Transvaginal ultrasonography and hysterosonography to monitor endometrial effects in tamoxifen-treated patients

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Summary

Purpose of investigation: Our purpose was to evaluate if, during tamoxifen treatment, hysterosonography may increase diagnostic accuracy when compared with transvaginal ultrasonography and to identify, when and in how many cases, further biopsies may be avoided.

Methods: We performed transvaginal utrasound in 310 asymptomatic women under tamoxifen treatment, using 8 mm endometrial thickness as the cut-off. One hundred and seven patients with an endometrium thicker than 8 mm were enrolled for hysterosonography. Parameters to be evaluated by transvaginal ultrasound and hysterosonography were thickness and structural features of the endometrium. It was possible to compare ultrasound examinations with histopathological findings obtained by biopsy in 83 patients.

Results: Globally only ten patients from the study cohort had true endometrial pathology. Based on structural features of the endometrium, we found a global accuracy of 95.6%, with 2.8% false negatives and 4.1% false positives.

Conclusion: Hysterosonography can increase diagnostic accuracy during tamoxifen treatment and may allow further invasive investigations to be avoided in patients with suggestive hysterosonographic features.

Key words: Tamoxifen; Endometrium; Transvaginal ultrasound; Hysterosonography.

Introduction

Tamoxifen is widely used in the hormone therapy of breast carcinoma. Side-effects include endometrial, myometrial and cervical stimulation, induction of ovarian pathology and growth of uterine fibromas.

Although breast and endometrial carcinoma share several risk factors, which are often simultaneously present in the same patients, the incidence of endometrial cancer in women treated with tamoxifen is 4.1 times higher than in non-treated patients [1]. Moreover, endometrial polyps are up to 11 times as frequent, and show histological peculiarities such as marked stromal representation [2]. Finally, the incidence of endometrial hyperplasia is five times higher than in patients who did not receive the drug [3].

Such evidence has made strict monitoring of tamoxifen-treated patients mandatory. Transvaginal ultrasounds (TU) demonstrated greater sensibility than transabdominal ultrasounds for such purpose; however, the detection of stromal changes or other benign lesions such as polyps caused an unacceptable increase in the amount of patients referred for invasive investigations for increased endometrial thickness [4].

It has been estimated that up to 18-35.5% of treated women show increased endometrial thickness; however, the possibility of an underlying endometrial cancer should not be underestimated [5]. It is therefore necessary to identify a minimally invasive diagnostic method which allows the differentiation of benign lesions such as polyps and simple endometrial thickening from hyperplasia and carcinoma.

Intrauterine fluid introduction aided ultrasounds, known as hysterosonography (HS) has proved useful to recognize such lesions and to assess their size and surface regularity. Moreover, it has shown promise in the evaluation of uterine cavity and endometrial characteristics.

It is well known that TU is unable to differentiate among adenocarcinoma, hyperplasia, polyps, and submucosal fibromas based on endometrial thickness, measured as the maximum thickness in a longitudinal section and including both sides of the mucosa [6, 8].

According to our experience, should 8 mm be used as a referral to biopsy cut-off, greater than 30% of our patients would be referred to a mostly useless invasive investigation. Therefore, the search for an ideally selective, minimally invasive study appears to be justified in order to reduce the burden of follow-up with TU.

Thus, our purpose was to evaluate if HS may increase diagnostic accuracy as compared to TU, and to identify when, and in how many cases, further biopsies may be avoided.

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Table 1. — *Adopted ultrasonographic evaluation criteria.*

	TU	HS	
		a	b
True positive cases	> 8 mm endometrium > 8 mm focal lesions	• Regular focal lesions + < 2 mm endometrium • Focal or diffuse endometrial thickening (> 2 mm) • Irregular focal lesion(s)	• Focal or diffuse endometrial thickening (> 2 mm) • Irregular focal lesion(s)
True negative cases		• < 2 mm endometrium • stromal alteration + > 2 mm endometrium	• < 2 mm endometrium • stromal alteration + > 2 mm endometrium • regular focal lesions + 2 mm endometrium

Materials and Methods

We performed TU in 310 asymptomatic women under treatment with tamoxifen; we used 8 mm endometrial thickness as the TU cut-off. The uterine cavity and endometrium were not clearly visible in 46 patients (14.8% of cases) due to fibromas, mural fibrosis, or uterine malposition; these patients were excluded, so that the study cohort was eventually represented by 264 patients.

A thicker than 8 mm endometrium was detected in 107 patients (40.5% of cases). These women were referred for further investigations, and HS was also proposed to them.

Ninety-six out of 107 patients volunteered to undergo HS; however, 13 of them (13.5%) were subsequently excluded because they refused biopsy or were lost at follow-up.

HS was performed using hystero-injectors, and sterile saline was employed as contrast medium. Neither systemic nor vaginal premedication was administered. A SSD 680 ultrasound apparatus (Aloka, Tokyo, Japan) with a 5 MHz endovaginal probe was used.

The parameters to be evaluated by TU included the thickness and structural features of the endometrium; endometrial thickness was measured in the uterine fundus, corresponding to the maximal thickness. Due to the adopted inclusion criteria, no false negative cases were present.

The evaluated parameters with HS were the presence of focal lesions, their number and surface features (ie smooth, regular, irregular, etc.), the thickness and structural features of the endometrium. A regular 2-mm thick endometrial line was considered consistent with atrophy.

Based on our premises, we considered that HS was positive in the presence of focal regular lesions associated with thin endometrial lining along the rest of the cavity, or diffuse or localized endometrial thickening over 2 mm, or focal, irregularly marginated lesions. HS was deemed negative when focal regular lesions were associated with atrophic endometrium, other than in the presence of a less than 2 mm thick, regular endometrial lining (Table 1).

Results

Hysteroscopy and/or dilatation and curettage was performed in 83 out of 96 patients. The results of ultrasound examinations were compared with those provided by biopsy.

Table 2 reports the results of histological examinations performed on the 83 patients who underwent hysteroscopy or dilatation and curettage.

HS could not be performed in 14 patients (14.5% of cases) due to stenosis (4 cases), reflux (2 cases), or insufficient cavity distension (8 cases); six of the latter patients experienced pain that forced us to interrupt the examination. The obtained data were considered sufficient for a reliable evaluation in 69 patients (65.5% of cases) (Table 3).

Histological results obtained in these 14 patients revealed two cases of simple or polypoid hyperplasia, seven cases of polyps associated with atrophic endometrium, and five cases of atrophic endometrium. The overall number of these pathologies in the study cohort was eight (9.7% of cases), 36 (43.9% of cases), and 72 (88.9% of cases), respectively.

On the whole, only ten patients (12.1% of cases) from the study cohort had a true endometrial pathology.

HS detected 46 of 61 cases of atrophic endometrium (76.6% of cases); 25 of these (54.3%) were associated to a polyp, usually of large size and showing typical vacuolar features (Figure 1).

HS detected 22 of 36 cases of isolated atrophic endometrium (61.1%). In four cases there were fibromas or sinechiae, whereas in nine (13.2%) stromal alterations were seen (Figure 2); often, the latter also displayed vacuolization similar to polyps. HS failed to detect atrophic endometrium in 14 cases due to focal thickening of the endometrial lining (false positives) between 4 and 8 mm (median 5.2 mm).

TU yielded a false positive absolute rate of 49.3% (41 cases with atrophic endometrium) as opposed to 22.8% yielded by HS. Because TU was not performed in five cases, the accuracy of the method exceeds 60% when sufficient data are provided. Regarding typical regular polyps associated with atrophic endometrium, a benign pathology

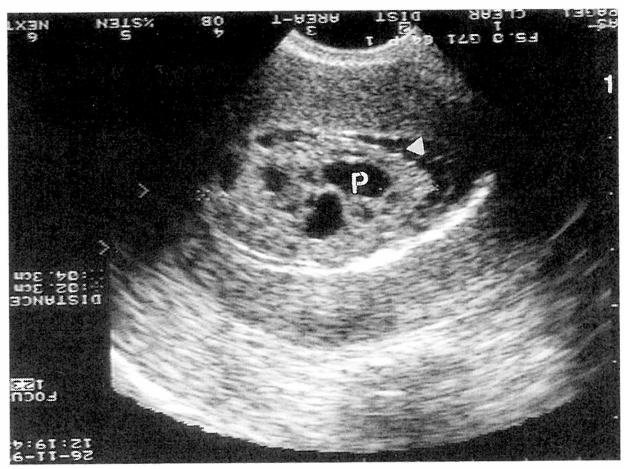

Figure 1. — Glandulo-cystic polyp (d) with typical vacuolar features.

Table 2. — *Histological findings in 83 treated patients.*

Histology	# cases	% cases	Failed HS, # (%)
Atrophy	32	38.5	
Stromal alterations	9	9.3	
Total atrophy	41	49.3	5 (12.1)
Polyp + atrophy	32	38.5	7 (21.8)
Polyp + hyperplasia	6	7.2	2 (33.3)
Hyperplasia	2	2.4	
Adenocarcinoma	2	2.4	

Table 3. — *HS findings obtained in 69 patients in whom HS was sufficient quality. OBS: All polyps were correctly identified; "undetected" refers to associated endometrial pathology. The recognition of malignant or benign lesions refers to lesion characteristics (margin regularity).*

Histology	Cases, # (%)	Detected by HS, # (%)	Undetected by HS, # (%)
Atrophic endometrium	23 (33.8)	10 (43.4)	13 (56.5)
Atrophic endometrium + sinechiae	4 (5.8)	4 (199)	0
Atrophic endometrium + stromal alterations	9 (13.2)	8 (88.8)	1 (11.1)
Total isolated atrophic endometrium	36 (51.4)	22 (61.1)	14 (38.8)
Atrophic endometrium + polyp	25 (36.7)	24 (96)	1 (4)
Total atrophic endometrium	61 (88.2)	46 (76.6)	15 (25)
Polyp + simple hyperplasia	4 (5.8)	2 (50)	2 (50)
Simple hyperplasia	2 (2.9)	2 (100)	0
Total hyperplasia	6 (8.8)	4 (66.6)	2 (33.3)
Adenocarcinoma	2 (2.8)	2 (100)	0
Total significant pathologies	8 (11.7)	6 (75)	2 (25)

that does not require further investigations, true negatives increase to 64.7%, with only 2.8% of false negatives (two cases of unidentified hyperplasia associated with polyps). Only in a single case did we find a false positive, represented by a benign, irregularly marginated polyp.

Twenty-five out of 29 benign polyps were associated with atrophic endometrium, whereas the remaining four with simple hyperplasia.

The eight cases of true significant pathology were represented by two endometrial adenocarcinomas and six simple hyperplasias and all were identified by HS. However, if lesions with particular morphological features (margin regularity) are considered suspect, two false negatives were found, represented by two cases of hyperplasia presenting as regularly marginated thickening (Figure 3).

In the six cases of hyperplasia, the thickening ranged between 4 and 10 mm, and was diffuse in one case and focal in the remainder. The two adenocarcinomas presented as complex proliferative lesions with irregular margins and vegetations (Figure 4).

Based on structural features of the endometrium and on account of the identified pathologies (Table 1), we found a global accuracy of 95.6%, with 2.8% false negatives and 4.1% false positives; if only thickening of the endometrial lining with atrophic endometrium is taken into consideration, then false positives increase to 21.7%, whereas no false negatives were found.

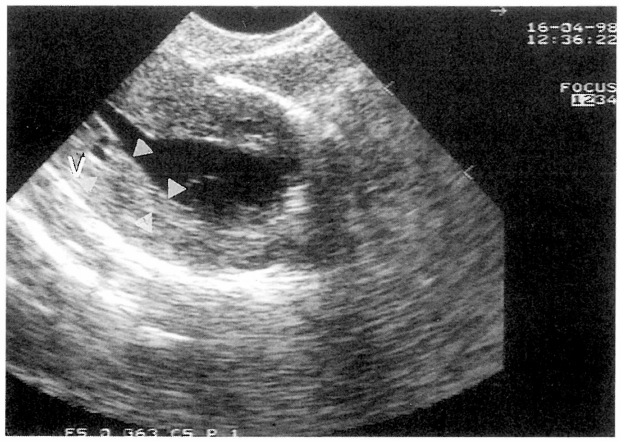

Figure 2. — Stromal thickening (triangle) at level of the posterior wall with vacuolar features (v).

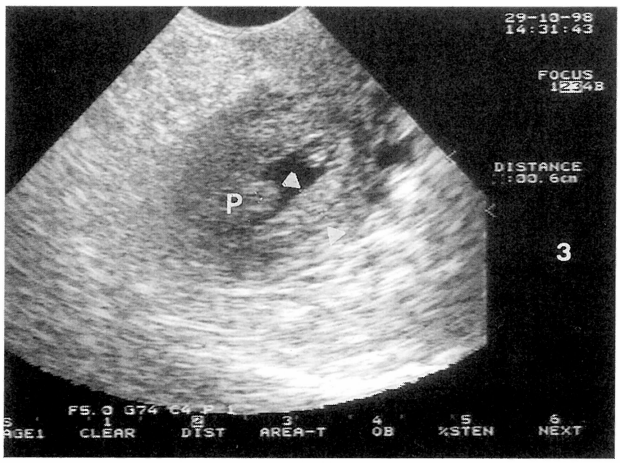

Figure 3. — Small polyp (p) associated with endometrial thickening (triangle) due to hyperplasia.

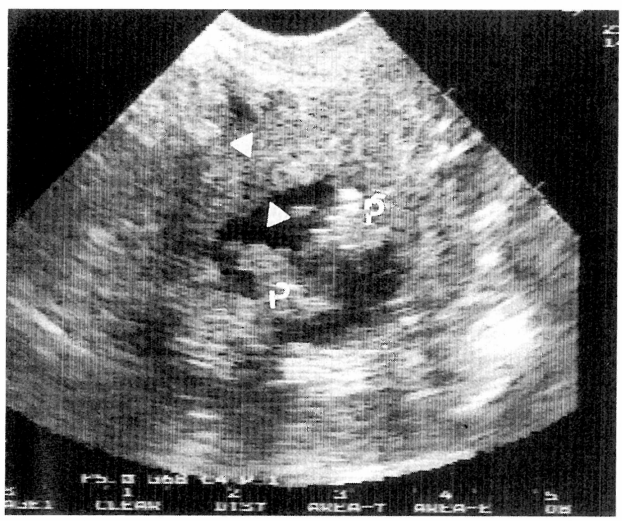

Figure 4. — Polyps (p) with irregular surfaces associated with endometrial thickening (triangle): endometrial adenocarcinoma, stage IB.

Discussion

The results of our study put in evidence that TU alone is not sufficient to monitor these patients. Almost 40% of patients are referred to biopsy but only 12% harbor significant pathology, and only 1.4% have malignancy. Absolute false positives, represented by patients with atrophic endometrium, amount to 50%. Such figure must be added to those patients in which TU does not visualize the uterine cavity (14.8%).

Moreover, we excluded patients in whom TU did not visualize the uterine cavity based on the aim of the present study and because we noticed in a prior study that the sensitivity of ultrasounds is greater with endometrial thickenings than with cavities devoid of mucosa. However, we had already considered absent cavity visualization as an indication of HS in women with postmenopausal bleeding [9]. Such indication is valid also in tamoxifen-treated patients in whom the failed visualization rate was higher than in postmenopausal women (14% versus 10%); this is probably due to tamoxifen effects on tissues.

In our experience the use of HS has allowed us to exclude 31.8% to 64.8% of patients from biopsy if the presence of a regularly marginated polyp associated with atrophic endometrium is not considered eligible for further study, which appears to be rational both from a clinical and diagnostic perspective. The specificity in such case is 75.4% versus 36.5% of TU alone and HS was able to identify the type of lesion based on structural features with a low number of false negatives (2.8%).

It should be stressed that in case of polyps the regularity of margins is diagnostically essential, whereas thickness is more important than surface regularity with focal and diffuse endometrial thickenings. It seems cautious to use 2 mm as a cut-off for the maximum thickness for each line.

Reviewing the literature it appears that since the introduction of HS it was hypothesized that its association with TU could significantly decrease the amount of false positives generated by TU alone. Schwartz *et al.* [10] reported in 1998 on a series of 44 patients in whom the use of HS resulted in a 55% decrease in the number of cases referred for further invasive studies. These authors were able to exclude all cases in which a thin endometrial lining was detected.

However, we found endometrial thickening in 38.8% of cases with atrophic endometrium, probably due to the failed detection of stromal alterations.

Moreover, these studies demonstrate that a greater deal of attention in the evaluation and knowledge of lesion morphology allows one to further decrease the need for invasive examinations.

In particular, polyps (30% of all lesions during treatment) are often associated with atrophic endometrium. Moreover, the glandulo-cystic variety presents as a smooth, regularly marginated lesion often showing prominent vacuolar features.

The optimal contrast yielded by the liquid within the cavity allows one to study the margins of the polyps and of the opposite free endometrial lining; using such criteria would lead us to avoid further invasive studies in 65% of cases.

It is true that the ultrasonographic criteria of evaluation of the sonographic morphology of focal lesions and endometrial thickening is based on wider studies dealing with untreated patients. However, these women represent a group of patients with a high incidence of pathology, which may yield more significant information even though the patient series may be smaller.

A promising observation is represented by the fact that all endometrial adenocarcinomas were suspected based on their complex structure. However, hyperplasia, which may represent a cancer precursor especially in subjects at risk. such as women with breast cancer, could be overlooked if an irregular surface is used as the sole criterium.

Based on present knowledge, greater care is suggested when evaluating endometrial thickening rather than focal lesions, in which only a single case of a benign polyp was found to have irregular margins in our series.

Our conclusions are therefore substantiated, and we suggest that HS may allow further invasive investigations to be avoided in patients with suggestive HS features.

We believe that HS does not completely solve the problem of follow-up in tamoxifen-treated patients; however, it represents a significant step towards the correct management of these patients.

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