LEADING ARTICLE

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# Guidelines for Monitoring Patients Taking Tamoxifen Treatment

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## Abstract

Tamoxifen is the most important anti–breast cancer drug in clinical use and has the potential to be used as a chemopreventive breast cancer agent. Using outpatient hysteroscopy and based on 2 case control and 2 cohort follow-up studies in our department, we were able to demonstrate that 50% of women receiving long term tamoxifen experienced some sort of adverse endometrial effects. Although many women retain an atrophic endometrial layer, tamoxifen intake can lead to extensive senile cystic atrophia of the human endometrium, to endometrial hyperplasia and to endometrial polyp formation. Based on a critical review of the literature, we have shown that tamoxifen doubles the risk for developing endometrial cancer in postmenopausal women, although this increased risk may be higher and is duration (i.e. time of use)-dependent.

Screening patients with breast cancer for endometrial abnormalities while they are taking tamoxifen is feasible and uterine morbidity related to tamoxifen intake is preventable. Although screening may increase drug compliance it may not be cost-beneficial. However, uterine safety becomes important when only a small benefit of the treatment is to be expected as in the use of tamoxifen in healthy women for breast cancer prevention.

The aim of this report is to discuss methods and guidelines for detecting endometrial adverse effects of tamoxifen and to provide the clinician with a current opinion on timing and frequency of screening patients taking tamoxifen for the development of endometrial cancer.

*In summary*, those who advocate screening should start with pretreatment uterine assessment using transvaginal ultrasonography or outpatient hysteroscopy. Symptom-free women with a normal pretreatment uterine cavity can be screened annually with transvaginal sonography from 2 to 3 years after the start of tamoxifen. Hysteroscopy or saline infusion sonography will be required if there is endometrial thickening because the only value of transvaginal ultrasonography is a normal finding being a thin rectilinear endometrium.

## 1. The Clinical Importance of Tamoxifen

Breast cancer is the leading cause of cancer deaths among women. It is clear that most breast cancers depend on estrogens for growth and progression. In 1927, Murray[1] showed that transplantation of the ovary to male rodents caused cancer in the male breast. Results from epidemiological studies have also indicated that female hormones and breast cancer are associated.

Consequently, therapies designed to reduce serum estrogen levels or to block the effects of estro-

gens on cancer cells are used to improve disease free survival of breast cancer patients. In 1896, Beatson[2] observed that bilateral oophorectomy could cause regression of advanced breast cancer in premenopausal women. Nowadays, endocrine therapies are the major treatment modality for the management of breast cancer. The first nonsteroidal estrogen, stilboestrol was developed in 1938 and at high doses, was shown to inhibit breast tumour growth. Successive chemical modifications of the weakly estrogenic stilbene nucleus led to the development of a class of less toxic molecules with antiestrogenic anti–breast cancer properties called the triphenylethylenes.[3] Tamoxifen, one of the triphenylethylenes, was synthesised in 1966[4] at about the same time as Toft and Gorski[5] discovered a possible biochemical marker for the hormone dependency of breast tumours with the description of the estrogen receptor in breast tumours.

Tamoxifen inhibits estrogen-induced cell growth predominantly by competitive blockade of the estrogen receptor. Because of the drug's efficacy preventing the progression of metastatic disease from advanced breast cancer and its general lack of toxicity, tamoxifen was approved in 1986 for adjuvant treatment in early-stage disease. Tamoxifen also prevents occult metastatic disease from early breast cancer and is now established as the front line endocrine treatment for breast cancer in more than 110 countries; there are more than 10 million women-years of experience with this agent. The worldwide overview on tamoxifen as an adjuvant for breast cancer therapy from the Early Breast Cancer Trialists' Collaborative Group published in 1998[6] showed that tamoxifen treatment in postmenopausal women reduced mortality by almost 25% and recurrence of breast cancer by 50%. Because of its favourable adverse effect profile, today's general recommendation is to prescribe the drug at a dosage of 20 mg/day for 5 years.

Tamoxifen has tissue-specific estrogenic or antiestrogenic properties. Whereas the molecule is an antiestrogen in the breast, it mainly behaves as an estrogen in other tissues. One hypothesis suggests that tamoxifen may have stronger estrogen agonist properties in the liver, uterus and bone because these tissues have proteins that augment transcription via one of the estrogen receptor's binding regions. Other mechanisms play an important role; this hypothesis is evolving at a time when new compounds of this class, which act as estrogens in 1 organ and antiestrogens in other, organs, and are referred to as selective estrogen receptor modulators (SERMs), are now available or in development. McDonnell[7] recently reviewed the complex pharmacology of SERMs illustrating how they differ mechanistically from estradiol, the physiological ligand of the estrogen receptor. The ability of tamoxifen to maintain bone mineral density and lower the incidence of osteoporotic fracture events involving hip, spine or lower radius in postmenopausal women[8] and to reduce serum cholesterol levels, in particular low density lipoproteins, with a trend in lowering myocardial infarct incidence in 1 study[9] has stimulated current trials exploring the use of tamoxifen as a prophylactic agent in healthy women at high risk of developing breast cancer.

Thousands of women in the US, Europe and Australia are participating in such trials. In a placebo-controlled trial conducted in the US, the National Surgical Adjuvant Breast and Bowel Project P-1 trial (NSABP P-1), which had an average follow-up of 3.6 years, tamoxifen was found to reduce estrogen receptor positive breast cancer risk in all age groups by 45%; this effect was increased with age (35% <49 years versus 53% >60 years) and with a longer duration of tamoxifen treatment.[10] Although other, smaller studies using tamoxifen in populations who are younger, with a lower risk of breast cancer, such as the studies by Veronesi et al.[11] in Italy and Powles et al.[12] in the UK, were less optimistic, it should not be surprising that millions of postmenopausal women, even those with a

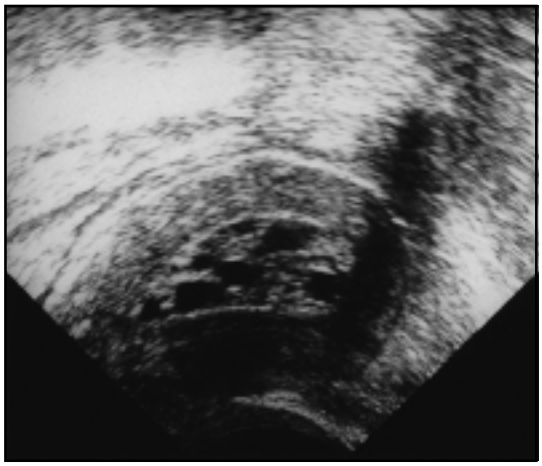

**Fig. 1.** An irregularly thickened endometrium with a typical Gruyère cheese appearance.

low probability of breast cancer, may be taking tamoxifen for an indefinite period.

## 2. Tamoxifen-Induced Endometrial Changes

Up to 30% of women taking tamoxifen have gynaecological symptoms of one degree or another; vaginal dryness and discharge are most often quoted. Increasing attention has been paid to the relationship between tamoxifen and endometrial changes.

Postmenopausal patients with breast cancer who experience vaginal bleeding while receiving tamoxifen 20 mg/day are more likely to have benign endometrial and endocervical polyps and a hyperplastic endometrial layer than a matched control group of women with postmenopausal vaginal bleeding who do not have breast cancer and who are not taking tamoxifen.[13] Long term tamoxifen intake leads to all sorts of asymptomatic endometrial changes and women using this drug have an increased risk of developing endometrial hyperplasia and polyps.[13] Case reports of endometrial cancer in patients receiving tamoxifen treatment show the same findings.[14]

Although evidence exists that some endometrial cancers reported in patients receiving tamoxifen were present before the affected women started taking the drug or were related to other risk factors, such as obesity and past estrogen replacement therapy, the few well designed studies adequately controlling for background risks, clearly show a carcinogenic effect of tamoxifen on the human endometrium. Three randomised clinical trials indicated that women treated with tamoxifen for breast cancer are at increased risk of developing endometrial cancer.[15-17] These 3 trials were large studies in which the participants were restricted to postmenopausal women with follow-up times of at least 4.5 years. In our literature review,[14] using all reported endometrial cancers from placebo-controlled trials with tamoxifen we found a 2-fold increase in the incidence rate of endometrial carcinoma risk in tamoxifen-treated patients (0.79 versus 0.37%). Therefore, tamoxifen was classified by the International Agency for Research on Cancer as a human endometrial carcinogen.[18] Although most clinicians agree that long term tamoxifen-users have a greater than chance risk of developing endometrial cancer they find that this risk should not be overestimated and does not alter

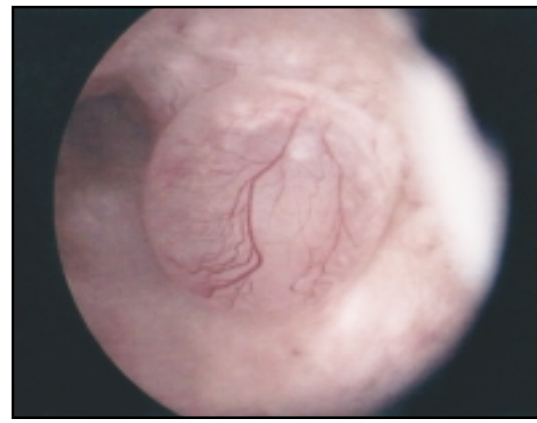

**Fig. 2.** Hysteroscopic image of pseudopolypoid glandulocystic endometrium.

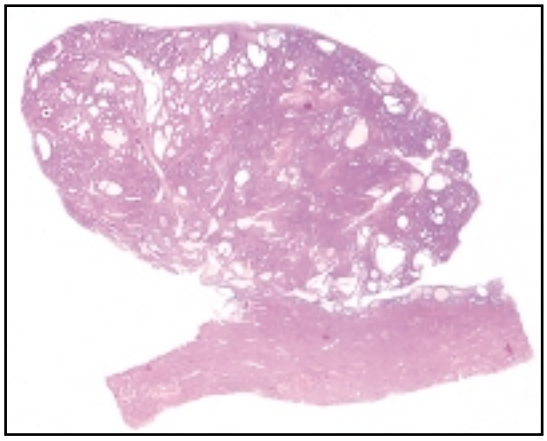

**Fig. 3.** Histopathological image of glandulocystic polyp (from Neven & Vergote,[23] with permission).

the risk-benefit ratio for breast cancer patients receiving tamoxifen.[19]

The effect of tamoxifen on the endometrium does not seem to differ in postmenopausal women without breast cancer. In healthy postmenopausal women assigned to receive either tamoxifen or placebo, who were followed-up for a mean of 22 months, histological evidence of abnormal endometrium (all changes were benign) was seen in 39% of the tamoxifen group versus 10% of the control group.[20]

In the NSABP P-1 study, a placebo-controlled breast cancer chemoprevention trial, tamoxifen intake led to a 2.5-fold excess risk of endometrial carcinoma.[10] This study involved a close to normal postmenopausal population and, to date, it is the first report in the literature of endometrial cancer developing in patients who never had breast cancer and who have received tamoxifen. The increased risk of endometrial cancer in this group of women receiving tamoxifen has caused concern over the safety of long term tamoxifen treatment. This potential adverse effect is especially important if large groups of healthy women could be exposed to antiestrogens for the prevention of breast cancer with the added benefits of receiving protection against osteoporosis and cardiovascular disease.

## 3. Ultrasonographic and Hysteroscopic Images

The best way to evaluate the effect of tamoxifen on the endometrium is to evaluate the uterine cavity prior to tamoxifen intake and at regular intervals thereafter. This method also allows exclusion of pretreatment endometrial abnormalities. In a prospective hysteroscopic follow-up study, we found that 9 out of 16 patients with breast cancer who were receiving tamoxifen experienced some endometrial changes.[21] Most of these changes were benign endometrial changes, such as pseudo and real polyps and endometrial hyperplasia. However, 1 patient did develop a new endometrial cancer. Other researchers,[22] who performed ultrasonographic follow-up have observed an irregularly thickened endometrium with a typical Gruyère cheese appearance in up to 75% of tamoxifen users (see fig. 1).

There are sonographic and hysteroscopic images which are pathognomonic for tamoxifen-induced endometrial lesions such as polyps. In cases with an ultrasonographic thickened endometrium, only hysteroscopy and saline infusion sonography

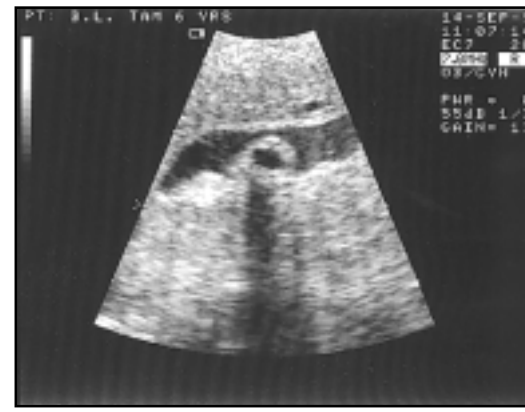

**Fig. 4.** Saline infusion sonography image of pseudopolypoid glandulocystic endometrium.

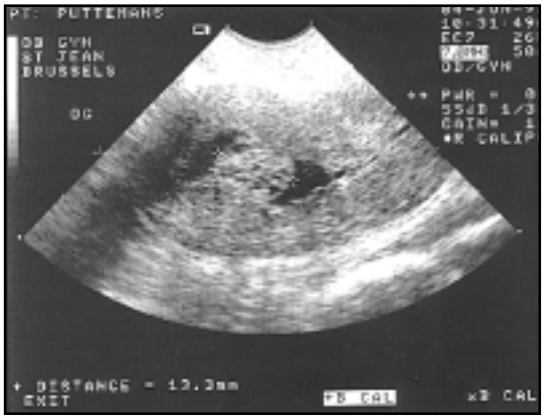


**Fig. 5.** Saline infusion sonography image of glandulocystic polyp.

are able to differentiate between two of tamoxifen's typical endometrial effects, namely pseudopolypoid glandulocystic endometrium (see fig. 2) and glandulocystic polyps (see fig. 3).

In the case of a pseudopolypoid glandulocystic endometrium there is, with hysteroscopy, a smooth white but hypervascularised endometrial layer with many scattered protuberances. When such a protuberance is opened there is a thin atrophic endometrium overlying a cystic dilated gland being an oedematous stroma. With saline infusion sonography (see fig. 4), there is an empty cavity with the Gruyère cheese appearance showing up in the subepithelial layer of the endometrium. Histologically, this endometrium typically shows periglandular stromal condensation, epithelial metaplasias and proliferative activity sometimes with varying degrees of cytological atypia.

In the case of a polyp, the glandulocystic structure is free floating and surrounded with saline with saline infusion sonography (see fig. 5); with hysteroscopy the endometrium surrounding the polyp is mostly not thin and regular. The majority of endometrial polyps occur on a background of simple endometrial hyperplasia, however, neighbouring endometrium may be atrophic. Microscopically, the polyps are characterised by patchy periglandular condensation of stroma, proliferative activity in epithelial and stromal cells and an admixture of epithelial metaplasias, including squamoid and mucinous metaplasias. It is highly unlikely that these 3 microscopic features coexist in the same polyp in women not taking tamoxifen.

## 4. Is Screening Worthwhile?

### 4.1 Screening in Patients with Breast Cancer

Most endometrial polyps and 'hyperplastic' lesions in tamoxifen-treated women, traditionally held as premalignant, rarely evolve into invasive cancers. Whereas the quoted annual incidence of endometrial cancer is 0.7 per 1000 women in an unscreened population, and 1.71 in a screened population,[24] only an extra 2 to 3 women who were previously asymptomatic per year and per 1000 women, will develop endometrial cancer because of tamoxifen. Many clinicians continue therefore to question general screening. According to some, screening may do more harm than good in terms of unnecessary interventions, subsequent complications, increased cost and no advantage to the patient. This notion is supported by: (i) the huge discrepancy between the high rates of asymptomatic endometrial lesions and the quite low frequency of symptomatic endometrial cancers; and, (ii) the fact that although aggressive screening would most probably lead to early diagnosis, there is, to date, no evidence that this would confer a survival advantage. Endometrial cancer is a rather slowly progressing malignancy with high 5-year survival rates, in contrast to breast cancer relapse that results in a significant increase in morbidity and death. Others researchers believe that the value of routine screening should be determined by prospective studies which are underway.

Indeed, from a histopathological and biological behaviour point of view, endometrial cancers from tamoxifen are not different from those developing in women not using tamoxifen.[17,25] Since tamoxifen-associated endometrial cancers seem to have a similar stage, grade and histology as endometrial cancers occurring in the general popula-

tion, their prognosis is generally good and early detection will probably not improve outcome significantly.[26] Therefore, the main purpose of a screening programme for endometrial cancer in tamoxifen users – lowering mortality related to endometrial cancer – is unlikely to be proven.[27] It can be therefore concluded that in patients with breast cancer receiving tamoxifen, endometrial monitoring is not cost-effective.

### 4.2 Screening in Women without Breast Cancer

In some cases, however, there is a need to consider prevention of endometrial cancer rather than cure. Those patients taking tamoxifen as a chemopreventive drug will request screening because of the potential endometrial cancer risk with long term use. In our view, offering endometrial surveillance in this group will improve compliance and is the only way forward to continue long term tamoxifen treatment for breast cancer prevention. In order to evaluate the possible benefit of treatment with progestins in reducing endometrial cancer risk, women who experienced persistent endometrial thickening while taking tamoxifen were given oral norethisterone for 21 days out of 28 for 3 consecutive cycles.[28] After 3 months of cyclical norethisterone, 96% of those women with a persistent thickened endometrium had a progesterone withdrawal bleed, indicating an estrogenically primed endometrium. The endometrial cysts and polyps which were detected in women receiving tamoxifen could, however, not be reversed by norethisterone. Further studies are required to ascertain whether a progestin, oral treatment or released through an intrauterine inserted device, would protect against endometrial polyp formation, endometrial hyperplasia or cancer.[28]

The new generation of antiestrogens, SERMs, have less proliferative or antiestrogenic effects on the human endometrium. Their protective effect against myocardial infarction, bone fractures and breast cancer is still under investigation, but preliminary results are as promising as those for tamoxifen. In a recently presented placebo-controlled trial,[29] involving healthy postmenopausal women (mean age 66.5 years) at increased risk for osteoporosis, the Multiple Outcomes of Raloxifene Evaluation (MORE) study, raloxifene markedly reduced bone fracture risk and the risk of newly diagnosed mainly estrogen receptor positive breast cancer by 74% following an average use of 33 months. Raloxifene decreased endometrial cancer incidence by more than half (relative risk = 0.38).[29]

## 5. Monitoring Techniques

When considering what techniques should be employed to screen women without symptoms of endometrial problems who are receiving tamoxifen, transvaginal sonography, saline infusion sonography and hysteroscopy have been advocated as the most applicable. In our practice, for almost 10 years now, when treatment with tamoxifen is started, the patient and her general practitioner are notified about tamoxifen's proliferative effect upon the endometrium which in some cases may lead to abnormal vaginal bleeding, which is not a good predictor for uterine pathology. We do advise a baseline (before initiation of tamoxifen) transvaginal endometrial assessment. In the case of an abnormal endometrium (endometrial thickness above 5mm or irregular endometrium), we perform an outpatient hysteroscopy, but a saline infusion sonography has a similar detection rate for intrauterine lesions. Such lesions should be removed upfront as they are predictive for tamoxifen-related uterine pathology.[30]

In a well informed woman without symptomatic endometrial problems, because of the low cost effectiveness profile of screening, a 'wait and see' policy is an option, but if abnormal vaginal bleeding occurs a diagnosis is required. The only valuable method to obtain such a diagnosis in case of abnormal vaginal bleeding is through direct visualisation of the uterine cavity using the hysteroscope

with guided endometrial biopsies. Polyps and localised endometrial changes are easily missed with blind intrauterine procedures and both require removal for diagnosis. Small patches of atypical hyperplasia within the polyp and polyp-cancers can only be diagnosed once the polyp is examined histologically.[31]

In women with no endometrial symptoms receiving tamoxifen, transvaginal ultrasonography as a tool for endometrial assessment is of limited value and can be misleading. However, transvaginal ultrasound is a valuable method for the visualisation of all uterine layers (e.g. fibroids) and the ovaries and ovarian pathology is not uncommon in breast cancer patients where tamoxifen-induced ovarian cysts have been reported. In tamoxifen users, as in those patients taking hormone replacement therapy,[32] transvaginal ultrasonography has a close to superb negative predictive value: pathology is unlikely in the case of a very thin (<5mm) endometrial line in an asymptomatic postmenopausal woman. Small, probably clinically irrelevant pathology will be missed, but all together ultrasound is a sensitive test. Unfortunately, tamoxifen abnormally thickens the endometrium in up to 75% of asymptomatic women without any pathological significance.[33] Tamoxifen-induced endometrial changes result in a sonographically unique picture of an irregularly echogenic endometrium that is attributed to cystic glandular dilation, stromal oedema and oedema and hyperplasia of the adjacent myometrium.[34,35] Therefore, the positive predictive value of transvaginal sonography is low.[36-40] To improve this positive predictive value, some authors use or recommend 8mm as a cut-off level for a thickened endometrium within postmenopausal women receiving tamoxifen.[28,36] However, also in these cases, the only way to obtain a correct diagnosis is to do additional tests such as contrast ultrasonography or hydrosonography, endometrial blood flow studies and hysteroscopy.

Saline infusion sonography was first described by Randolph et al.[41] in 1986 when they injected saline into the uterine cavity through a thin flexible cervical catheter and observed the intra-uterine contours using the abdominal ultrasound probe. Using the transvaginal probe this technique delineates the uterine cavity accurately providing a contrast medium as well as a distending agent facilitating a more precise endometrial thickness measurement. Saline infusion sonography will easily detect free-floating polyps and localised endometrial thickening[42] but in comparison with hysteroscopy the interpretation of a shadow remains less accurate compared with direct visualisation, in which case a guided biopsy can also be taken. It has been proven that in experienced hands saline infusion sonography and outpatient hysteroscopy are equally good.[43]

Doppler flow studies as an endometrial surveillance test in women receiving tamoxifen therapy have been tested but changes are not specific for endometrial pathology.[44] Tamoxifen induces significant reductions of the impedance to blood flow in the endometrial and subendometrial vasculature regardless of the presence or absence of endometrial pathology. This is probably due to dilation of the existing vascular bed.[20,38]

## 6. Screening Guidelines

### 6.1 Consensus Meeting Guidelines

In an earlier study, we found a close relationship between the total (cumulative) dose of tamoxifen and the appearance of benign endometrial lesions;[45] this relationship was later confirmed for endometrial cancers.[46-48] To evaluate the numbers of years the uterine cavity can be left without screening, we performed another longitudinal hysteroscopic follow-up study. We evaluated the effect of duration of tamoxifen intake and the appearance of endometrial lesions in 57 postmenopausal women receiving tamoxifen.[49] All had an atrophic endometrium and an empty uterine cavity and were regularly evaluated by means of

outpatient panoramic hysteroscopy using $CO_2$ as distension medium. Although there was no comparator cohort of non–tamoxifen-exposed patients with breast cancer to differentiate background events that may be unrelated to tamoxifen, we found that during the 3 years following a normal baseline endometrium, postmenopausal women receiving tamoxifen 20 mg/day did not develop endometrial hyperplasia or endometrial cancer; in this time period however, benign endometrial polyps and glandulocystic endometria did appear. Although more data from women participating in such studies are needed to confirm our findings, on the basis of this study we concluded that with a hysteroscopically normal uterus at the start of therapy (i.e. an empty uterus with an atrophic endometrium), atypical endometrial hyperplasia or cancer is unlikely to be found in the first 2 to 3 years. Therefore, women in whom there is concern for potential uterine adverse effects should, ideally, be screened prior to tamoxifen use. This finding was recently confirmed by Berlière et al.[50] Predictive factors other than the cumulative dose that can be used for identifying those women at risk of developing endometrial adverse effects while receiving tamoxifen have been reported. Chang et al.[51] noted that premenopausal women at the start of tamoxifen/placebo who developed amenorrhoea may be at particular risk of endometrial cancer. Tamoxifen led to endometrial thickening in amenorrheic women with low estradiol but had an opposite antiestrogenic endometrial effect in women with high estradiol.

At a recent international meeting in Brussels, organised by the Flemish Gynaecological Oncology Group and the gynaecologists at the Algemene Kliniek St.-Jan in Brussels, it was agreed that pretreatment uterine assessment should be started using transvaginal sonography or outpatient hysteroscopy.[52,53] In the absence of pretreatment endometrial pathology, asymptomatic long term tamoxifen users are followed up on a yearly basis starting after 2 to 3 years of treatment because of the effect of cumulative doses. Hysteroscopy or saline infusion sonography will be required if there is endometrial thickening because the only value of transvaginal sonography is a normal finding. The participants at the conference agreed that screening breast cancer patients receiving tamoxifen for endometrial cancer is unlikely to be cost-beneficial and that women without breast cancer who are being treated with tamoxifen within a chemopreventive trial should be monitored closely for the development of endometrial hyperplasia or cancer. Others have proposed a similar algorithm.[54]

### 6.2 American College Obstetricians and Gynecologists' Guidelines

To overcome inappropriate testing, anxiety and large expenses, the American College of Obstetricians and Gynecologists published its own guidelines in February 1996.[55] These recommendations for women taking tamoxifen are as follows.

1. Women with breast cancer should have annual gynaecological examinations, including PAP tests and bimanual and rectovaginal examinations.

2. Any abnormal bleeding, including bloody discharge, spotting, or any other gynaecological symptoms, should be evaluated thoroughly. Any bleeding or spotting should be investigated by biopsy.

3. Practitioners should be alerted to the increased incidence of endometrial malignancy. Screening procedures or diagnostic tests should be performed at the discretion of the individual gynaecologist.

4. Women without breast cancer who are being treated with tamoxifen within a chemopreventive trial should be monitored closely for the development of endometrial hyperplasia or cancer.

5. If atypical hyperplasia develops, use of tamoxifen should be discontinued, and dilation and curettage or other appropriate gynaecological management should be instituted within an appropriate interval.

6. If tamoxifen therapy must be continued, hysterectomy should be considered in women with atypical endometrial hyperplasia.

7. Tamoxifen use may be reinstituted following hysterectomy for endometrial carcinoma in consultation with the physician responsible for the woman's breast care.

These guidelines do make the gynaecologist aware of the potential risk with long term tamoxifen use but are of no practical help to the gynaecologist dealing with women taking tamoxifen. 'Close monitoring' and 'screening at the discretion of the individual clinician' can be interpreted in many different ways. Points 1 and 2 are in not relevant to patients taking tamoxifen. Furthermore, any postmenopausal woman with abnormal vaginal bleeding needs other tests than 'biopsy' especially if the patient is receiving tamoxifen; any blind procedure will lead to false negative tests. A dilation and curettage is not the appropriate treatment for atypical endometrial hyperplasia and is also not appropriate for the patient who is receiving or is considering stopping tamoxifen. Any such patient may have a focus of invasive endometrial cancer and may require a hysterectomy.

## 7. Conclusion

The association between long term tamoxifen use and endometrial pathology including endometrial cancer is a real one. This adverse reaction is acceptable in the context of the expected benefits of tamoxifen for breast cancer and screening for endometrial abnormalities is unlikely to be cost-beneficial. However, screening becomes an important issue because of tamoxifen's troublesome endometrial effect in healthy women considering taking this treatment to improve postmenopausal health, i.e. providing protection against breast cancer, osteoporosis and myocardial infarction.

Several methods for detecting gynaecological adverse effects of tamoxifen have been discussed. Simple transvaginal ultrasonography may be sensitive, but should be considered as a rather a specific procedure. Saline infusion sonography and hysteroscopy in case of endometrial thickening are more specific but consequently, treatment of all visible lesions will undoubtedly lead to a high ratio of benign to malignant lesions.

The guidelines for monitoring that reduce the number of invasive sampling are as following: start with pretreatment uterine assessment using transvaginal sonography or outpatient hysteroscopy. In the absence of pretreatment endometrial pathology, asymptomatic long term tamoxifen users are followed up on a yearly basis starting after 2 to 3 years of treatment because of the effect of cumulative doses. Hysteroscopy or saline infusion sonography will be required if there is endometrial thickening.

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