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ORIGINAL ARTICLE

Endometrial surveillance in tamoxifen treated women for breast cancer: correlation between ultrasonographic, hysteroscopic and histological findings

Avaliação do endométrio em usuárias de tamoxifeno por câncer de mama: correlação entre achados ultrassonográficos, histeroscópicos e histológicos

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ABSTRACT

Objective: During Tamoxifen (TAM) use, the most frequent endometrial pathology is polyps and the calculated relative risk (RR) for endometrial cancer is 2.3. However, there is no current indication for screening. For patients with abnormal uterine bleeding (AUB), workup should include hysteroscopy with biopsy. The objective was to establish the correlation between the echographic and hysteroscopic findings of the endometrium with the histological diagnosis in women with a history of breast cancer and use of TAM. **Methods:** This is a retrospective study in which medical records of women with breast cancer and TAM use who had undergone hysteroscopy due to endometrial alteration on ultrasonography (US) or AUB were reviewed (n=30). Some patients were recruited and evaluated with transvaginal ultrasound and referred to outpatient hysteroscopy if there were abnormalities (n=20). Only postmenopausal patients were included. A control group was formed with postmenopausal women without a history of breast cancer or TAM use (n=47). **Results:** US showed good sensitivity in the case group (94,1%) and very unsatisfactory specificity (15,2%) in relation to the final histological result, with 63.6% of false positives. Hysteroscopy also had high sensitivity (94.1%), but greater specificity (72.7%). The percentage of false positives was 36.0%. Abnormal anatomopathological findings were related to older age (p=0.036). In the control group, US was also less accurate compared to uterine cavity evaluation at hysteroscopy. **Conclusion:** The correlation between ultrasonography, hysteroscopic images and histology in women using TAM is poor, especially in asymptomatic cases. Although hysteroscopy is more accurate, it should not be used as a screening method either.

Keywords: Tamoxifen; Endometrium; Ultrasonography; Hysteroscopy; Histology.

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RESUMO

Objetivo: durante o tratamento com tamoxifeno (TAM), a patologia endometrial mais frequente é o pólipo e o risco relativo (RR) para câncer de endométrio é calculado em 2,3. Entretanto, não há indicação para rastreamento. Em paciente com sangramento uterino anormal (SUA), a propedêutica deve incluir histeroscopia com biópsia. Nosso objetivo foi estabelecer a correlação entre achados ao ultrassom (US) e histeroscopia com o diagnóstico anatomopatológico em mulheres com história de câncer de mama e uso de TAM. **Métodos:** trata-se de estudo retrospectivo, em que foram revisados prontuários de mulheres com câncer de mama e submetidas a histeroscopia por alteração endometrial ao US ou sangramento uterino anormal (n=30). Algumas pacientes foram convidadas a participar, avaliadas com US endovaginal e encaminhadas à histeroscopia ambulatorial se alterações (n=20). Apenas mulheres na pós-menopausa foram incluídas. Um grupo-controle foi formado por mulheres na pós-menopausa sem história de câncer de mama ou uso de TAM (n=47). **Resultados:** US mostrou boa sensibilidade no grupo caso (94,1%) e especificidade insatisfatória (15,2%) em relação ao resultado anatomopatológico final, com 63,6% de falsos positivos. Histeroscopia também apresentou alta sensibilidade (94,1%) e maior especificidade (72,7%). A porcentagem de falso-positivos foi 36,0%. O anatomopatológico alterado foi relacionado a maior idade (p=0,036). No grupo-controle, US também apresentou pior acurácia que a avaliação da cavidade pela histeroscopia. **Conclusão:** a correlação entre US, imagem histeroscópica e histologia nas mulheres em uso de TAM é ruim, especialmente nas assintomáticas. Apesar da maior acurácia da histeroscopia, também não deve ser usada como método de rastreamento.

Palavras-chave: Tamoxifeno; Endométrio; Ultrassonografia; Histeroscopia; Histologia.

INTRODUCTION

Female breast cancer is the most common cancer after non-melanoma skin cancers. In Brazil, for the three-year period 2023 to 2025, 73,610 new cases are estimated, corresponding to 66.54 cases per 100,000 inhabitants. The greatest number of cases occurs in metropolitan regions and the disease is more frequent in developed countries, suggesting a relationship with socioeconomic issues[1]. As a result of better survival, these women need to keep screening for other neoplasms, monitor their comorbidities and be encouraged to adopt better life habits, including avoidance of obesity and alcoholism.

Hormone therapy is one of the cornerstones of breast cancer treatment. In pre-menopause, TAM is the drug of choice in tumors with positive estrogen receptor (ER), as aromatase inhibitors (AI) are not able to inhibit the ovaries. In postmenopausal women, the drugs of choice are AIs, such as anastrozole. The side effects of TAM are less frequent than with anastrozole and include vaginal discharge, AUB, venous thromboembolism, endometrial cancer and cerebrovascular ischemia[2,3]. TAM is a selective estrogen receptor modulator (SERM). The distribution of ERα and ERβ in tissues and the function of co-regulatory proteins explain the differences in the effect of this drug in specific organs. In breast cancer, it exerts an antagonistic effect on estrogen-induced proliferation. On the other hand, its action is agonistic on the endometrium, on bone metabolism, the coagulation system and the liver (causes decrease in total serum cholesterol and low-density lipoproteins and increase apolipoprotein A-1)[4].

A subprotocol of the National Surgical Adjuvant Breast and Bowel Project (NSABP) evaluated the occurrence of other primary cancers in patients receiving TAM versus placebo. The only statistically significant one was endometrial cancer, with an incidence of 1.6/1000/year during the follow-up period and a calculated RR of 2.3. Most cases occurred in women over 50 years old. The incidence of invasive endometrial cancer found in NSABP P1, with the objective of evaluating TAM for breast cancer prevention in high-risk patients, was similar, with 2/1000 women/year. The RR was 2.52, higher in women aged 50 years or older (RR 4.01) and lower in women aged 49 years or younger (RR 1.21)[5]. Most of these are endometrioid, but rare cases of mixed malignant mullerian tumors (MMMT) and sarcomas are more frequent than in the general population[6,7].

Garuti et al. (2007)[8] found 2.7% of atypia (atypical hyperplasia or endometrial cancer) in 146 patients evaluated before treatment with TAM, performing hysteroscopy when the endometrium ≥4 mm. There were 105 patients who completed the proposed follow-up, with 36 (31.5%) new diagnoses, but no atypia. The incidence of endometrial changes before treatment may be even higher, as most studies use endometrial thickness as the first screening approach. During treatment, the most frequent endometrial disease is endometrial polyps and incidence varies around 20%, depending on the criteria used for invasive workup[9]. The incidence of endometrial atypia is significantly higher in patients with lesions, mainly endometrial polyps, prior to TAM treatment, even if polypectomy has been performed. Berlière et al. (2000)[10] recorded 11.7% of endometrial disease with atypia in these patients during a follow-up of up to five years, in contrast to 0.7% in cases without changes in the initial evaluation. Other factors related to endometrial cancer during breast cancer treatment, in addition to the use of TAM, include a history of isolated estrogen therapy, age, body mass index (BMI) >28 and, to a lesser extent, systemic arterial hypertension (SAH)[11]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) referred RR of 2.4, ranging from 1.04 in women <45 years to 2.96 between 55 and 69 years, most studies with five years of treatment[12].

Screening for endometrial cancer has been recommended only in women who have or belong to families with possible Hereditary Non-polypoid Colorectal Cancer (Lynch Syndrome). European Consensus on Diagnosis, Treatment and Follow-up of Endometrial Cancer suggests that, in the face of risk factors, that is, use of exogenous estrogen, late menopause, nulliparity, infertility or anovulatory cycles, obesity, diabetes *mellitus* (DM), SAH and use of TAM, patients be instructed to report abnormal bleeding. When dealing with an asymptomatic postmenopausal patient with endometrial thickness >11 mm or other abnormalities, such as heterogenicity on US or fluid in the uterine cavity, the management must be individualized. For TAM users, follow-up with a gynecological consultation and monitoring for symptoms, especially AUB, are advised[13]. The American College of Obstetrics and Gynecology (ACOG) advises appraisal of risk factors before workup in case of the incidental finding of the endometrium >4 mm. Regarding the use of TAM and uterine cancer, it also suggests monitoring of symptoms without a defined cutoff value for endometrial thickness as a criterion for invasive workup[14].

Most studies on the effectiveness of endometrial cancer screening on patients with TAM therapy date back to more available hysteroscopy, mainly on an outpatient basis, the gold standard for endometrial surveillance and when most patients using TAM were postmenopausal. Evaluating conducts, seeking to standardize better recommendations for identified abnormalities, is paramount, as TAM remains part of the treatment of breast cancer, for 5 years or an extended period.

Our proposal was to establish the correlation between abnormal echographic and hysteroscopic findings of the endometrial study with clinical manifestations and histological diagnosis in women with breast cancer and TAM use.

Methods

This is a retrospective study. Data from the medical records of patients that had already undergone hysteroscopy due to endometrial alteration at US or AUB, with a history of breast cancer and use of TAM, were reviewed. Some patients under current or previous treatment for breast cancer and use of TAM were also invited and had an endovaginal US. Considering the probability of any alteration, benign or malignant, if endometrial thickness was ≥10 mm, a sample of 62 patients was determined[15].

The inclusion criteria were patients undergoing current or previous treatment for breast cancer with TAM; for prospectively evaluated patients, signature of the free informed consent form; availability of data from endovaginal US, appearance of the cavity at hysteroscopy and histology of endometrial biopsy. Exclusion criteria were patients undergoing chemotherapy, using aromatase inhibitor or the impossibility of performing endovaginal US.

Data were collected from medical records of 41 patients who underwent surgical hysteroscopy or outpatient hysteroscopy with biopsy (Bettocchi® forceps, aspiration or Novak curette) at the Hospital das Clínicas at Universidade Federal de Minas Gerais (UFMG) from 01/01/2019 to 03/31/2023, with a history of breast cancer treatment and use of TAM. All cases were referred from the Gynecology Clinic for evaluation due to changes in US and/or AUB. Of this group, 37 cases were finalized, 30 postmenopausal.

From 03/01/2020 to 03/31/2023, women who attended a consultation at the Mastology Service of the Hospital das Clínicas at UFMG, using TAM, were invited to participate in this study and the informed consent form was presented. 83 assessments of 77 patients were performed; six women were reassessed after a 12-month interval. Previous users of TAM were considered when the interruption was greater than six months before the US. Physical examination and cytological screening for cervical cancer were performed by the author. The US was most often performed on the same day and with the same professional, as it was not repeated if there had been a recent exam. The measurement of endometrial thickness was performed in the sagittal plane, at the thickest point, with the sum of the endometrial layers. The appearance of the endometrium, homogeneous or heterogeneous, and other alterations, such as liquid in the uterine cavity, suggestive images of polyps or submucous myoma, were also described. The cut-off value for indicating hysteroscopy in asymptomatic patients was an endometrium ≥9 mm, a value below which the risk of cancer is close to zero in the absence of symptoms[15-17]. Patients with endometrial thickness ≥9 mm, intracavitary image or AUB were referred for outpatient hysteroscopy. Of this group, 24 cases were finalized, 20 postmenopausal.

The outpatient hysteroscopies were performed at the Human Reproduction Laboratory at the Hospital das Clínicas at UFMG by the same professional, using a Karl Storz device with a 2.9 mm camera, 30° angle of view, and saline solution as the distension medium. The exams were performed with vaginoscopy, without a speculum. A speculum and local anesthesia with 2% lidocaine without a vasoconstrictor were used if dilatation of the cervix was necessary. The appearance of the endometrium was described as atrophic, functional (proliferative, secretory, or menstrual), diffusely thickened or suggestive of hyperplasia, atrophic with focal thickening, endometrial polyps or suggestive of cancer. It was considered normal when atrophic or functional. All other findings were considered altered[18]. Directed biopsy was performed when semi-rigid scissors and gripping forceps were available, in only two cases, using a 5 mm Bettocchi® set. In the endometrium with an atrophic aspect and in the diffuse alterations, a Pipelle® like device was used to collect material for histological evaluation. Patients with focal changes were referred to surgical hysteroscopy.

Hystology was categorized as normal when the endometrium was atrophic or functional. All others were considered altered. Biopsies with insufficient material were considered as atrophy, if according to the macroscopic evaluation of the cavity at hysteroscopy. Endometrial hyperplasia followed the 2014 Classification of Endometrial Hyperplasia: hyperplasia without atypia; atypical hyperplasia/ endometrioid intraepithelial neoplasia[19].

A control group consisted of 47 postmenopausal patients, with no history of breast cancer or use of TAM, who underwent outpatient hysteroscopy between 01/01/2019 and 12/31/2022 at the same service. Data were collected from medical records.

For data analysis, only postmenopausal patients on current or previous use of TAM for at least six months before endovaginal US or hysteroscopy were included. Menopause was defined as the last menstrual period >12 months before the US or hysteroscopy, regardless of the history of chemotherapy.

To evaluate categorical variables, Pearson's non-parametric chi-square test and/or Fisher's exact test were applied to the data. When comparing quantitative variables, with the objective of investigating whether or not there is a statistically significant difference in means between the groups, the Student's t test for independent samples (parametric test) was used. The age and histology differences between the groups were evaluated using the medians and quartiles. All results were considered significant for a significance probability of less than 5% ($p<0.05$). To assess the diagnostic accuracy of US and hysteroscopy in the light of the hytological result, by group of patients, the parameters of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false-positive (FP) and false-negative (FN) were applied.

The study was approved by the Research Ethics Committee (COEP) of UFMG, registered on Plataforma Brasil with certificate n. 26397219.4.0000.5149.

Results

In Table 1 there is a comparison between the case and control groups according to variables of interest. In the case group, 24% had an endometrium <9 mm. A much higher percentage of the control group (53.3%) had an endometrium below this measurement, because patients with an endometrium between 5 and 9 mm were also referred

Table 1. Comparison between groups according to variables of interest.

	Case		Control		*p*
	n		**n**		
Age (mean)	50	59.2±8.8 years	47	61.1±7.7 years	*P*=0.265
	n	**%**	**n**	**%**	
SAH	50	68.0%	43	55.8%	*P*=0.227
DM	50	20.0%	43	25.6%	*P*=0.521
AUB	50	44.0%	47	55.3%	*P*=0.265
Altered ultrasonography	50	88.0%	47	91.5%	*P*=0.742
Endometrial thickness <9 mm	50	24.0%	45	53.3%	*P*=0.036
Altered hysteroscopy	50	50.0%	47	68.1%	*P*=0.071
Altered histology	50	34.0%	46	54.3%	*P*=0.045

Legend: SAH = systemic arterial hypertension; DM = diabetes *mellitus*; AUB = abnormal uterine bleeding.
Source: Prepared by authors, 2023.

for workup. Even so, the percentage of altered histological results was lower in the case group (p=0.045) (Table 2). The proportion of the uterine cavity altered at hysteroscopy was also lower, however, without statistical significance.

Regarding the accuracy of the tests, the US showed good sensitivity in the case group (94.1%) and very unsatisfactory specificity (15.2%) in relation to the final histological result, with 63.6% of FP. The PPV was 36.4% and the NPV, 83.3% (Table 3). The evaluation of the uterine cavity by hysteroscopy in this group also had good sensitivity (94.1%) and higher specificity than endovaginal US (72.7%). The percentage of FP was 36.0%, with a PPV of 64.0% and a NPV of 96.0% (Table 3).

In evaluating the accuracy of the tests in the control group, the US also showed good sensitivity (96%) and poor specificity (14.3%) in relation to the final histological result, with 42.9% of FP. The PPV was 57.1% and the NPV 75.0%. The evaluation of the uterine cavity by hysteroscopy in this group had high sensitivity (96%) and specificity also higher than US (66.7%). The percentage of FP was 22.6%, PPV 77.4% and NPV 93.3% (Table 3).

The only variable that can be related to an altered histological result is the median age, specifically in the case group: 66.0 (55.0-69.0) *X* 55.0 (50.5-61.0) (p=0.036). The same difference was not observed in the control group. There was no relationship between the diagnosis of SAH, DM our AUB and the altered final histological result in both groups (p>0.05). There was no statistically significant influence of the appearance of the endometrium, heterogeneous or homogeneous, in the case group (p=0.295). This data was not available for all patients, as well as for the control group. The same happened with BMI (p=0.150).

The number of patients was not sufficient to determine the relationship between the endometrial thickness and the altered final result (Table 4).

In the group of patients with a history of breast cancer and use of TAM, there were only two cases with atypical endometrial lesions. In a 45-year-old pre-menopause woman, with hypertension, increased and prolonged menstrual flow, using TAM for 1.5 year, US showed a homogeneous endometrium, 13.4 mm thick, with an intrauterine device (IUD TCu 380). Outpatient hysteroscopy presented

Table 2. Final histology.

Histology	Case		Control	
	n	%	n	%
Scant material	13	26.0%	2	4.3%
Atrophy	18	36.0%	16	34.8%
Functional endometrium	2	4.0%	3	6.5%
Hyperplasia	2	4.0%	1	2.2%
Polyp	14	28.0%	16	34.8%
Atypia and cancer	1	2.0%	8	17.4%

Source: Prepared by authors, 2023.

Table 3. Accuracy of ultrasonography and hysteroscopy.

Case	**Histology**		**Total**
Ultrasonography	**Normal**	**Altered**	
Normal	5	1	6 (12%)
Altered	28	16	44(88%)
Hysteroscopy	**Normal**	**Altered**	
Normal	24	1	25(50%)
Altered	9	16	25(50%)
Control	**Histology**		**Total**
Ultrasonography	**Normal**	**Altered**	
Normal	3	1	4 (8.7%)
Altered	18	24	42(91.3%)
Hysteroscopy	**Normal**	**Altered**	
Normal	14	1	15(32.6%)
Altered	7	24	31(67.4%)

Source: Prepared by authors, 2023.

Table 4. Endometrial thickness and histology.

	Histology					
	Altered		Normal		TOTAL	
	n	%	n	%	n	%
Case group – endometrial thickness						
< 9.00 mm	3	25.0	9	75.0	12	100.0
9.00 a 10.99 mm	4	25.0	12	75.0	16	100.0
11.00 a 14.99 mm	2	20.0	8	80.0	10	100.0
15.00 a 19.99 mm	3	50.0	3	50.0	6	100.0
≥ 20.00 mm	5	83.3	1	16.7	6	100.0
TOTAL	**17**	**34.0**	**33**	**66.0**	**50**	100.0
Control group – endometrial thickness						
< 9.00 mm	12	52.2	11	47.8	**23**	100.0
9.00 a 10.99 mm	3	30.0	7	70.0	**10**	100.0
11.00 a 14.99 mm	5	71.4	2	28.6	**7**	100.0
15.00 a 19.99 mm	1	100.0	0	0.0	**1**	100.0
≥ 20.00 mm	3	100.0	0	0.0	**3**	100.0
TOTAL	**24**	**54.5**	**20**	**45.5**	**44**	100.0

Source: Prepared by authors, 2023.

menstrual endometrium and IUD. The biopsy was performed by aspiration, with histology compatible with endometrial hyperplasia without atypia. She underwent a total hysterectomy three months and 18 days later and the histology revealed atypical glandular hyperplasia and adenomyosis.

The second patient was 75 years old, with dyslipidemia and hypothyroidism, a history of breast cancer treatment and TAM use for 12 months seven years ago. An US was done to evaluate a uterine mass, with an endometrium measure of 8 mm and an anechoic image in the uterine cavity. She did not have AUB but reported mucous and abundant vaginal discharge for several months. Outpatient hysteroscopy revealed focal thickening suggestive of cancer. Biopsy with Novak curette showed atypia but required surgical hysteroscopy to confirm high-grade clear cell adenocarcinoma.

In this group there were also three cases of endometrial hyperplasia without atypia, all with AUB, one in pre-menopause. Premenopausal cases were not part of statistical analysis.

In the control group, all postmenopausal, cases of endometrial hyperplasia without atypia, hyperplasia with atypia or cancer also had AUB.

To assess the tolerability of outpatient hysteroscopy by patients with a history of breast cancer and current or past use of TAM, only prospective cases were considered. Among the 38 hysteroscopies performed, seven were hampered by stenosis of the internal cervical os, two by active bleeding, and five patients complained of pain (36.8%). It was not possible to perform four exams due to pain or stenosis (10.5%).

Discussion

One of the first studies that compared US with hysteroscopy and histhology was by Exacoustos et al. (1995)[20]. There were only 38 postmenopausal patients, users of TAM, which did not allow relating endometrial thickening to atypia or TAM duration. The incidence of polyps was 50%. All cases of hyperplasia, only one with atypia, had an endometrium ≥10 mm. The low positivity of hysteroscopy with biopsy after ultrasonographic endometrial thickening in a patient with TAM has been demonstrated in several studies (Table 5). The proportion of false positives (FP) is higher when considering only the final histological results with atypia as not normal. These findings led authors to suggest endometrial workup just if AUB[21,22]. Others indicated cutoff values for endometrial thickness between 9 or 10 mm[15,16,23]. Pre-treatment assessment can identify women at higher risk of developing endometrial cancer, as well as the diagnosis of endometrial polyps[10,21,23,24].

Endovaginal US is frequently performed in asymptomatic patients and referral for surveillance due to endometrial thickening is common. In the present study, the choice of a cut-off value for endometrial thickness ≥9 mm was based on studies that didn't find atypia below 10 mm, in the absence of symptoms[16,23]. As in the literature, good sensitivity was demonstrated, but very poor specificity. In the control group, US was also not a good diagnostic test, with sensitivity and specificity like the case group. The lower accuracy than in the studies can be explained by the lack of final data on patients with endometrial polyps in outpatient hysteroscopy who were referred for polypectomy and were not included in the statistical analysis.

Table 5. Literature review.

Autor	Population	Indication of propaedeutics	Ultrasonography Accuracy	Hysteroscopy accuracy
Love et al., 1999[25]	357 pre- and post-menopausal, asymptomatic	a-Endometrium > 5 mm post menopause b-Endometrium > 8 mm follicular phase and > 12 mm luteal phase	False positives: 46% (PPV 54%) 0 atypia	-
Franchi et al., 1999[16]	163 post-menopausal	a-Endometrium > 4mm b-AUB	For abnormalities: Cutoff value > 9 mm: S 86.7% E 78.0% PPV 60.0% NPV 93.9% Asymptomatic: S 84.2% E 79.6% PPV 44.4% NPV 96.3%	-
Vosse et al., 2002[22]	406 post-menopausal	Endometrium > 8 mm	For abnormalities: Cutoff value > 8 mm: PPV 64.0%	-
Garuti et al., 2002[26]	98 post-menopausal (31 with AUB)	Endometrium ≥4 mm. Biopsy with Vabra®, directed biopsy or curettage	For abnormalities: Cutoff value ≥ 6 mm: S 92.1% E 55.2% PPV 40.6 NPV 95.4 Cutoff value ≥8 mm: S 84.8% E 62.7% PPV 63.6 NPV 88.7	For abnormalities: S 89.2% E 98.4%
Giorda et al., 2002[27]	310 post-menopausal, 274 asymptomatic and 49 with AUB	Novak or directed biopsy	For hyperplasia and atypia: Cutoff value ≥6 mm: S 87% E 27% PPV 8% NPV 96% Cutoff value ≥ 10 mm: S 36% E 57% PPV 6% NPV 92%	For hyperplasia and atypia: S 50% E 98% PPV 65% NPV 96%
Fung et al., 2003[15]	304 post-menopausal 1.061 serial US	a-Before treatment b-Endometrium > 9 mm and/or c-AUB	For abnormalities: Cutoff value > 9 mm: S 63.3% E 60.4% PPV43.3% NPV 77.5%	-
Medeiros, 2004[28]	64 pre- and post-menopausal, asymptomatic	Endometrium ≥ 5 mm All amenorrheic	For abnormalities: Cutoff value ≥ 5 mm: S 100% E 32.6% PPV 42% NPV 100%	For abnormalities: S: 100% E: 86 % PPV:77.8% NPV: 100%
Saccardi et al., 2013[23]	151 pre- and post-menopausal	a-Endometrium >5 mm b-AUB c-Screening	For atypia: Cutoff value ≥ 5 mm: S 100% E15% PPV 4% NPV 100% Cutoff value ≥ 10 mm: S 84% E 69% PPV 10% NPV 99%	For atypia: S 83,3% E 99% PPV 83,3% NPV 99%

Legend: E = specificity; S = sensibility; NPV = negative predictive value; PPV = positive predictive value.

Premenopausal women were not included in this study, as the number was too small. Defining normal endometrial thickness in premenopausal patients is more difficult. Zhang et al. (2021)[29] retrospectively evaluated only premenopausal patients at baseline, all using TAM, excluding those with >24 months of amenorrhea. There were 115 cases, with 29.6% of polyps, 3.5% of hyperplasia without atypia, 3.5% of hyperplasia with atypia and no cases of cancer. The endometrial thickness of 15 mm had a NPV of 100% for hyperplasia. Lee, Piao and Jeon (2020)[30], in 284 premenopausal biopsies with endometrium >10 mm, polyps on US and/or AUB, found seven (2.5%) atypical hyperplasias and five (1.8%) endometrial cancers. The only significant factor was AUB.

The alterations responsible for the thickened and heterogeneous appearance of the endometrium are reversible over the months that follow the interruption of the TAM, which occurs slowly and may remain for up to two and a half years[31,32]. Furthermore, patients are sometimes instructed to interrupt the medication until the end of the workup. For this reason, in our study, current use was considered when the interruption occurred up to six months before the US. Women with a history of breast cancer and use of TAM were included in the case group because, although a simple change in the ultrasound image due to the drug is no longer expected, there is an increased risk of endometrial cancer for at least four years after the end of treatment[33]. There were 10 women with this profile, seven of them within four years of the end of treatment.

The macroscopic evaluation of the cavity had better accuracy than US in TAM users, but PPV of 64% was worse than described by other authors[23,26]. Hysteroscopy also had better accuracy than US in the control group, but still with a NPV of 93.3%, reinforcing the need for endometrial biopsy.

Outpatient hysteroscopy with biopsy allows for faster scheduling. It can be done on the same day of the gynecological visit and/or US. In our prospective cases, the exam was not performed in only 4/38 (10.5%). Several authors also report impairment mainly due to stenosis, ranging from 3 to 20% of hysteroscopies not performed[8,16,26,34].

Women with breast cancer at high risk of developing endometrial disease should have adequate follow-up and, in case of alterations, a timely workup. Due to the small number, the present study was unable to demonstrate other clinical factors related to a higher risk of benign or malignant disease besides age in the case group. Actually, the relationship of endometrial cancer with age exists both in pre and post menopause[35]. It was also not possible to relate the time of TAM to the changes detected in the histology.

The incidence of endometrial alterations (hyperplasia, polyps, and cancer) is higher in postmenopausal and symptomatic patients using TAM. If AUB occurs, endometrial biopsy should be performed, especially if recurrent, even with a thin endometrium. Uterine bleeding was present in the only case of atypical endometrial hyperplasia in patients with breast cancer, diagnosed in a premenopausal patient, as well as in the three cases of endometrial hyperplasia without atypia. The case of endometrial cancer didn't present bleeding, but reported mucorrhea for months, which had not been investigated. In the control group, there were nine patients with atypical hyperplasia or cancer and one with endometrial hyperplasia without atypia, all with AUB.

The limitations of this research were the reduced number of cases, the retrospective analysis of most data, the impossibility of performing outpatient guided biopsy and the prolonged time until surgical hysteroscopy was performed.

The reduction in breast cancer mortality overlaps the slight increase in risk for endometrial cancer with TAM[19]. Despite that, the possibility of using the drug for up to 10 years justifies monitoring symptoms and choosing the best propaedeutics, also avoiding unnecessary tests.

Conclusion

The correlation between US and hysteroscopic images and histology in women using TAM is poor. The only clinical variable studied that was related to altered anatomopathological results was the median age. It was not possible to connect the changes to the presence of SAH, DM or AUB. Although hysteroscopy has a lower percentage of false positives, it should also not be used to screen for endometrial disease.

Author's Contributions:

We describe contributions to the papers using the taxanomy (CRediT) provided above:

Conceptualization, Investigation, Methodology, Visualization & Writing-review & Editing: JN; AM; CL. *Project Administration, Supervision & Writing-original draft:* JN; CL. *Data Curation and Formal Analysis:* JN; CL.

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