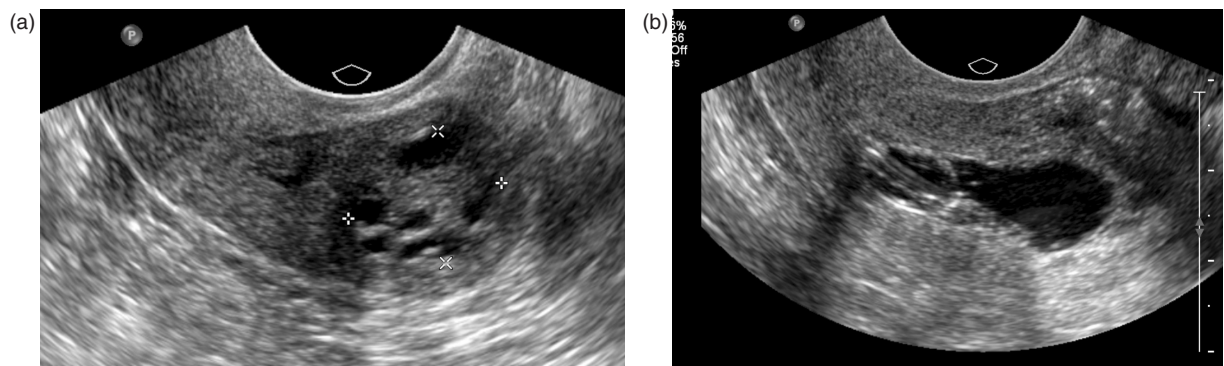


Figure 2 Hysterosonography as an adjunct to transvaginal ultrasound. (a) Sagittal transvaginal ultrasound in a women treated with tamoxifen demonstrates a retroverted uterus with a thickened endometrium. Calipers denote the endometrium. (b) Sagittal hysterosonogram showed no evidence of endometrial mass or thickening. The apparent thickening on the transvaginal ultrasound was secondary to subendometrial/myometrial cysts.

demonstrated a large polyp, which was confirmed and excised at hysteroscopy. Later, Goldstein described five women with a thick, 'irregular, bizarre, heterogeneous' endometrium on endovaginal US images.

At hysterosonography, anechoic areas were noted in the subendometrial proximal myometrium, not in the endometrium as originally interpreted on the basis of endovaginal US images. At endometrial biopsy, all

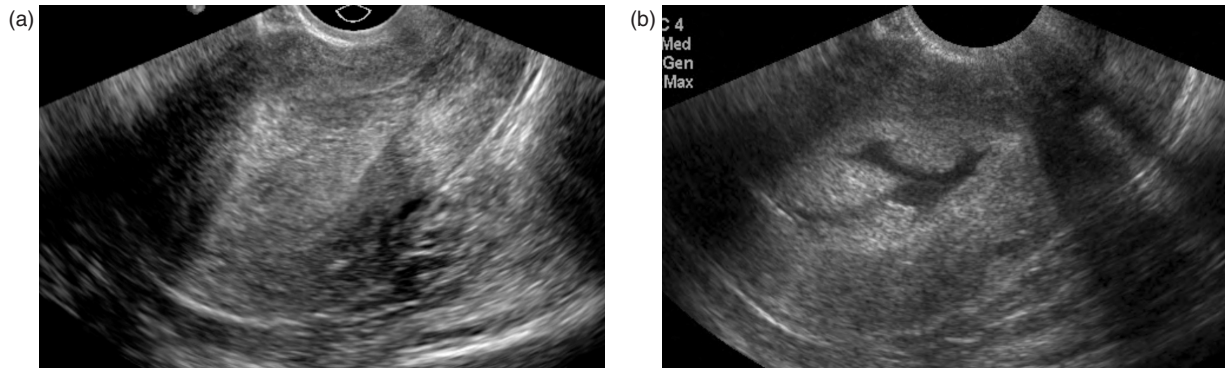


Figure 3 Hysterosonography as an adjunct to transvaginal ultrasound. (a) Sagittal transvaginal ultrasound demonstrates markedly thickened endometrium. (b) Sagittal hysterosonogram shows three broad based polyps. These were found to represent malignant endometrial polyps.

patients had an inactive endometrium. On the basis of these findings, albeit from a small sample, the author cautioned against over-interpreting a 'thickened' endometrium on transvaginal US images that have not been enhanced with fluid^[45].

Achiron *et al.* also investigated the discrepancy between a thickened endometrium at transvaginal US and benign results at sampling in patients with breast cancer treated with tamoxifen. They evaluated 20 women with cystic thickening (>5 mm) of the endometrium at transvaginal US who underwent hysterosonography followed by hysteroscopy and endometrial curettage. In 8 patients, hysterosonography delineated polyps; the remaining 12 patients had endometrial or subendometrial cysts. At inspection and sampling, polyps were confirmed in the first group, whereas 11 of the 12 women in the second group had scanty, senile cystic atrophy. The remaining patient had benign proliferative endometrial changes. The authors concluded that to increase specificity, postmenopausal women treated with tamoxifen who demonstrate thickening of the endometrium on endovaginal US images should undergo hysterosonography^[46].

Tepper *et al.* found that 68 of 114 patients with breast cancer treated with tamoxifen had an endometrial thickness of more than 8 mm at transvaginal ultrasound. Hysterosonography revealed hyperechoic or polypoid masses in 22 patients, and histologic results confirmed the presence of benign endometrial polyps (12 patients), polyps with simple or complex hyperplasia (4 patients), leiomyomas (2 patients), and no tissue obtained (4 patients). In the remaining 46 patients, hysterosonography did not reveal any intracavity pathology. Correlative hysteroscopy and biopsy revealed complex hyperplasia (2 patients), simple hyperplasia (5 patients), and atrophic endometrium or no tissue (39 patients). There were no false negative hysterosonographic diagnoses. The authors concluded that hysterosonography has high sensitivity (100%) and a high positive predictive value (95.5%) in patients receiving tamoxifen

who have an endometrial thickness of more than 8 mm at transvaginal US^[84].

In a retrospective study of 51 patients treated with tamoxifen, Hann found a significantly higher sensitivity of hysterosonography (100%) versus endometrial biopsy (4%) for the diagnosis of endometrial polyps. She concluded that sonohysterography should be considered for evaluation of abnormal uterine bleeding or thickened endometrium on ultrasound even if endometrial biopsy results are negative^[85]. In a prospective study by Fong, the combination of transvaginal ultrasound and hysterosonography for diagnosing endometrial abnormalities increased the specificity to 77.1% compared with a specificity of 55.7% with ultrasound alone^[63,67].

At hysterosonography, polyps appear as smoothly marginated echogenic masses with or without cystic areas. Polyps often have a narrow attachment to the endometrium but may be broad-based (Fig. 3). Submucosal fibroids appear as round structures arising from the myometrium, commonly with wide attachment to the myometrium, although they are occasionally pedunculated. Hysterosonographic features of adenomyosis include small cysts which appear in the inner myometrium^[63]. Diffuse smooth thickening of the endometrium suggests hyperplasia, however, hyperplasia may also appear as irregular asymmetric endometrial thickening^[86]. An irregular heterogenous mass or irregular focal thickening of the endometrium is suggestive of endometrial carcinoma^[63] (Fig. 4).

Doppler

In an attempt to increase the specificity of sonography for detecting endometrial pathology, Doppler studies of the endometrium of women on tamoxifen have been performed. Several studies have shown lower impedance of the uterine and endometrial flow compared with control groups^[12,46,65,87]. However, in the majority of these studies Doppler indices have been unable to differentiate between benign and pathologic etiologies^[12,46,65,87,88]. In certain cases, color Doppler US can improve the

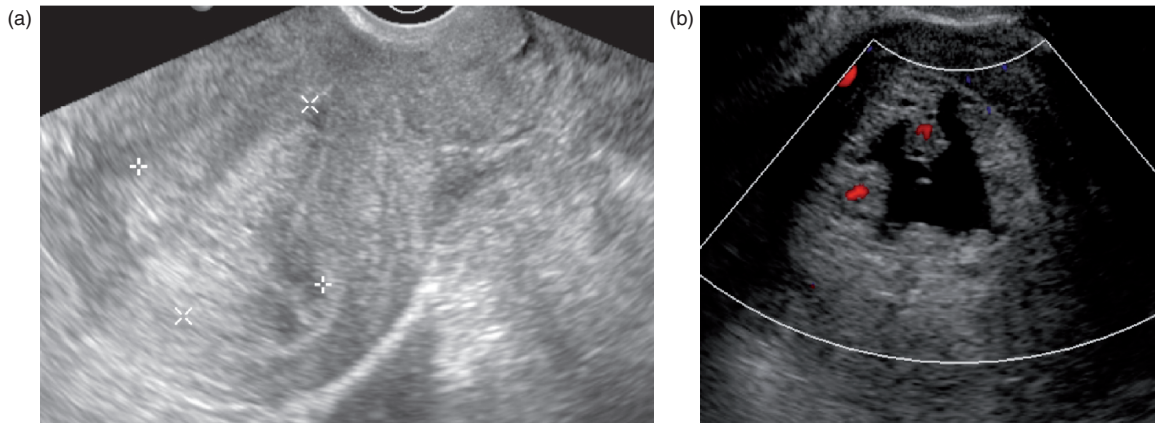


Figure 4 Hysterosonography as an adjunct to transvaginal ultrasound. Sagittal transvaginal ultrasound demonstrates a markedly thickened, heterogeneous endometrium. Calipers denote the endometrium. (b) Transverse view from hysterosonogram demonstrates irregular thickening with of the endometrium with internal vascularity which was found to represent endometrial carcinoma.

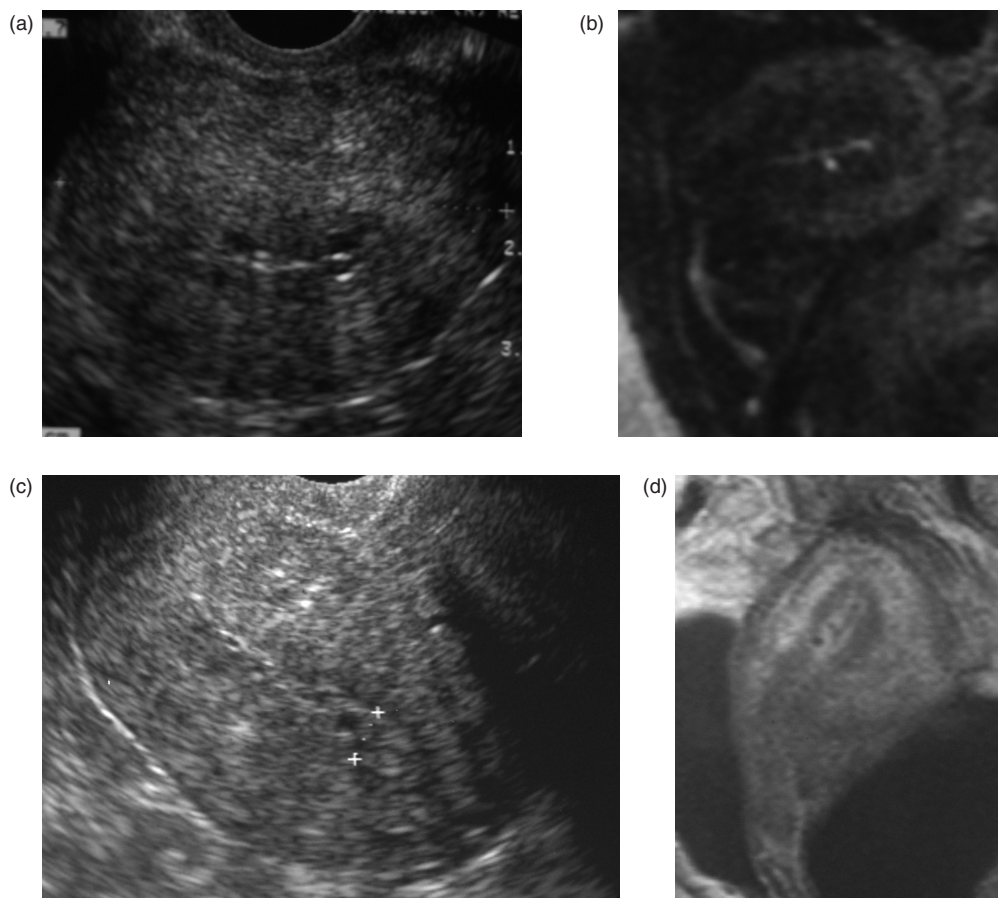


Figure 5 Pattern 1 MRI findings of the uterus in breast cancer patients treated with tamoxifen. (a) Transverse transvaginal ultrasound image shows small cysts around the endometrial complex. (b) Sagittal T2-weighted fast spin-echo MR image demonstrates a retroverted uterus with a normal thin homogeneously high signal intensity endometrium and cysts at the endometrial–myometrial junction. (c) Sagittal transvaginal ultrasound shows a retroverted uterus with a thickened endometrial complex measuring 6 mm (calipers) with small cystic spaces. Sagittal gadolinium-enhanced spoiled gradient-echo MR image shows the endometrial lumen is a signal void. Enhancement of the endometrial–myometrial interface with endometrial–myometrial cysts. (a,b) Reprinted with permission from Ascher *et al.*^[16]. (c,d) Reprinted with permission from Ascher *et al.*^[90]

specificity of sonography by showing the feeding artery in the pedicle of a polyp^[12,46,65,73,87].

MR imaging

MR imaging can demonstrate both endometrial and myometrial pathologic conditions. MR imaging may be appropriate in patients with an equivocal or abnormal endovaginal US who are unable to undergo hysterosonography due to cervical stenosis and at centers that do not offer hysterosonography^[16].

MR imaging has been shown to have a higher specificity than ultrasound in evaluating the uterus. One study compared MR imaging with transvaginal US for uterine evaluation in 28 women with breast cancer treated with tamoxifen. Histopathologic correlation was obtained in 21 patients. Histopathologic results included polyps (8 patients, 1 with superficial carcinoma), cystic atrophy (10 patients), and proliferative change (3 patients). For the correlation of imaging findings with histopathologic results, MR imaging had 100% sensitivity and 61.5% specificity, whereas endovaginal US had 87.5% sensitivity and 7.7% specificity. There was no statistically significant difference between the two modalities in terms of mean endometrial thickness. Of interest, tamoxifen-associated cysts were noted on MR images in eight of 12 patients with a false-positive endovaginal US diagnosis, including seven of 10 patients with cystic atrophy. These cysts may be responsible for spurious endometrial thickening on endovaginal US images. The authors concluded that both modalities are sensitive for the detection of endometrial abnormalities, although neither is very specific^[89].

Ascher *et al.* described two different MRI appearances of the endometrium in 35 postmenopausal women with breast cancer who were undergoing tamoxifen treatment, and they correlated the imaging findings with histopathologic results. The first pattern, found in 18 patients, showed homogeneously high signal intensity in the endometrium on T2-weighted MR images (mean thickness, 0.5 cm) associated with contrast material enhancement of the endometrial–myometrial interface and a signal void lumen on a gadolinium-enhanced image (Fig. 5). Ten of 18 patients with this pattern had an atrophic or proliferative endometrium at histopathologic analysis. The second pattern found in 17 patients showed an endometrium with heterogeneous signal intensity on T2-weighted MR images (mean thickness, 1.8 cm) associated with enhancement of the endometrial–myometrial interface and lattice-like enhancement traversing the endometrial canal on gadolinium-enhanced images (Fig. 6). Twelve of 17 patients with this pattern had polyps, one of which had a focus of endometrial carcinoma. Although larger studies are needed to determine if MR imaging can help reliably distinguish the various endometrial pathologic conditions associated with tamoxifen use, Ascher *et al.* concluded that MR imaging may (a) help identify those patients who should undergo a sampling procedure versus those who can be followed up non-invasively with MR imaging and (b) lead to a more aggressive intervention (dilation and curettage vs endometrial biopsy) if a non-diagnostic or normal result is obtained in a patient with abnormal MR imaging findings^[90,91].

Gadolinium enhancement can improve the evaluation of endometrial abnormalities. Specifically, an enhancing stalk is seen in many polyps, allowing the diagnosis to

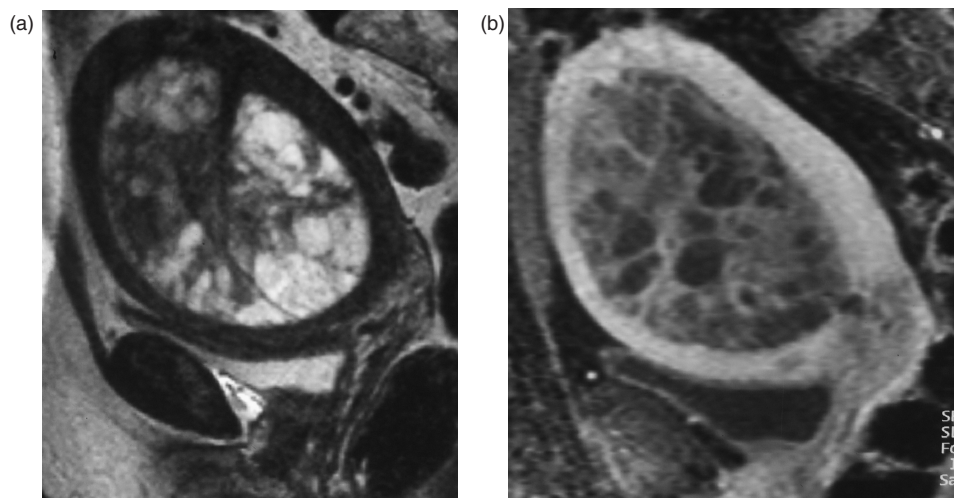


Figure 6 Pattern 2 MRI findings of the uterus in a breast cancer patient treated with tamoxifen. (a) Sagittal T2-weighted fast spin-echo MR shows a thickened endometrium with heterogeneous signal intensity. (b) The corresponding sagittal gadolinium-enhanced spoiled gradient-echo MR image shows lattice-like enhancement traversing the endometrial canal and was found to represent a benign endometrial polyp. (The corresponding ultrasound is shown in Fig. 1b.) Reprinted with permission from Silva *et al.*^[91].

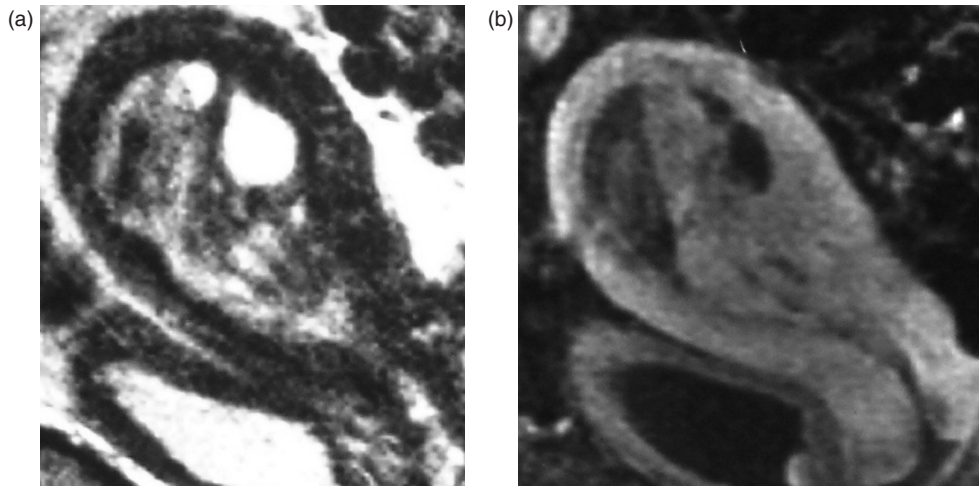


Figure 7 A 71-year-old woman with breast cancer treated with tamoxifen. (a) Sagittal T2-weighted fast spin-echo image of the uterus shows a widened endometrial canal with heterogeneous signal intensity. (b) Contrast enhanced sagittal-T1-weighted fat-suppressed spoiled gradient-echo image shows enhancing tissue traversing the endometrial canal. An enhancing stalk originating from the posterior endometrium allows the diagnosis of polyp to be established with confidence. Reprinted with permission from Ascher *et al.*^[90].

be established with confidence (Fig. 7). The ability of MR imaging to help accurately predict myometrial invasion has been established in the general (untreated) postmenopausal population, and these findings should hold true for women receiving tamoxifen^[92–95].

Conclusion

Currently no active screening for patients treated with tamoxifen, other than routine annual gynecologic surveillance, is recommended. Patients presenting with vaginal symptoms require evaluation and surveys have indicated that some physicians favor surveillance of asymptomatic breast cancer patients treated with tamoxifen. Therefore radiologist must be familiar with the effects of tamoxifen on the genital tract and the strengths and weaknesses of the imaging modalities.

To aid in that process, we offer an imaging algorithm based on results in published reports. Transvaginal US should be the first-line imaging modality for evaluation of the uterus in asymptomatic women undergoing tamoxifen treatment. Although there is no consensus, we conservatively use 5 mm as the upper limit for normal endometrial thickness in asymptomatic women treated with tamoxifen. Asymptomatic women can then be screened annually with transvaginal ultrasound from 1 to 2 years after the start of tamoxifen. The strength of transvaginal US is in the normal findings. In cases where the transvaginal US image is non-diagnostic or is suggestive of an abnormality, hysterosonography can provide additional information. That is, hysterosonography can be used to image polyps and endometrial-myometrial/subendometrial cysts with confidence and can help direct sampling procedures when necessary. MR imaging may be appropriate in

patients with an equivocal or abnormal endovaginal US scan who are unable to undergo hysterosonography due to cervical stenosis and at centers that do not offer hysterosonography^[16].

References

- [1] Machado F, Rodriguez JR, Leon JP, Parrilla JJ, Abad L. Tamoxifen and endometrial cancer. Is screening necessary? A review of the literature. *Eur J Gynaecol Oncol* 2005; 26: 257–65.
- [2] Neven P, Vernaev H. Guidelines for monitoring patients taking tamoxifen treatment. *Drug Saf* 2000; 22: 1–11.
- [3] ACOG committee opinion.No. 336: Tamoxifen and uterine cancer. *Obstet Gynecol* 2006; 107: 1475–8.
- [4] Althuis MD, Sexton M, Langenberg P, *et al.* Surveillance for uterine abnormalities in tamoxifen-treated breast carcinoma survivors: a community based study. *Cancer* 2000; 89: 800–10.
- [5] Varras M, Polyzos D, Akrivis C. Effects of tamoxifen on the human female genital tract: review of the literature. *Eur J Gynaecol Oncol* 2003; 24: 258–68.
- [6] Neven P, Vergote I. Should tamoxifen users be screened for endometrial lesions? *Lancet* 1998; 351: 155–7.
- [7] Cohen I, Altaras MM, Shapira J, Tepper R, Beyth Y. Postmenopausal tamoxifen treatment and endometrial pathology. *Obstet Gynecol Surv* 1994; 49: 823–9.
- [8] Cohen I, Beyth Y, Tepper R, *et al.* Adenomyosis in postmenopausal breast cancer patients treated with tamoxifen: a new entity? *Gynecol Oncol* 1995; 58: 86–91.
- [9] Ugwumadu AH, Bower D, Ho PK. Tamoxifen induced adenomyosis and adenomyomatous endometrial polyp. *Br J Obstet Gynaecol* 1993; 100: 386–8.
- [10] Lahti E, Blanco G, Kauppila A, Apaja-Sarkkinen M, Taskinen PJ, Laatikainen T. Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen. *Obstet Gynecol* 1993; 81: 660–4.
- [11] Cheng WF, Lin HH, Torng PL, Huang SC. Comparison of endometrial changes among symptomatic tamoxifen-treated and nontreated premenopausal and postmenopausal breast cancer patients. *Gynecol Oncol* 1997; 66: 233–7.

- [12] Kedar RP, Bourne TH, Powles TJ, *et al.* Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet* 1994; 343: 1318–21.
- [13] Barakat RR. Tamoxifen and endometrial neoplasia. *Clin Obstet Gynecol* 1996; 39: 629–40.
- [14] Schlesinger C, Kamoi S, Ascher SM, Kendell M, Lage JM, Silverberg SG. Endometrial polyps: a comparison study of patients receiving tamoxifen with two control groups. *Int J Gynecol Pathol* 1998; 17: 302–11.
- [15] Ismail SM. Pathology of endometrium treated with tamoxifen. *J Clin Pathol* 1994; 47: 827–33.
- [16] Ascher SM, Imaoka I, Lage JM. Tamoxifen-induced uterine abnormalities: the role of imaging. *Radiology* 2000; 214: 29–38.
- [17] Cohen I, Bernheim J, Azaria R, Tepper R, Sharony R, Beyth Y. Malignant endometrial polyps in postmenopausal breast cancer tamoxifen-treated patients. *Gynecol Oncol* 1999; 75: 136–41.
- [18] Gal D, Kopel S, Bashevkin M, Lebowicz J, Lev R, Tancer ML. Oncogenic potential of tamoxifen on endometria of postmenopausal women with breast cancer – preliminary report. *Gynecol Oncol* 1991; 42: 120–3.
- [19] Berliere M, Charles A, Galant C, Donnez J. Uterine side effects of tamoxifen: a need for systematic pretreatment screening. *Obstet Gynecol* 1998; 91: 40–4.
- [20] Corley D, Rowe J, Curtis MT, Hogan WM, Noumoff JS, Livolsi VA. Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy. *Obstet Gynecol* 1992; 79: 111–6.
- [21] Karlsson B, Granberg S, Wikland M, *et al.* Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding – a Nordic multicenter study. *Am J Obstet Gynecol* 1995; 172: 1488–94.
- [22] Kurman RJ NH. Blaustein's pathology of the female genital tract. Endometrial hyperplasia and related cellular changes. New York: Springer-Verlag, 1994: 411–437.
- [23] Osborne CK. Tamoxifen in the treatment of breast cancer. *N Engl J Med* 1998; 339: 1609–18.
- [24] Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994; 86: 527–37.
- [25] Fisher B, Costantino JP, Wickerham DL, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; 90: 1371–88.
- [26] van Leeuwen FE, Benraadt J, Coebergh JW, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994; 343: 448–52.
- [27] Uziely B, Lewin A, Brufman G, Dorembus D, Mor-Yosef S. The effect of tamoxifen on the endometrium. *Breast Cancer Res Treat* 1993; 26: 101–5.
- [28] Andersson M, Storm HH, Mouridsen HT. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. *J Natl Cancer Inst* 1991; 83: 1013–7.
- [29] Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998; 351: 1451–67.
- [30] Mignotte H, Lasset C, Bonadona V, *et al.* Iatrogenic risks of endometrial carcinoma after treatment for breast cancer in a large French case-control study. Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC). *Int J Cancer* 1998; 76: 325–30.
- [31] Peters-Engl C, Frank W, Danmayr E, Friedl HP, Leodolter S, Medl M. Association between endometrial cancer and tamoxifen treatment of breast cancer. *Breast Cancer Res Treat* 1999; 54: 255–60.
- [32] Barakat RR, Gilewski TA, Almadrones L, *et al.* Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. *J Clin Oncol* 2000; 18: 3459–63.
- [33] Magriples U, Naftolin F, Schwartz PE, Carcangiu ML. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* 1993; 11: 485–90.
- [34] Wilder JL, Shajahan S, Khattar NH, *et al.* Tamoxifen-associated malignant endometrial tumors: pathologic features and expression of hormone receptors estrogen-alpha, estrogen-beta and progesterone; a case controlled study. *Gynecol Oncol* 2004; 92: 553–8.
- [35] Narod SA, Pal T, Graham T, Mitchell M, Fyles A. Tamoxifen and risk of endometrial cancer. *Lancet* 2001; 357: 65–6; author reply 67.
- [36] Lasset C, Bonadona V, Mignotte H, Bremond A. Tamoxifen and risk of endometrial cancer. *Lancet* 2001; 357: 66–7.
- [37] Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of liver and endometrial cancer risk following tamoxifen. *Lancet* 2000; 356: 881–7.
- [38] Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. *Gynecol Oncol* 2004; 94: 256–66.
- [39] Deligdisch L, Kalir T, Cohen CJ, de Latour M, Le Bouedec G, Penault-Llorca F. Endometrial histopathology in 700 patients treated with tamoxifen for breast cancer. *Gynecol Oncol* 2000; 78: 181–6.
- [40] Ragaz J, Coldman A. Survival impact of adjuvant tamoxifen on competing causes of mortality in breast cancer survivors, with analysis of mortality from contralateral breast cancer, cardiovascular events, endometrial cancer, and thromboembolic episodes. *J Clin Oncol* 1998; 16: 2018–24.
- [41] Senkus-Konefka E, Konefka T, Jassem J. The effects of tamoxifen on the female genital tract. *Cancer Treat Rev* 2004; 30: 291–301.
- [42] Mourits MJ, De Vries EG, Willems PH, Ten Hoor KA, Hollema H, Van der Zee AG. Tamoxifen treatment and gynecologic side effects: a review. *Obstet Gynecol* 2001; 97: 855–66.
- [43] McGonigle KF, Shaw SL, Vasilev SA, Odom-Maryon T, Roy S, Simpson JF. Abnormalities detected on transvaginal ultrasonography in tamoxifen-treated postmenopausal breast cancer patients may represent endometrial cystic atrophy. *Am J Obstet Gynecol* 1998; 178: 1145–50.
- [44] Neven P, De Muylder X, Van Belle Y, Van Hooff I, Vanderick G. Longitudinal hysteroscopic follow-up during tamoxifen treatment. *Lancet* 1998; 351: 36.
- [45] Gompel C SS. Pathology in gynecology and obstetrics. In: Gompel C SS, editor. The corpus uteri. 4th ed. Philadelphia: Lippincott; 1994. p. 163–283.
- [46] Goldstein SR. Unusual ultrasonographic appearance of the uterus in patients receiving tamoxifen. *Am J Obstet Gynecol* 1994; 170: 447–51.
- [47] Achiron R, Lipitz S, Sivan E, Goldenberg M, Mashiah S. Sonohysterography for ultrasonographic evaluation of tamoxifen-associated cystic thickened endometrium. *J Ultrasound Med* 1995; 14: 685–8.
- [48] Dilts Jr PV, Hopkins MP, Chang AE, Cody RL. Rapid Gynecol growth of leiomyoma in patient receiving tamoxifen. *Am J Obstet* 1992; 166: 167–8.
- [49] Lumsden MA, West CP, Hillier H, Baird DT. Estrogenic action of tamoxifen in women treated with luteinizing hormone-releasing hormone agonists (goserelin) – lack of shrinkage of uterine fibroids. *Fertil Steril* 1989; 52: 924–9.
- [50] Klopfer A, Hall M. New synthetic agent for the induction of ovulation: preliminary trials in women. *BMJ* 1971; 1: 152–4.
- [51] Cohen I, Rosen DJ, Altaras M, Beyth Y, Shapira J, Yigael D. Tamoxifen treatment in premenopausal breast cancer patients may be associated with ovarian overstimulation, cystic formations and fibroid overgrowth. *Br J Cancer* 1994; 69: 620–1.
- [52] Ismail SM. Gynaecological effects of tamoxifen. *J Clin Pathol* 1999; 52: 83–8.

- [53] Cook LS, Weiss NS, Schwartz SM, *et al.* Population-based study of tamoxifen therapy and subsequent ovarian, endometrial, and breast cancers. *J Natl Cancer Inst* 1995; 87: 1359–64.
- [54] Lahti E, Vuopala S, Kauppila A, Blanco G, Ruukonen A, Laatikainen T. Maturation of vaginal and endometrial epithelium in postmenopausal breast cancer patients receiving long-term tamoxifen. *Gynecol Oncol* 1994; 55: 410–4.
- [55] Gill BL, Simpson JF, Somlo G, McGonigle KF, Wilczynski SP. Effects of tamoxifen on the cytology of the uterine cervix in breast cancer patients. *Diagn Cytopathol* 1998; 19: 417–22.
- [56] Ferrazzi E, Cartei G, Mattarazzo R, Fiorentino M. Oestrogen-like effect of tamoxifen on vaginal epithelium. *BMJ* 1977; 1: 1351–2.
- [57] Boccardo F, Bruzzi P, Rubagotti A, Nicolo GU, Rosso R. Estrogen-like action of tamoxifen on vaginal epithelium in breast cancer patients. *Oncology* 1981; 38: 281–5.
- [58] Mortimer JE, Boucher L, Baty J, Knapp DL, Ryan E, Rowland JH. Effect of tamoxifen on sexual functioning in patients with breast cancer. *J Clin Oncol* 1999; 17: 1488–92.
- [59] Mattsson LA, Cullberg G. Vaginal absorption of two estriol preparations. A comparative study in postmenopausal women. *Acta Obstet Gynecol Scand* 1983; 62: 393–6.
- [60] Ganz PA, Coscarelli A, Fred C, Kahn B, Polinsky ML, Petersen L. Breast cancer survivors: psychosocial concerns and quality of life. *Breast Cancer Res Treat* 1996; 38: 183–99.
- [61] Granberg S, Wikland M, Karlsson B, Norstrom A, Friberg LG. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. *Am J Obstet Gynecol* 1991; 164: 47–52.
- [62] Goldstein SR, Nachtigall M, Snyder JR, Nachtigall L. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. *Am J Obstet Gynecol* 1990; 163: 119–23.
- [63] Cohen I, Rosen DJ, Shapira J, *et al.* Endometrial changes with tamoxifen: comparison between tamoxifen-treated and nontreated asymptomatic, postmenopausal breast cancer patients. *Gynecol Oncol* 1994; 52: 185–90.
- [64] Fong K, Causer P, Atri M, Lytwyn A, Kung R. Transvaginal US and hysterosonography in postmenopausal women with breast cancer receiving tamoxifen: correlation with hysteroscopy and pathologic study. *Radiographics* 2003; 23: 137–50; discussion 151–5.
- [65] Levine D, Gosink BB, Johnson LA. Change in endometrial thickness in postmenopausal women undergoing hormone replacement therapy. *Radiology* 1995; 197: 603–8.
- [66] Gerber B, Krause A, Muller H, *et al.* Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol* 2000; 18: 3464–70.
- [67] Franchi M, Ghezzi F, Donadello N, Zanaboni F, Beretta P, Bolis P. Endometrial thickness in tamoxifen-treated patients: an independent predictor of endometrial disease. *Obstet Gynecol* 1999; 93: 1004–8.
- [68] Cohen I, Rosen DJ, Tepper R, *et al.* Ultrasonographic evaluation of the endometrium and correlation with endometrial sampling in postmenopausal patients treated with tamoxifen. *J Ultrasound Med* 1993; 12: 275–80.
- [69] Hulka CA, Hall DA. Endometrial abnormalities associated with tamoxifen therapy for breast cancer: sonographic and pathologic correlation. *AJR Am J Roentgenol* 1993; 160: 809–12.
- [70] Cecchini S, Ciatto S, Bonardi R, *et al.* Screening by ultrasonography for endometrial carcinoma in postmenopausal breast cancer patients under adjuvant tamoxifen. *Gynecol Oncol* 1996; 60: 409–11.
- [71] Atri M, Nazarnia S, Aldis AE, Reinhold C, Bret PM, Kintzen G. Transvaginal US appearance of endometrial abnormalities. *Radiographics* 1994; 14: 483–92.
- [72] Hann LE, Giess CS, Bach AM, Tao Y, Baum HJ, Barakat RR. Endometrial thickness in tamoxifen-treated patients: correlation with clinical and pathologic findings. *AJR Am J Roentgenol* 1997; 168: 657–61.
- [73] Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. *J Clin Oncol* 1999; 17: 2050–4.
- [74] Mourits MJ, Van der Zee AG, Willemse PH, Ten Hoor KA, Hollema H, De Vries EG. Discrepancy between ultrasonography and hysteroscopy and histology of endometrium in postmenopausal breast cancer patients using tamoxifen. *Gynecol Oncol* 1999; 73: 21–6.
- [75] Wolman I, Jaffa AJ, Hartoov J, Bar-Am A, David MP. Sensitivity and specificity of sonohysterography for the evaluation of the uterine cavity in perimenopausal patients. *J Ultrasound Med* 1996; 15: 285–8.
- [76] Dubinsky TJ, Parvey HR, Maklad N. The role of transvaginal sonography and endometrial biopsy in the evaluation of peri- and postmenopausal bleeding. *AJR Am J Roentgenol* 1997; 169: 145–9.
- [77] Langer RD, Pierce JJ, O'Hanlan KA, *et al.* Transvaginal ultrasonography compared with endometrial biopsy for the detection of endometrial disease. Postmenopausal Estrogen/Progestin Interventions Trial. *N Engl J Med* 1997; 337: 1792–8.
- [78] Shipley 3rd CF, Simmons CL, Nelson GH. Comparison of transvaginal sonography with endometrial biopsy in asymptomatic postmenopausal women. *J Ultrasound Med* 1994; 13: 99–104.
- [79] Lev-Toaff AS. Sonohysterography: evaluation of endometrial and myometrial abnormalities. *Semin Roentgenol* 1996; 31: 288–98.
- [80] Cullinan JA, Fleischer AC, Kepple DM, Arnold AL. Sonohysterography: a technique for endometrial evaluation. *Radiographics* 1995; 15: 501–14; discussion 515–6.
- [81] Bourne TH, Lawton F, Leather A, Granberg S, Campbell S, Collins WP. Use of intracavity saline instillation and transvaginal ultrasonography to detect tamoxifen-associated endometrial polyps. *Ultrasound Obstet Gynecol* 1994; 4: 73–5.
- [82] Tepper R, Beyth Y, Altaras MM, *et al.* Value of sonohysterography in asymptomatic postmenopausal tamoxifen-treated patients. *Gynecol Oncol* 1997; 64: 386–91.
- [83] Hann LE, Kim CM, Gonen M, Barakat R, Choi PH, Bach AM. Sonohysterography compared with endometrial biopsy for evaluation of the endometrium in tamoxifen-treated women. *J Ultrasound Med* 2003; 22: 1173–9.
- [84] Fong K, Kung R, Lytwyn A, *et al.* Endometrial evaluation with transvaginal US and hysterosonography in asymptomatic postmenopausal women with breast cancer receiving tamoxifen. *Radiology* 2001; 220: 765–73.
- [85] Laifer-Narin SL, Ragavendra N, Lu DS, Sayre J, Perrella RR, Grant EG. Transvaginal saline hysterosonography: characteristics distinguishing malignant and various benign conditions. *AJR Am J Roentgenol* 1999; 172: 1513–20.
- [86] Develioglu OH, Omak M, Bilgin T, Esmer A, Tufekci M. The endometrium in asymptomatic breast cancer patients on tamoxifen: value of transvaginal ultrasonography with saline infusion and Doppler flow. *Gynecol Oncol* 2004; 93: 328–35.
- [87] Sladkevicius P, Valentin L, Marsal K. Endometrial thickness and Doppler velocimetry of the uterine arteries as discriminators of endometrial status in women with postmenopausal bleeding: a comparative study. *Am J Obstet Gynecol* 1994; 171: 722–8.
- [88] Achiron R, Lipitz S, Sivan E, *et al.* Changes mimicking endometrial neoplasia in postmenopausal, tamoxifen-treated women with breast cancer: a transvaginal Doppler study. *Ultrasound Obstet Gynecol* 1995; 6: 116–20.
- [89] Ascher SM JJ, Zeman RK, Patt RH. Uterine changes in women receiving tamoxifen therapy: prospective comparison of MR imaging and transvaginal sonography with pathologic correlation. *Radiology* 1995; 197 (P): 353–354 (abstract).
- [90] Ascher SM, Johnson JC, Barnes WA, Bae CJ, Patt RH, Zeman RK. MR imaging appearance of the uterus in

- postmenopausal women receiving tamoxifen therapy for breast cancer: histopathologic correlation. *Radiology* 1996; 200: 105–10.
- [91] Silva A, Ascher S, Reinhold C. Magnetic resonance imaging versus ultrasound in the assessment of benign uterine lesions. In: Lang EK, editor. *Radiology of the female pelvic organs*. Berlin, Heidelberg, New York: Springer-Verlag; 1998, p. 43–67.
- [92] Hricak H, Stern JL, Fisher MR, Shapeero LG, Winkler ML, Lacey CG. Endometrial carcinoma staging by MR imaging. *Radiology* 1987; 162: 297–305.
- [93] Hricak H, Hamm B, Semelka RC, *et al*. Carcinoma of the uterus: use of gadopentetate dimeglumine in MR imaging. *Radiology* 1991; 181: 95–106.
- [94] Ito K, Matsumoto T, Nakada T, Nakanishi T, Fujita N, Yamashita H. Assessing myometrial invasion by endometrial carcinoma with dynamic MRI. *J Comput Assist Tomogr* 1994; 18: 77–86.
- [95] DelMaschio A, Vanzulli A, Sironi S, *et al*. Estimating the depth of myometrial involvement by endometrial carcinoma: efficacy of transvaginal sonography vs MR imaging. *AJR Am J Roentgenol* 1993; 160: 533–8.