Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634118-125

Evaluation of Saline Sonohysterography Findings in Patients with Breast Cancer Receiving Tamoxifen Adjuvant Therapy

Maryam Rahmani*[a], Leila Farmanbordar[a], Ramesh Omranipour[b], Mahrooz Malek[a], Sanaz Zand[c]

[a] *Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Department of Radiology, Tehran University of Medical Sciences, Tehran, Iran*

[b] *Division of Surgical Oncology, Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran*

[c] *Kaviani Breast Diseases Institute (KBDI), Tehran, Iran*

ARTICLE INFO

Received:
17 October 2016
Revised:
7 November 2016
Accepted:
13 November 2016

Keywords:
Tamoxifen,
breast cancer,
endometrial lesions,
endometrial cancer,
saline sonohysterography

ABSTRACT

Background: Transvaginal ultrasound is one of the most common means to examine endometrial cavity lesions although its negative results are more valuable. Saline sonohysterography can reduce the number of false negative rates of endometrial lesions diagnoses in Tamoxifen consumers. The Objective of this study was to determine the diagnostic values of saline infusion sonohysterography (SIS) and hysteroscopy as gold standard in diagnosis of endometrial pathologies in patients with breast cancer receiving adjuvant therapy with Tamoxifen for at least 6 months.

Methods: This cross-sectional study was conducted on 40 patients with breast cancer who were treated with for at least 6 months and referred by the gynecologist for evaluation. Age, duration of Tamoxifen use and symptoms were recorded. Patients were examined by saline sonohysterography. Ultrasonic endometrial findings were recorded. Patients with positive findings were referred for hysteroscopy and biopsy was taken for pathologic examination. Then we compared the results.

Results: In total, 40 patients with a mean age of 46.5±7.81 years and mean duration of Tamoxifen treatment 18.4 ±13.98 months were included. There were intrauterine lesions in 22 patients and they did not undergo hysteroscopy. For others, 9 patients with endometrial polyp (21.41%), 3 patients with endometrial hyperplasia (7.14%) were found. The accuracy of SSH in diagnosing endometrial polyp, endometrial hyperplasia and submucosal fibroma were 87.5%, 92.5% ,97.5%, respectively.

Conclusions: Saline sonohysterography is a viable option for screening of the patients instead of endometrial biopsy as it has great negative predictive value. Sonohysterography is easy, non-invasive, inexpensive and has great accuracy.

Introduction

Transvaginal ultrasound is one of the most common means to examine endometrial cavity lesions although its negative results are more valuable.[1] Elderly women with breast cancer who are treated with Tamoxifen are among the patients with higher risk of endometrial neoplastic lesions.[2] Tamoxifen has anti-estrogenic effects on breast tissue; but can act as an estrogen agonist on endometrial receptors, therefore it appears that Tamoxifen consumption can increase the risk of endometrial cancers.[3] Salazar *et al.* in 1985 for the first time reported an association

Address for correspondence:
Maryam Rahmani, MD
Address: Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Medical Imaging Center, Imam Khomeini Hospital, 1419733141, Tehran, Iran
Tel: +98 21 66581579
Fax: +98 21 66581578
Email: m49rahmani@yahoo.com

between Tamoxifen consumption and development of endometrial cancer.[3,4] Still, some of the researchers believe only patients who have abnormal vaginal bleeding should be evaluated for endometrial pathologies.[5] On the other hand, others believe that all those patients should undergo careful pelvic examination and ultrasonic endometrial thickness evaluation every 6 months.[3] Some studies on the effect of Tamoxifen on endometrial thickness in breast cancer patients, have shown that by regular repeated examinations of these patients and evaluation of endometrial thickness with ultrasound, endometrial cancer can be detected in early stages.[6,7] Essentially, Tamoxifen can be the cause of endometrial thickening by initiating polyps, hyperplasia and/or neoplasia, or can reduce the thickness and cause atrophy.[3,8] It appears that the main cause of developing malignancy from endometrial hyperplasia is the duration of Tamoxifen consumption.[8]

Recent studies have shown that sonohysterography with limited intrauterine injection of sterile saline can reduce the number of false negative diagnosis of endometrial lesions in Tamoxifen consumers.[9,10] Since this technique can better distinct focal and diffuse lesions compared to other methods such as transvaginal ultrasonography. Also with SIS, in order to make a definitive diagnosis, a biopsy can be taken.[11,12] Multiple studies have shown that sonohysterography with normal saline has higher sensitivity, specificity, positive predictive value and negative predictive value than transvaginal ultrasound and it is comparable to hysteroscopy as the gold standard, therefore, we can use this technique as the first screening tool in patients with abnormal uterine bleeding prior to hysteroscopy since it's simple, minimally invasive, cost-effective.[13-16]

Since breast cancer is one of the most common cancers among Iranian women population and most of them receive adjuvant therapy with Tamoxifen for their treatment, thus they're exposed to a high risk of endometrial pathologies.[4,17,18]

We conducted this study to evaluate relation of endometrial pathologies with abnormal saline infusion sonohysterography (SIS) features and hysteroscopic findings as the gold standard in patients with breast cancer receiving adjuvant therapy with Tamoxifen for at least 6 months, thereby to investigate the diagnostic values of SIS and hysteroscopy, to estimate whether SIS can be a good alternative for hysteroscopy as a screening tool in diagnosis of endometrial pathologies.

Methods

This cross-sectional study was approved by research committee of Tehran University of Medical Sciences. Written informed consent was obtained from all patients. The study population were patients with breast cancer who received adjuvant therapy with full dose Tamoxifen (20mg, Daily) for at least 6 months and referred by the gynecologist for evaluation of endometrial pathologies to the radiology department of Imam Khomeini hospital from March 2012 to March 2014. Patients who had endometrial wall thickness of more than 4mm with transvaginal ultrasound were included in the study; and patients older than 70 years old, with vaginal infections, with positive βHCG results, and patients who did not take their medications regularly were excluded.

The variables recorded at the beginning were age, duration of Tamoxifen use and symptoms such as abnormal uterine bleeding (AUB) or vaginal discharge. First, a saline sonohysterography was performed (as described by Ogutcuoglu *et al.*[19]). Ten to twenty ml normal saline were infused through a foley catheter and transvaginal ultrasound was performed and ultrasonic endometrial findings were recorded including thickness, presence of hyperplasia, polyp, Adenomyosis, submucosal fibrosis, endometrial cancer signs, and adhesions in endometrial cavity.

Ultrasounds were done by Medison™ instrument and transvaginal endocavitary probes were used. Then symptoms such as AUB and pelvic pains were explained to the patients and they were encouraged for follow-up. Patients with positive saline sonohysterography finding was referred to gynecologist for hysteroscopy and biopsy was taken for pathologic examination.

Collected data were analyzed by SPSS software (IBM Inc.) v.19. Continuous variables were reported as mean ± standard deviation and categorical variables as absolute and relative frequency.

Results

After applying inclusion and exclusion criteria, 40 patients who were referred to ultrasound clinic for evaluation of endometrial pathologies after receiving Tamoxifen for more than 6 months, were included in the study. Mean age of patients was 46.5±7.8 (Range: 32-65, Median: 46.50).

Most the patients had at least two pregnancies in their lifetime, In fact, 42.5% of them had more than two, 40% of them had only 2 and only 7.5% just 1 pregnancy. Also 10% of patients didn't have history of prior pregnancy.

As demonstrated in table 1, most of the patients (62.2%) didn't have any symptoms. For the symptomatic patients, the most common symptom was abnormal discharge (16.66%) and abnormal uterine bleeding (11.9%). Other symptoms such as pelvic pain and mass palpation were only reported in two patients.

Regarding SIS findings, as reported in table 1, there was suspicious pathologic finding in most of the patients (14 patient, 34.14%). The most common

pathologic finding was endometrial polyp which was seen in 12 patients (29.26%) and after that adenomyosis in 5 patients (12.19%). Other findings such as hyperplasia, fibroid and adhesions were reported in fewer number of patients.

As shown in table 1, there were intrauterine lesions in 22 patients and they did not undergo hysteroscopy. Also, it was not performed for 2 more patients due to technical difficulties. For others, the most common pathologic finding was endometrial polyp which was found in 9 patients (21.41%). Also, endometrial hyperplasia was seen in 3 patients (7.14%) and other findings such as fibroid, leiomyoma, adenomyosis and adenomyoma were only seen in 1 patient. Two patients had simultaneous polyp hyperplasia and endometrial polyp. Biopsy was technically not possible in one patient because of multiple linear, fixed, bridging adhesion bands.

Nearly 75% of the patients who were referred to ultrasound clinic for evaluation of endometrial pathologies had been treated with Tamoxifen for less than 30 months. Mean duration of treatment was 13.985±18.4 months (Range: 6-56).

Table 1. Patients' Characteristics

	N (%)
Age (mean±SD)	46.5±7.818
Duration of Tamoxifen Treatment (mean±SD)	18.4 ±13.985
Pregnancy	
0	4 (10%)
1	3 (7.5%)
2	16 (40%)
>=3	17 (42.5%)
Symptoms	
Asymptomatic	25 (59.52%)
AUB	5 (11.90%)
Abnormal Discharge	7 (16.66%)
Pelvic Pain	2 (4.76%)
Mass	2 (4.76%)
Others	1 (2.38%)
Ultrasound	
Normal	14 (34.14%)
Hyperplasia	4 (9.75%)
Polyp	12 (29.26%)
Fibroid	2 (4.87%)
Adenomyosis	5 (12.19%)
Adhesion	1 (2.43%)
Others	3 (7.31%)
Pathology	
Not performed	22 (52.38%)
Polyp	9 (21.41%)
Hyperplasia	3 (7.14%)
Endometrium	1 (2.38%)
Fibroid	1 (2.38%)
Leiomyoma	1 (2.38%)
Adenomyosis	1 (2.38%)
Adenomyoma	1 (2.38%)
Inconclusive	1 (2.38%)
Technical Problem	2 (4.76%)

As shown in the table 2, in 16 patients both SIS, and histologic biopsy were done, which in 12 subjects (30% of total subjects) the results were concordant but in 4 subjects (10% of total subjects), they were incompatible. There were no indications for histologic biopsy in 24 subjects.

In table 3, sensitivity, specifity, positive predictive value (PPV) and negative predictive value (NPV) of SIS findings compared to pathology report (as the gold standard) are reported. SIS has the best accuracy for diagnosis of submucosal fibroma (97.5%) followed by hyperplasia (92.5%) and polyps (87.5%). Sensitivity of the test was the highest for submucosal fibroma (100%) and the lowest for endometrial hyperplasia (66.7%) but specifity of the test for diagnosis of three pathologies were rather similar (97.4% for submucosal fibroma and 94.6% for endometrial hyperplasia). Positive predictive value of the test for diagnosis of all three pathologies was less than 70%, but it had more than 95% negative predictive value for the diagnosis of all pathologies.

Table 2. Comparison of histopathologic and radiologic findings

	N (%)
Histopathologic finding the same as radiologic finding	12 (30%)
Histopathologic findings Different than radiologic findings	4 (10%)
No histopathologic report	24 (60%)
Total	40 (100%)

Table 3. Evaluation of the performance of saline sonohysterography per diagnosis

	Submucosal Fibroma	Endometrial Hyperplasia	Endometrial polyps p
Sensitivity	100%	66.7%	88.9%
Specificity	97.4%	94.6%	87.1%
Positive predictive value	50%	50%	66.7%
Negative Predictive Value	100%	97.2%	96.4%
Accuracy	97.5%	92.5%	87.5%

Discussion

In our study, as mentioned before, most of the patients who were referred to ultrasound clinic for evaluation of endometrial pathologies have been treated with Tamoxifen for 6-30 months (13.98±18.4). In the study by Fung, *et al.* 20 patients were treated with Tamoxifen for 48.2±27 months and in Elhelw *et al.* study patients received treatment for 12-28 months.[13,21]

Develioglu *et al.* reported that patients with an endometrial pathology had been treated with Tamoxifen for 30±16.9 months while patients without endometrial pathology had received treatment for 19.1±15.6 months.[22] These findings are verified by Franchi *et al.* and Ito *et al.* which reported that Tamoxifen consumption for 27 and 24 months (respectively) is associated with development of endometrial pathology.[23, 24] Yet, due to the limited number of subjects in our study it was not possible to find any association between duration of Tamoxifen treatment and endometrial pathologies.

Regarding number of pregnancies, almost half of our study population had a history of 3 pregnancies or more. Develioglu *et al.* study has showed that number of pregnancies in patients with intrauterine pathologies was 2.6 ±1.6 and this number for patients without pathology was 2.4 ±1.2 which the difference is not statistically significant.[22]

Our study showed most of the patients were asymptomatic. In a report by Yusefi *et al.* only 4.6% of the patients reported AUB and it appears that this finding is associated with increased endometrial thickness.[3] Jindal *et al.* evaluated the symptoms in patients using Tamoxifen and they found that 88% of the patients have no symptoms and AUB and abnormal discharge was reported in 8% and 4% of the patients respectively.[25] In Kochar *et al.* study 66% of the patients receiving Tamoxifen treatment were asymptomatic and 34% had a symptom and in another study by Gaber *et al.* on 247 patients receiving Tamoxifen, 175 had no symptoms, 52 had a suspicious finding in their endometrium and 20 patients presented with AUB.[26,27]

Endometrial polyp was the most common SIS finding in our study population. Deligdisch *et al.* reported that endometrial polyp is present in 23% of referrals, but Elhelw *et al.* reported than endometrial polyp was present in 45% of the patients, cystic irregularity in endo-myometrial junction and endometrial thinness were present in 41% and 13.6% of the patients, respectively.[21, 28] In some other studies, endometrial polyp prevalence was reported between 49-63% in patients receiving Tamoxifen treatment.[29-31] More importantly, Fong *et al.* reported SIS can thoroughly diagnose small polyps that are not detectable by transvaginal ultrasound or blind biopsy.[29]

In our study, the most common pathology finding was endometrial polyp. Of all the patients' biopsy samples, 22 patients were without any pathologic findings. The most common pathologic finding in others were endometrial polyp (9 subjects) and endometrial hyperplasia (3 subjects). In Yusefi *et al.* study endometrium was atrophic in 34.2% of the patients and there was no sufficient tissue for sampling.[3] In Fong *et al.* study endometrial pathologies were present in 40.2% of the patients receiving Tamoxifen and 38.5% had endometrial polyps.[29] Only 1.7% had submucosal fibroid. But Fung *et al.* reported significant changes were present in 32.3% of the patients which 5.3% were hyperplasia, 23.56% endometrial polyp and less than 5% endocervical polyp, atypical hyperplasia, adenocarcinoma or sarcoma.[20] Although in our study endometrial polyps were less frequent than others, but they are benign and have no significant clinical impact. For comparison in Elhelw *et al.* study, 10 endometrial polyps, 3 were hyperplasia and 1 was adenocarcinoma.[21] Also of 9 subjects with irregular endo-myo junction, 2 were hyperplasia. Overall, studies have shown than chronic consumption of Tamoxifen is associated with three times increase in risk of endometrial polyp and 5 times increase in endometrial hyperplasia, although duration and dosage of consumption should be considered.[32]

In comparison of SIS and pathologic findings, 16 patients had done both. In 12 subjects, pathologic evaluation confirmed the diagnosis of SIS and in 4 patients the diagnosis was different.

Hann *et al.* reported that from 28 endometrial polyps that were reported by SIS, 23 were confirmed by pathology and of 5 endometrial hyperplasia diagnosed by SIS, just 2 were confirmed by pathology.[30] Also in 19 patients who undergone endometrial biopsy first and no finding was reported by pathology, SIS evaluation found 10 polyps and 2 endometrial thickness. In another study by Hann group, in SIS of 50 patients, endometrial polyp was found in 32 subjects, yet, 81% of endometrial biopsies were normal, in 13% there was not enough sample and only in 6% endometrial polyp was reported.[31] In 4 patients, even with endometrial thickness of 5mm, endometrial biopsy was reported normal. Furthermore, endometrial biopsy was reported by endometrial biopsy in 4 patients but SIS was negative in 2 cases. It seems that this disagreement between pathology reports and SIS findings was due to insufficient endometrial sampling or movement of the stalk of the pedunculated polyps caused by curette.

In our study, we didn't find any cases of endometrial carcinoma or blood clots. But other studies have shown that chronic consumption of Tamoxifen is associated with increased risk of endometrial cancer.[31] Cohen *et al.* reported that in 3% of patients who were treated with Tamoxifen for a long period, there were some evidence of neoplastic changes in polyps but the incidence in control group was only 0.48%.[33] Yusefi *et al.* also estimated the prevalence of endometrial carcinoma in this patient group to be about 0.61% and reported a higher risk of cacncer development after 5 years of Tamoxifen consumption.[3] Per some epidemiologic studies, annual incidence of endometrial carcinoma in Tamoxifen users, some researchers believe that there's no need for screening in patients without clinical symptoms.[34]

As reported, in our investigation, SIS compared to gold standard (which is pathology biopsy) overall has high accuracy, sensitivity, specifciity and NPV in diagnosis of endometrial pathologies but not PPV. Several other studies, have assessed the results of SIS which we summarized them in table 4.[14, 19, 29, 35-42] Almost all their results are in concordance to our study showing more than 80% sensitivity and specificity and more than 90% NPV and accuracy for SIS. Only PPV is smaller in our study which might be due to small sample size.

In this report for evaluation of sensitivity and specificity of SIS, we used endometrial thickness of more than 5mm as cut-off point, but Develioğlu *et al.* used 9.5mm as the cut-off point and reported 89% sensitivity and 78% specificity.[22] Other studies have used 4-10mm as cut-off point and overall, whenever a smaller cut-off point has been used, false positive cases were more and subsequently sensitivity decreased.[16,43,44] The American College of Obstetricians and Gynecologists (ACOG) and the Society of Radiologists in Ultrasound (SRU) advise that either TVUS (with an endometrial thickness of ≤4 mm [ACOG] or ≤5 mm [SRU]) or endometrial sampling are recommended as a diagnostic tool in women with postmenopausal bleeding.[45,46]

Overall, our study showed that SIS evaluation has great negative predictive value for diagnosis of endometrial lesions which is important for a screening test and since this test is non-invasive and cheap, and without risk of radiation to the patient, we can recommend it as a screening test for patients receiving Tamoxifen for a long period.

Yet, since this test does not have great positive predictive value, it's better not to use it as a diagnostic test in this group of patients as many of the patients will be referred for endometrial biopsy eventually.

Although small sample size is a limitation of our study but overall, we conclude that SIS is an easy, non-invasive and inexpensive test and has great accuracy. Since chronic Tamoxifen consumption is associated with increased risk of endometrial carcinomas, these patients should be screened for endometrial pathologies. This study showed that SIS is a viable option for screening of these patients instead of endometrial biopsy because it has great negative predictive value, as 55% of the subjects in our study were ruled out of endometrial pathologies. But it doesn't have great positive predictive value for making the diagnosis, therefore it should be used by caution.

Table 2. Characteristics that have been shown to effect outcome of ECT treatment

		N	Sensitivity	Specificity	PPV	NPV	Accuracy
Our Study	Overall	40					
	Endometrial polyps		88.9%	87.1%	66.7%	96.4%	87.5%
	Endometrial Hyperplasia		66.7%	94.6%	50%	97.2%	92.5%
	Submucosal Fibroma		100%	97.4%	50%	100%	97.5%
Bingol *et al.*[35]	Overall	346	98%	83%	96%	91%	
	Endometrial polyps		100%	93%	90%	100%	
	Endometrial Hyperplasia		87%	100%	100%	95%	
Ogutcuoglu *et al.*[19]	Endometrial lesions	100	60%	96%	87.8%	83.8%	87%
Radwan *et al.*[14]	Endometrial polyps	241	97.3%	95.8%	91.1%	98.7%	96.27%
Luterek *et al.*[36]	Overall	40					
	Endometrial polyps		100%	100%	100%	100%	
	Submucosal Fibroma		75%	75%	75%	75%	
Kowalczyk *et al.*[37]	Overall	97	>72%	96%			
Erdem *et al.*[38]	Overall	133	97.7%	%82.4	93.5%	93.3%	93.4%
	Endometrial polyps		100%	91.8%	92.4%	100%	95.5%
	Submucosal Fibroma		95.7%	100%	100%	99%	100%
Jafari *et al.*[40]	Overall	99	%91.67	%86	%85.9	%85.7	
Ludwin *et al.*[39]	Overall	35	97%	90%			
	Endometrial polyps		100%	83%			
	Endometrial Hyperplasia		84%	95%			
Fong *et al.*[29]	Overall	104	89.7%	79.2%	76.1%	91.3%	
Kamel *et al.*[41]	Overall	106	64.5%	75.5%			
Kimiai *et al.*[42]	Endometrial Hyperplasia	100	83%	93%	83%	97%	
	Endometrial polyps		83%	95%	58%	98%	

References

1. Gao WL, Zhang LP, Feng LM. Comparative study of transvaginal ultrasonographic and diagnostic hysteroscopic findings in postmenopausal breast cancer patients treated with tamoxifen. Chin Med J (Engl) 2011; 124(15): 2335-9.
2. Chen JY, Kuo SJ, Liaw YP, Avital I, Stojadinovic A, Man YG, *et al.* Endometrial cancer incidence in breast cancer patients correlating with age and duration of tamoxifen use: a population based study. J Cancer 2014; 5(2): 151-5.
3. Yousefi Z, Homayie F, Rafei S. The evaluation of the endometrial thickness of amenorrhea breast cancer patients treated with tamoxifen. AMUJ. Arak Medical University Journal 2011; 14(5): 101–7.
4. Salazar EL, Paredes A, Calzada L. Endometrial thickness of postmenopausal breast cancer patients treated with tamoxifen. Gynecol Endocrinol 2005; 21(6): 312-6.
5. Fong K, Causer P, Atri M, Lytwyn A, Kung R. Transvaginal US and hysterosonography in postmenopausal women with breast cancer receiving tamoxifen: correlation with hysteroscopy and pathologic study. Radiographics 2003; 23(1): 137-50; discussion 51-5.
6. Lindahl B, Andolf E, Ingvar C, Ranstam J, Willen R. Adjuvant tamoxifen in breast cancer patients affects the endometrium by time, an effect remaining years after end of treatment and results in an increased frequency of endometrial carcinoma. Anticancer Res 2008; 28(2B): 1259-62.
7. Sinawat S, Chiyabutra T. Increased risk of endometrial abnormalities in breast cancer patients taking tamoxifen: the need for gynaecologic surveillance. Asian Pac J Cancer Prev 2004; 5(2): 183-7.
8. Decensi A, Gandini S, Serrano D, Cazzaniga M, Pizzamiglio M, Maffini F, *et al.* Randomized dose-ranging trial of tamoxifen at low doses in hormone replacement therapy users. J Clin Oncol 2007; 25(27): 4201-9.
9. Tepper R, Beyth Y, Altaras MM, Zalel Y, Shapira J, Cordoba M, *et al.* Value of sonohysterography in asymptomatic postmenopausal tamoxifen-treated patients. Gynecol Oncol 1997; 64(3): 386-91.
10. Markovitch O, Tepper R, Aviram R, Fishman A, Shapira J, Cohen I. The value of sonohysterography in the prediction of endometrial pathologies in asymptomatic postmenopausal breast cancer tamoxifen-treated patients. Gynecol Oncol 2004; 94(3): 754-9.
11. Aslam M, Ijaz L, Tariq S, Shafqat K, Meher Un N, Ashraf R, *et al.* Comparison of transvaginal sonography and saline contrast sonohysterography in women with abnormal uterine bleeding: correlation with hysteroscopy and histopathology. Int J Health Sci (Qassim) 2007; 1(1): 17-24.
12. Cepni I, Ocal P, Erkan S, Saricali FS, Akbas H, Demirkiran F, *et al.* Comparison of transvaginal sonography, saline infusion sonography and hysteroscopy in the evaluation of uterine cavity pathologies. Aust N Z J Obstet Gynaecol 2005; 45(1): 30-5.
13. Seshadri S, El-Toukhy T, Douiri A, Jayaprakasan K, Khalaf Y. Diagnostic accuracy of saline infusion sonography in the evaluation of uterine cavity abnormalities prior to assisted reproductive techniques: a systematic review and meta-analyses. Hum Reprod Update 2015; 21(2): 262-74.
14. Radwan P, Radwan M, Kozarzewski M, Polac I, Wilczynski J. Evaluation of sonohysterography in detecting endometrial polyps - 241 cases followed with office hysteroscopies combined with histopathological examination. Wideochir Inne Tech Maloinwazyjne 2014; 9(3): 344-50.
15. Hajishafiha M, Zobeiri T, Boroumandan F, Oroji R, Rajabpoor M. A comparative study of sonohysterography with diagnostic curettage in patients with abnormal uterine bleeding. The Journal Of Urmia University Of Medical Scinces 2006; 17(3): 181-7.
16. Mathew M, Gowri V, Rizvi SG. Saline infusion sonohysterography - an effective tool for evaluation of the endometrial cavity in women with abnormal uterine bleeding. Acta Obstet Gynecol Scand 2010; 89(1): 140-2.
17. Mehrabi E, Hajian S, Simbar M, Hoshyari M, Zayeri F. The Lived Experience of Iranian Women Confronting Breast Cancer Diagnosis. J Caring Sci 2016; 5(1): 43-55.
18. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994; 86(7): 527-37.
19. Ogutcuoglu B, Karadag C, Inan C, Dolgun ZN, Yoldemir AT, Aslanova L. Diagnostic utility of saline infusion doppler sonohysterography in endometrial mass lesions. Pak J Med Sci 2016; 32(2): 284-8.
20. Fung MF, Reid A, Faught W, Le T, Chenier C, Verma S, *et al.* Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecol Oncol 2003; 91(1): 154-9.
21. Elhelw B, Ghorab MN, Farrag SH. Saline sonohysterography for monitoring asymptomatic postmenopausal breast cancer patients taking tamoxifen. Int J Gynaecol Obstet 1999; 67(2): 81-6.
22. Develioglu OH, Omak M, Bilgin T, Esmer A, Tufekci M. The endometrium in asymptomatic breast cancer patients on tamoxifen: value of

transvaginal ultrasonography with saline infusion and Doppler flow. Gynecol Oncol 2004; 93(2): 328-35.
23. Franchi M, Ghezzi F, Donadello N, Zanaboni F, Beretta P, Bolis P. Endometrial thickness in tamoxifen-treated patients: an independent predictor of endometrial disease. Obstet Gynecol 1999; 93(6): 1004-8.
24. Ito T, Katagiri C, Murata Y, Hamazoe R, Morita K. Indication for histological examination of endometrium in breast carcinoma patients receiving tamoxifen therapy. J Obstet Gynaecol Res 2001; 27(3): 141-5.
25. Jindal A, Mohi MK, Kaur M, Kaur B, Singla R, Singh S. Endometrial evaluation by ultrasonography, hysteroscopy and histopathology in cases of breast carcinoma on Tamoxifen therapy. J Midlife Health 2015; 6(2): 59-65.
26. Kochar S, Arora P, Chattopadhyay AB. Tamoxifen Therapy for Breast Cancer and Endometrial Pathology. Med J Armed Forces India 2005; 61(4): 313-5.
27. Gerber B, Krause A, Muller H, Reimer T, Kulz T, Makovitzky J, *et al.* Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. J Clin Oncol 2000; 18(20): 3464-70.
28. Deligdisch L, Kalir T, Cohen CJ, de Latour M, Le Bouedec G, Penault-Llorca F. Endometrial histopathology in 700 patients treated with tamoxifen for breast cancer. Gynecol Oncol 2000; 78(2): 181-6.
29. Fong K, Kung R, Lytwyn A, Trudeau M, Chapman W, Nugent P, *et al.* Endometrial evaluation with transvaginal US and hysterosonography in asymptomatic postmenopausal women with breast cancer receiving tamoxifen. Radiology 2001; 220(3): 765-73.
30. Hann LE, Gretz EM, Bach AM, Francis SM. Sonohysterography for evaluation of the endometrium in women treated with tamoxifen. AJR Am J Roentgenol 2001; 177(2): 337-42.
31. Hann LE, Kim CM, Gonen M, Barakat R, Choi PH, Bach AM. Sonohysterography compared with endometrial biopsy for evaluation of the endometrium in tamoxifen-treated women. J Ultrasound Med 2003; 22(11): 1173-9.
32. van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrere CH, Otter R, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994; 343(8895): 448-52.
33. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol 2004; 94(2): 256-66.
34. Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. J Clin Oncol 1999; 17(7): 2050-4.
35. Bingol B, Gunenc Z, Gedikbasi A, Guner H, Tasdemir S, Tiras B. Comparison of diagnostic accuracy of saline infusion sonohysterography, transvaginal sonography and hysteroscopy. J Obstet Gynaecol 2011; 31(1): 54-8.
36. Luterek K, Szymusik I, Bartkowiak R, Wielgos M. Sonohysterography in peri- and postmenopausal women with abnormal uterine bleeding or abnormal endometrial appearance. Neuro Endocrinol Lett 2014; 35(4): 297-300.
37. Kowalczyk D, Guzikowski W, Wiecek J, Sioma-Markowska U. Clinical value of real time 3D sonohysterography and 2D sonohysterography in comparison to hysteroscopy with subsequent histopathological examination in perimenopausal women with abnormal uterine bleeding. Neuro Endocrinol Lett 2012; 33(2): 212-6.
38. Erdem M, Bilgin U, Bozkurt N, Erdem A. Comparison of transvaginal ultrasonography and saline infusion sonohysterography in evaluating the endometrial cavity in pre- and postmenopausal women with abnormal uterine bleeding. Menopause 2007; 14(5): 846-52.
39. Ludwin A, Pitynski K, Szczudrawa A, Biernat I, Loster J. [Value of saline infusion sonohysterography and hysteroscopy in postmenopausal patient with persistent abnormal ultrasonographic images after endometrial curettage with normal histological results]. Ginekol Pol 2003; 74(9): 786-92.
40. Mohammad jafari R, Barati M, Najafian M, Saadati N, Shojaei K. Comparison of sensitivity & specificity of transvaginal sonography, saline infusion sonohysterography and hysteroscopy in evaluation of women with abnormal uterine bleeding. Journal Of Shahid Sadoughi University Of Medical Sciences And Health Services 2009; 17(4): 249-54.
41. Kamel HS, Darwish AM, Mohamed SA. Comparison of transvaginal ultrasonography and vaginal sonohysterography in the detection of endometrial polyps. Acta Obstet Gynecol Scand 2000; 79(1): 60-4.
42. Kimiaei P, Kalantari M. Efficacy of vaginal sonohystrography in the diagnosis of uterine abnormalities. Pejouhandeh Quarterly Research Journal 2000; 17(5): 77-83.
43. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. Am J Obstet Gynecol 2003; 188(2): 401-8.
44. Litta P, Merlin F, Saccardi C, Pozzan C, Sacco G, Fracas M, *et al.* Role of hysteroscopy with endometrial biopsy to rule out endometrial

cancer in postmenopausal women with abnormal uterine bleeding. Maturitas 2005; 50(2): 117-23.
45. Langer JE, Oliver ER, Lev-Toaff AS, Coleman BG. Imaging of the female pelvis through the life cycle. Radiographics 2012; 32(6): 1575-97.
46. Alcazar JL, Errasti T, Zornoza A. Saline infusion sonohysterography in endometrial cancer: assessment of malignant cells dissemination risk. Acta Obstet Gynecol Scand 2000; 79(4): 321-2.