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Review

Efficacy of sonohysterography and hysteroscopy for evaluation of endometrial lesions in tamoxifen treated patients: a systematic review

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Abstract

Objective: This review aims to evaluate the incidence of endometrial lesions in tamoxifen-treated breast cancer patients identified by hysteroscopy (HS) and sonohysterography (SIS) and the diagnostic accuracy of the two methods to detect them. **Methods**: A systematic review of the literature concerning the role of HS and SIS for evaluation of the endometrium in tamoxifen-treated breast cancer patients was performed. We searched MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, IBECS, BIOSIS, Web of Science, SCOPUS, congress abstracts, and Grey literature (Google Scholar; British Library). The search terms used were "hysteroscopy", "hysterosonography", "sonohysterography" combined with "tamoxifen"; 89 citations were identified and selected in the initial screening. **Results**: 28 studies were included in the systematic review. There were 61 citations excluded because they were review articles (n = 9) or case report (n = 5) and non-English articles (n = 8), and had too little information in the full text (n = 39). Similar accuracy between SIS and HS in detection of endometrial tamoxifen-related lesions was found. **Conclusions**: SIS may represent a minimally invasive, simple, safe, well-tolerated and cost-effective alternative to HS, associated with few contraindications and no potential complications.

Keywords: Hysteroscopy; Hysterosonography; Sonohysterography; Tamoxifen; Breast cancer

1. Introduction

Tamoxifen is a nonsteroidal selective estrogen receptor modulator that is widely used for the treatment of estrogen receptor-positive breast cancer patients [1,2]. Clinical trials have shown that long-term therapy for at least 5 years, is more effective than short-term treatment (<2 years). Although it acts as an antiestrogen in breast tissue [3], it has a partial agonist effect on other tissues, such as the endometrium and myometrium [4]; hence, prolonged therapy is associated with various uterine pathologies, including endometrial polyps, submucosal leiomyomas, endometrial hyperplasia, and endometrial cancer [5–8]. However, literature background showed that the benefits achieved in breast cancer treatment, may overcome any potential uterine abnormalities that may occur [9]. In this scenario, it is emerging the necessity to develop adequate methods to diagnose endometrial complications. Nevertheless, the optimal method of surveillance has not yet been determined [6,9–11].

Transvaginal sonography (TVS) is the imaging technique of choice for first-line investigation of intrauterine abnormalities [12–14]. This procedure is relatively painless, well accepted by patients, and can be easily performed by the gynecologist at a relatively low cost [15]. Nevertheless, several studies reported a limited value of TVS in tamoxifen-treated patients due to false-negative [16] as well as false positive results [10,15] and proposed additional diagnostic procedures, such as hysteroscopy (HS) or transvaginal saline infusion sonohysterography (SIS).

HS, combined with histological examination of an endometrial aspiration or biopsy, remains the current gold standard for uterine cavity assessment [16–19]. Moreover, it represents a highly effective therapeutic approach to treat various conditions [20] and it can be useful to assess their eventual recurrence [21]. However, discomfort due to anatomical impediments may represent a cause of office hysteroscopy failure, requiring the necessity for anesthesia and operating theater [22]; a fact that increases both risks and costs. Furthermore, it should be performed by a gynecologist with enough facilities and expertise [23].

In the last 20 years, several studies have proposed the use of SIS, as a less invasive alternative to HS [22,23]. Indeed, it is an affective "add-on" to TVS which involves the use of slow instillation of sterile saline solution into the endometrial cavity through a 5-French catheter under continuous TVS guidance, providing both a contrast medium and an expanding agent [24]. Along this line, sensitivity, specificity, and predictive values of SIS are clearly superior in comparison to TVS. Moreover, SIS is associated with minimal discomfort and lower costs, being easily performed by most of gynecologists [25–29]. With regards to contraindications, only few has been reported in literature [30] eventually leading to no potential complications. Finally, it can accurately differentiate focal lesions such as polyps and

submucous fibroids [31,32] from diffuse lesions like hyperplasia and cancer [26,30]. Conversely, although the use of HS in detection of intrauterine alteration has widely gained a strong agreement [33], there is a trend towards encouraging the use of SIS as primary method to detect endometrial abnormalities also related to tamoxifen use [32–39].

Given this, the aim of the current review is to evaluate the incidence of endometrial diseases in tamoxifen-treated breast cancer patients identified by HS and SIS and the diagnostic accuracy of the two methods to detect them.

2. Material and methods

2.1 Data sources

A systematic review of the literature concerning the role of HS and SIS for evaluation of the endometrium in tamoxifen-treated breast cancer patients was performed. We searched MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, IBECS, BIOSIS, Web of Science, SCOPUS, congress abstracts, and Grey literature (Google Scholar; British Library). The following keywords were used: "hysteroscopy", "hysterosonography", "sonohysterography". These terms were further combined with "tamoxifen".

2.2 Screening of abstract for eligibility

According to all Authors, the inclusion or exclusion of studies were established at first. Two investigators (F.D.G. and G.G.I.) screened abstracts and titles of the research. A third investigator (G.D.) screened the abstract and the title in case of disagreement.

2.3 Study selection and eligibility criteria

The main criteria selection of the literature were original article and clinical trials conducted on human. Only papers written in English were included. Case report and review of the literature were disregarded.

Our systematic search strategy identified a total of 222 citations, after screening of abstracts and titles and removal duplicates, 89 records were identified and selected, finally 28 studies were included in the systematic review (Fig. 1). There were 61 citations excluded because they were review articles (n = 9) or case report (n = 5) and non-English articles (n = 8), and had too little information in the full text (n = 39). The selection process of suitable studies is displayed in Fig. 1.

3. Results

The incidence of endometrial lesions in tamoxifen-treated breast cancer patients identified by HS and SIS, respectively are displayed in Tables 1 (Ref. [11,40–57]) and 2 (Ref. [58–63]). The mean incidence of all lesions was 38.7%. 39.7% of patients had endometrial polyp that was the most common finding. Only 4 studies reported data about submucosal leiomyoma with an incidence ranging from 1.7% to 4.5%. The second most common finding was endometrial hyperplasia (mean incidence of 6%). Finally, 3% of patients had endometrial cancer.

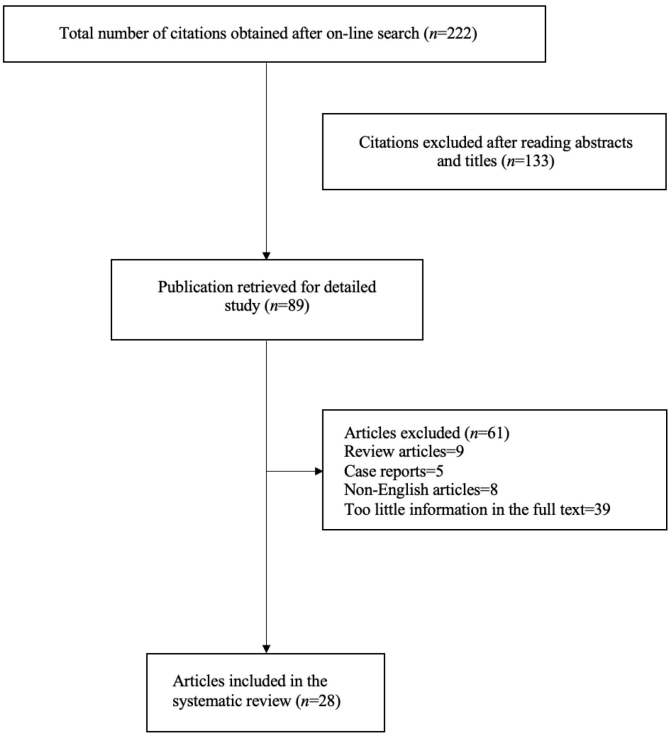

Fig. 1. Selection process for the inclusion of suitable studies for the systematic review. *n*, number.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of the two procedures compared to gold standard (which is HS combined with biopsy) are reported in Tables 3 (Ref. [46,56,64–66]) and 4 (Ref. [45,46]). Sensitivity, specificity, PPV, and NPV of SIS were approximately 89, 80, 76, and 91%, respectively, whereas HS provided corresponding values of approximately 89, 83, 66, and 98%, respectively.

4. Discussion

The first large, prospective study showing the association between endometrial cancer and tamoxifen intake was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial [6] published in 1994. Subsequent studies showed the incidence of endometrial lesions in tamoxifen-treated breast cancer patients ranges from 15.6% to 62.2% [10,38,44,56,62,65,66], in agreement with our mean incidence (38.7%).

The long-term endometrial sequels of prolonged tamoxifen treatment necessitate adequate endometrial monitoring for women on tamoxifen therapy. However, what is the most effective and acceptable procedure is controversial [6,9–11]. TVS is widely used for endometrial assessment [13]. Nevertheless, considering that some studies showed a high incidence of false-negative [16] and false positive

Table 1. Endometrial lesions detected at HS in the included studies.

Study	Setting	Patients	Endometrial polyp		Submucosal leiomyoma		Endometrial hyperplasia		Endometrial cancer	
			(n)	*(%)*	*(n)*	*(%)*	*(n)*	*(%)*	*(n)*	*(%)*
Ceci *et al*. 2000 [40]	Italy	65 postmenopausal breast cancer patients taking tamoxifen 20 mg/day for 12–72 months with endometrial thickness ≥5 mm at TVS or AUB	26	40	0	0	11	16.9	4	6.1
Ceci *et al*. 2003 [41]	Italy	33 breast cancer postmenopausal patients taking tamoxifen 20 mg/day for 24–68 months with endometrial thickness ≥5 mm at TVS or AUB	23	69.7	0	0	5	15.2	4	12.1
De Muylder *et al*. 1991 [42]	Belgium	46 breast cancer patients taking tamoxifen for 6–36 months	13	28	0	0	8	17	2	4
Dibi *et al*. 2009 [43]	Brazil	40 postmenopausal breast cancer patients taking tamoxifen 20 mg/day with thickened endometrium or suggestive of polyps at TVS or AUB	13	32.5	0	0	0	0	0	0
Exacoustòs *et al*. 1995 [44]	Italy	38 postmenopausal, asymptomatic breast cancer patients taking tamoxifen 20–30 mg/day for at least 12 months	19	50	0	0	4	10	0	0
Fong *et al*. 2001 [45]	USA	117 postmenopausal, asymptomatic breast cancer patients taking tamoxifen 20–30 mg/day for 13–37 months	45	38.5	2	1.7	0	0	0	0
Garuti *et al*. 2002 [46]	Italy	98 menopausal breast cancer patients taking tamoxifen 20–30 mg/day for 6–60 months with endometrial thickness ≥4 mm at TVS	18	18	0	0	11	11	6	6
Giorda *et al*. 2002 [47]	Italy	310 breast cancer postmenopausal patients taking tamoxifen 20–30 mg/day for at least 6 months	139	44.8						
Lahti *et al*. 1993 [48]	Finland	49 breast cancer postmenopausal patients taking tamoxifen 20–40 mg/day for a mean of 32 months (range 6–95 months)	17	35	0	0	0	0	0	0
Le Donne *et al*. 2013 [49]	Italy	236 peri/postmenopausal breast cancer patients taking tamoxifen 20–60 mg/day for a mean of 41.1 months with AUB or endometrial thickness at TVS	91	38.6	0	0	17	7.2	7	3
Love *et al*. 1999 [11]	UK	134 asymptomatic breast cancer patients taking tamoxifen 20 mg/day for a mean of 66 months (range 5–91 months) median 62) with endometrial thickness >5 mm in postmenopausal women and >8 mm in the follicular phase and >12 mm in the luteal phase in premenopausal women at TVS	21	15.7	6	4.5	0	0	0	0
Marchesoni *et al*. 2001 [50]	Italy	162 postmenopausal breast cancer patients taking tamoxifen 20 mg/day for a mean of 3 years (range 1–5 years)	16	9.9	6	3.7	18	11.1	7	4.3
Mourits *et al*. 1999 [51]	The Netherlands	22 postmenopausal, asymptomatic breast cancer patients taking tamoxifen 20–40 mg/day with endometrial thickness >5 mm at TVS	7	45	0	0	0	0	0	0
Neis *et al*. 2000 [52]	Germany	33 postmenopausal breast cancer patients taking tamoxifen with endometrial thickness >8 mm at TVS	18	55	0	0	0	0	0	0
Neven *et al*. 1998 [53]	Belgium	57 postmenopausal breast cancer patients taking tamoxifen 20 mg/day	20	39.2	0	0	2	3.5	3	5.3
Neven *et al*. 1990 [54]	Belgium	16 postmenopausal breast cancer patients taking tamoxifen 20 mg/day for a mean of 17 months (6–30 months)	4	25	0	0	0	0	1	6.2
Pérez-Medina *et al*. 2011 [55]	Spain	278 postmenopausal breast cancer patients taking tamoxifen 20 mg/day	19	7.1	0	0	0	0	5	1.7
Saccardi *et al*. 2013 [56]	Italy	151 postmenopausal breast cancer patients taking tamoxifen	38	25.2	0	0	1	1	0	0
Teixeira *et al*. 2007 [57]	Brazil	25 breast cancer patients taking tamoxifen 20 mg/day for a mean of 3 years (range 1–7 years) with endometrial thickness >5 mm at TVS	7	28	0	0	4	16	0	0

HS, hysteroscopy; (n), number; (%), percentage; AUB, abnormal uterine bleeding.

Table 2. Endometrial lesions detected at SIS in the included studies.

Study	Setting	Patients	Endometrial polyp		Submucosal leiomyoma		Endometrial hyperplasia		Endometrial cancer	
			(n)	*(%)*	*(n)*	*(%)*	*(n)*	*(%)*	*(n)*	*(%)*
Bertelli *et al*. 2000 [58]	Italy	41 postmenopausal, asymptomatic breast cancer, patients taking tamoxifen 20 mg/day for a mean of 13 months (range 8–25 months) with endometrial thickness >8 mm at TVS	19	46.3					0	0
El Sheikh *et al*. 2013 [59]	Egypt	37 postmenopausal breast cancer patients taking tamoxifen 20 mg/day for a mean of 2.5 years (1–4 years) with endometrial thickness >8 mm at TVS	23	62	0	0	8	22	0	0
Elhelw *et al*. 1999 [60]	Egypt	22 postmenopausal breast cancer patients taking tamoxifen 20–30 mg/day for 12–28 months with endometrial thickness >5 mm at TVS	10	45.5						
Hann *et al*. 2003 [61]	USA	51 breast cancer patients taking tamoxifen with AUB or endometrial thickness ≥8 mm at TVS	32	63	2	4	1	2	0	0
Hann *et al*. 2001 [62]	USA	46 postmenopausal breast cancer patients taking tamoxifen for a mean of a mean of 2.6 years (range 0.2–6 years) with AUB or endometrial thickness ≥8 mm at TVS	31	62						
McElrath *et al*. 2000 [63]	USA	25 breast cancer patients taking tamoxifen for a mean of 40 months (range 11–70 months) with AUB or endometrial thickness ≥5 mm at TVS or for screening	17	68						

SIS, sonohysterography; (n), number; (%), percentage; AUB, abnormal uterine bleeding.

Table 3. Sensitivity, specificity, PPV, NPV of HS for endometrial lesions in the included studies.

Study	Setting	Patients	Sensitivity *(%)*	Specificity *(%)*	PPV *(%)*	NPV *(%)*
Garuti *et al*. 2002 [46]	Italy	98 menopausal breast cancer patients taking tamoxifen 20–30 mg/day for 6–60 months with endometrial thickness ≥4 mm at TVS	89.2			
Garuti *et al*. 2004 [64]	Italy	176 postmenopausal, breast cancer patients taking tamoxifen 20 mg/die for 6–60 months with endometrial thickness ≥4 mm at TVS	100	68.9	43.7	100
Jung *et al*. 2018 [65]	Korea	46 postmenopausal breast cancer patients taking tamoxifen for a mean of 27.1 months (range 13–68 months) with AUB or endometrial thickness ≥4 mm at TVS	85	83	79	87
Saccardi *et al*. 2013 [56]	Italy	151 postmenopausal breast cancer patients taking tamoxifen	83.3	99	83.3	99
Timmermann *et al*. 1998 [66]	Belgium	37 asymptomatic breast cancer patients taking tamoxifen 20–40 mg/day for a mean of 23 months (range 13–40 months)	77		91	

PPV, positive predictive value; NPV, negative predictive value; HS, sonohysterography; (n), number; (%), percentage; AUB, abnormal uterine bleeding.

Table 4. Sensitivity, specificity, PPV, NPV of SIS for endometrial lesions in the included study.

Study	Setting	Patients	Sensitivity *(%)*	Specificity *(%)*	PPV *(%)*	NPV *(%)*
Fong *et al*. 2001 [45]	USA	117 postmenopausal, asymptomatic breast cancer patients taking tamoxifen 20–30 mg/day for 13–37 months	89.7	79.2	76.1	91.3
Garuti *et al*. 2002 [46]	Italy	40 postmenopausal, asymptomatic breast cancer patients taking tamoxifen for a mean of 20.5 months (range 6–50 months) with endometrial thickness ≥4 mm at TVS	86	83		

PPV, positive predictive value; NPV, negative predictive value; SIS, sonohysterography; (n), number; (%), percentage; AUB, abnormal uterine bleeding.

[10,15] findings in tamoxifen-treated patients, most investigators proposed other diagnostic procedures, such as HS or SIS.

Few studies resembling SIS role in the evaluation of uterine cavity of tamoxifen-treated cases have been published. Fong *et al*. [67] reviewed the spectrum of uterine findings at SIS in women with breast cancer who were undergoing tamoxifen therapy and summarized the features that can help in recognizing each lesion. A polyp appears as an echogenic mass with smooth margins that often has a narrow attachment to the adjacent endometrium and is completely surrounded by fluid and contains cystic areas. A submucosal leiomyoma is seen as a round structure arising from the myometrium with a thin, overlying echogenic endometrium. Diffuse, smooth thickening of the endometrium suggests endometrial hyperplasia. Finally, an irregular inhomogeneous mass or irregular, focally thickened endometrium is highly suggestive of endometrial carcinoma and lack of distensibility of the endometrial cavity has been described as a potential sign. In this scenario, the development of a new system is desirable for classifying uterine lesions on the basis of sonographic findings and estimating the probability of malignancy, similarly to that used for adnexal masses (GI-RADS) [68].

Some studies suggested that SIS has high sensitivity and specificity rates, ranging from 79% to 100% [60,67,69]. We compared diagnostic accuracy of SIS and HS in distinguish between normal and abnormal endometrium in postmenopausal tamoxifen-treated breast cancer women, founding similar results between the two methods.

Several studies have compared HS with SIS, some of which demonstrated that SIS can detect lesions not seen by HS. Hann *et al*. [62] found that 5 of 31 endometrial polyps diagnosed using SIS were not confirmed by HS despite their classic appearance. Similar results were shown by Schwärzler *et al*. [70], who reported that HS missed 2 of 25 polyps detected using SIS. In patients with positive endometrial features by basal SIS, postoperative SIS identified endometrial polyps, which were histologically verified in 16/22 (72%) patients. Although the study patients constituted a selected group, the rate of endometrial pathologies, primarily endometrial polyps, was still very high, especially when compared with other documented studies in literature not using SIS [40,46,70,71]. This high rate concurs with the findings of Achiron *et al*. [72], who performed SIS in a group of 20 tamoxifen-treated patients and identified endometrial polyps in 8 (40%) of them. Bourne *et al*. [73] also claimed that SIS revealed a higher proportion of polyps in such patients. In 46 patients who had no specific basal endometrial features by SIS, no endometrial polyps were identified by HS. Thus, SIS yielded no false-negative findings, and its accuracy was not significantly different from the accuracy of HS.

Uterine pathologies correlated with tamoxifen intake include endometrial polyps, submucosal leiomyomas, endometrial hyperplasia, and endometrial carcinoma [5–7]. As most endometrial lesions are benign [10,15,74,75], a minimally invasive procedure as SIS may represent an alternative to HS. We showed that endometrial polyps are the most frequent endometrial findings with a mean incidence of 39.7%, in agreement with previous reports in the literature. If tamoxifen-associated polyps are premalignant lesions is still under debate [76,77]. Nevertheless, given the very high prevalence of endometrial polyps and the low prevalence of endometrial cancer compared to these, many studies support the hypothesis that they are not premalignant lesions [78]. To further incentivize the use of a non-invasive approach, some studies referred to the existence of controversies in the risk for endometrial cancer with the use of tamoxifen. In a case-controlled study about the use of this drug in patients with breast cancer, Cook *et al*. [79] did not find a significant incidence of endometrial cancer with 2 years use. Tandon *et al*. [69] did not confirm an increased frequency of endometrial cancer as reported by Mourits *et al*. [51]. Lahti *et al*. [48], Neven *et al*. [80], Cohen *et al*. [81] and all their co-workers observed only a few cases of endometrial cancer, which were not sufficient to demonstrate a clear relationship between it and tamoxifen administration.

Moreover, SIS is virtually devoid of complications [82]. HS complications are rare, but if left unrecognized can become life threatening. The overall complication rate

of the latter procedure is 0.28% and uterine perforation is its most common complication (0.13%) [83].

Patients undergoing tamoxifen are often those that have been received a surgical treatment for breast cancer and that may probably benefit (also psychologically) of SIS as a less invasive alternative to HS. Timmermann *et al*. [66] compared the acceptability of the two methods, including 52 patients with breast cancer who had taken tamoxifen and underwent HS and/or SIS. When asked which test patients would prefer to have in the future, 68% opted for SIS and 21% opted for HS. Garuti *et al*. [64], showed that pelvic pain experienced by breast cancer patients taking tamoxifen at HS was not significantly higher than in the group of women underwent SIS, although the trend favors the latest approach.

A study by Saidi *et al*. [84] showed that the average cost for SIS was $195 and the cost for HS was $675, concluding that SIS may represent a cost-effective alternative to HS.

In conclusion, long-term tamoxifen use for the treatment of breast cancer seems to be associated with an increased incidence of endometrial polyps, submucosal leiomyomas, endometrial hyperplasia, and endometrial cancer. Adequate monitoring of endometrial response to tamoxifen in these patients is crucial. We showed similar accuracy between SIS and HS in detection of endometrial tamoxifen-related lesions. Along this line, SIS may represent a minimally invasive, simple, safe, well-tolerated and cost-effective alternative to HS, associated with few contraindications and no potential complications.

Author contributions

FDG was responsible for the main concept. GGI wrote the first draft of the manuscript, is responsible for the tables design. CL and MP contributed to the manuscript review. FG, GGI, FDG, GD contributed to the research of studies suitable for the review. All authors discussed the results and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. MP is serving as one of the Editorial Board members of this journal. We declare that MP had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Prof. Enrique Hernandez.

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