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Role of hysteroscopy with endometrial biopsy to rule out endometrial cancer in postmenopausal women with abnormal uterine bleeding

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Abstract

Objective: To compare the diagnostic accuracy of ultrasonographic endometrial thickness and outpatient hysteroscopy, to establish the most appropriate exam for the diagnosis of endometrial cancer in postmenopausal women with abnormal uterine bleeding (AUB). The secondary aim was to develop a multivariable approach considering clinical history as an added value for these diagnostic procedures. *Methods:* This prospective study was conducted on 220 consecutive postmenopausal patients with AUB, who underwent ultrasonographic evaluation of endometrial thickness, outpatient hysteroscopy and endometrial biopsy. Evaluation of sensitivity, specificity, positive and negative predictive value was performed. Receiver operator characteristic curve (ROC) was calculated to assess the global performance of ultrasonographic measurement of endometrial thickness and diagnostic hysteroscopy as tests for detecting endometrial cancer and atrophy. *Results:* Histological findings for <4 mm level revealed that atrophy was present in 48 (65%) and in 2 cases (2.7%) endometrial cancer was found; for ≥ 4 mm values polyps and myomas were present in 86 (59%) and there were 11 (7.5%) endometrial cancer. Sensibility and specificity for trans-vaginal ultrasound, with a cut-off value ≥ 4 mm, was 55.6% and 49.7% while positive predictive value was 83.3% and negative predictive value 98.1% (ROC curve 0.597). Hysteroscopy revealed sensitivity 100%, specificity 49.6%, positive predictive value 81.3% and negative predictive value 100% (ROC curve 0.993). *Conclusions:* In conclusion, endometrial thickness <4 mm can miss malignancies but trans-vaginal ultrasound remains the first line diagnostic procedure in postmenopausal women without AUB, because it is not invasive and has high sensitivity for detecting endometrial cancer and other endometrial disease; according to our experience, outpatient hysteroscopy with biopsy is mandatory in all postmenopausal women with AUB.

Keywords: Endometrial cancer; Hysteroscopy; Postmenopausal AUB; Trans-vaginal ultrasonography

1. Introduction

Endometrial cancer is the most common neoplasia of the female genital tract [1] with an incidence of 3.7–17.9% in postmenopausal women with abnormal

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uterine bleeding (AUB) [2] and it is diagnosed at stage I in 73% of cases. More than 90% of endometrial malignancies occur in women over 50 years of age with abnormal uterine bleeding as presenting symptom in 95% [3].

Early diagnosis is necessary but there is not a common agreement for the most adequate approach [4–6]. For a long time dilatation and curettage (D&C) was considered the "gold standard" for the investigation of AUB, although most focal lesions in the uterine cavity were missed (58% polyps, 50% hyperplasia, 60% atypical hyperplasia, 11% cancers) [7] with false negative rates between 3% and 7% [8].

Some authors proposed the use of ultrasound examination of endometrial thickness in all postmenopausal women. A Nordic Trial [9] and an Italian Multicentric Trial [10], revealed that in patients with uterine bleeding without hormonal replacement therapy (HRT), an endometrial thickness <4 mm safely excluded endometrial cancer and accurately predicted atrophy. Patients on HRT with an endometrial thickness ≥ 4 mm should be considered for endometrial sampling [11].

Outpatient hysteroscopy is an excellent procedure to evaluate uterine cavity, and it is used widely for the evaluation of women with AUB [12]. Its high sensibility and specificity allows the diagnosis of endometrial cancer and it is simple and safe [13–15].

The objective of this prospective study was to compare the diagnostic accuracy of sonographic endometrial thickness and outpatient hysteroscopy, to establish the most appropriate exam for diagnosis of endometrial cancer in postmenopausal women with AUB. The secondary aim was to develop a multivariable approach considering clinical history as an added value for these diagnostic procedures.

2. Materials and methods

The selection criteria for admission into this study were AUB after at least 12 months of postmenopausal amenorrhea and no evidence of cervical cancer after Pap smear test, no use of anti-coagulants or anti-estrogenic therapy such as tamoxifen. These patients were latter excluded because tamoxifen use is related to some increase in the risk of endometrial cancer and to a significant rise in the incidence of benign endometrial pathologies [16].

Two hundred and twenty consecutive patients satisfying these criteria from January 1999 to June 2002, referred to the Department of Gynecology and Obstetrics, University of Padua, (Italy). Age, years since menopause, HRT were recorded.

Abnormal uterine bleeding is any abnormal bleeding occurring in pre- and postmenopausal women due to several causes such as organic (polyps, myomas, hyperplasia, atrophy, endometrial cancer) or not organic (dysfunctional uterine bleeding). The women on sequential combined HRT have a good cycle control and any irregular bleeding or any withdrawal bleeding that occurs should be considered AUB. When unscheduled bleeding occurs, especially if it is heavy or prolonged, further investigations such as trans-vaginal ultrasound and, hysteroscopy with biopsy if indicated, are needed [17].

For sequential HRT regimens, the evaluation of endometrial thickness was performed within 5–10 days of progestinic therapy [18].

Each patient was investigated with trans-vaginal ultrasound, outpatient hysteroscopy and endometrial biopsy.

Ultrasonography was always performed with 6.5 MHz curvilinear endovaginal probe (Siemens sonoline System) by the same operator. Endometrial thickness was measured as the maximal distance between the two myometrial interfaces in a longitudinal scan, and patients were divided into three groups: below 4 mm, between 4 and 8 mm and above 8 mm.

Hysteroscopy was performed using a Ø 2.9 mm hysteroscope with a 30° foreoblique lens by vaginoscopy. Distension medium (normal saline) was infused with a 100 mmHg pressure bag. No local anaesthesia or systemic drugs were given to perform hysteroscopies.

No local treatment such as estrogen therapy was used before hysteroscopy in all postmenopausal patients.

All hysteroscopic procedures were performed by the same skilled operator. Hysteroscopist was not aware of the results of the ultrasound.

The histological diagnosis was based on the results of the endometrial biopsy performed by Novak curette. The results of ultrasound scan and hysteroscopic findings were withheld from the pathologists, who studied the endometrial biopsy by microscope. Evaluation of predictive power was based on sensitivity, specificity, positive, negative predictive value and diagnostic

accuracy according to Bayes' theorem [19]. In addition to this, a receiver operator characteristic curve (ROC) was calculated to assess the global performance of sonographic measurement of endometrial thickness and diagnostic hysteroscopy as tests for detecting endometrial cancer and atrophy. ROC curve characterizes the performance of a particular diagnostic model [20]. An ROC area of 0.5 describes a non-informative test, whereas, an ROC area of 1.0 represents a test that discriminates perfectly between disease presence and absence. ROC area is a commonly used approach in research for evaluating diagnostic accuracy of tests [21].

3. Results

In 220 studied women: 139 (63.2%) did not take any therapy, while 81 (36.8%) received HRT (sequential or continuous combined estrogen–progesterone therapy) since 33.6 months ± 26.7 (range 2–120).

The mean age was 60.5 ± 8.4 (range 44–84) and years since menopause were 9.7 ± 8.3 (range 1–41).

Considering sonographic cut-off levels: 74 (33.6%) patients had an endometrial thickness <4 mm, 71 (32.3%) from 4 to 8 mm, 75 (34.1%) >8 mm and no significantly different distribution was observed in women on HRT or not in therapy.

Hysteroscopy was performed in all patients without failure. We did not report adverse experiences such as uterine perforation or failure to visualize the uterine cavity during the performance of all the hysteroscopies.

Histological findings for <4 mm level revealed that atrophy was present in 48 (65%) and in 2 cases (2.7%) endometrial cancer was found; for ≥4 mm values polyps and myomas were present in 86 (59%) and there were 11 (7.5%) endometrial cancer (Table 1). All malignant lesions were found in patients not undergoing hormonal therapy.

Hysteroscopic findings were histologically confirmed in almost all cases, all endometrial cancer were detected by hysteroscopy (Table 2). In fact, 59 cases of atrophy at hysteroscopic observation resulted to be at histology (by endometrial biopsy): 57 atrophy, one case each of proliferative/secretory and endometritis. Three cases of proliferative/secretory at hysteroscopic observation were then at histological examination: two cases of atrophy and one case of proliferative/secretory. All 92 polyps and myomas at hysteroscopic examination were confirmed at histological examination by biopsy. Fifty cases of simple hyperplasia at hysteroscopic observation were five cases of atrophy, eight cases of proliferative/secretory and thirty seven cases of simple hyperplasia at histological examination. Sixteen cases suspected to be endometrial cancers at hysteroscopic observation were then two cases of simple hyperplasia, thirteen endometrial cancers and one case of progesterone effect at histological examination (Table 2).

Only in one continuous-combined HRT, a progesterone effect (decidual reaction) at biopsy was considered as suspect at hysteroscopy.

All patients (13) with a diagnosis of endometrial cancer at endometrial biopsy underwent hysterectomy and histology of surgical specimens confirmed the findings of hysteroscopy.

The grade and stage of the endometrial cancers (overall 13 cases) were: five cases grade two, stage IB and eight cases grade two, stage IC. The two cases with endometrial thickness at trans-vaginal ultrasound <4 mm were grade two, stage IB and corresponded to serous-papilliferous forms.

Table 1
Correlation between ultrasound endometrial thickness and biopsy

Ultrasound				Biopsy				Total (%)
Endometrial thickness (mm)	Atrophy	Proliferative/ secretory	Polyps and myomas	Simple hyperplasia	Endometrial cancer	Endometritis	Progesterone effect	
<4	48	4	6	13	2	–	1	74 (33.63)
4–8	12	2	38	17	1	1	–	71 (32.27)
>8	4	4	48	9	10	–	–	75 (34.10)
Total	64	10	92	39	13	1	1	220 (100)

Table 2
Correlation between hysteroscopy and biopsy

Hysteroscopy				Biopsy				Total (%)
	Atrophy	Proliferative/ secretory	Polyps and myomas	Simple hyperplasia	Endometrial cancer	Endometritis	Progesterone effect	
Atrophy	57	1	–	–	–	1	–	59 (26.82)
Proliferative/secretory	2	1	–	–	–	–	–	3 (1.36)
Polyps and myomas	–	–	92	–	–	–	–	92 (41.82)
Simple hyperplasia	5	8	–	37	–	–	–	50 (22.73)
Endometrial cancer	–	–	–	2	13	–	1	16 (7.27)
Total	64	10	92	39	13	1	1	220 (100)

Sensibility and specificity of trans-vaginal ultrasound with a cut-off value $\geq$4 mm were 55.6% and 49.7% respectively, while positive predictive value was 83.3% and negative predictive value 98.1% (ROC curve 0.597).

Hysteroscopy revealed a sensitivity of 100%, specificity 49.6%, positive predictive value 81.3% and negative predictive value 100% (ROC curve 0.993).

The mean age in women with endometrial cancer was 62.6 $\pm$ 7.5 years and years since menopause were 10.8 $\pm$ 7.3; in women without endometrial cancer data were similar: mean age 60.4 $\pm$ 8.5 and years since menopause 9.6 $\pm$ 8.4.

In women with atrophy the mean age was 60.3 $\pm$ 6.6 years and years since menopause were 9.9 $\pm$ 7.3; in women without atrophy mean age was 60.6 $\pm$ 8.5 years and years since menopause were 9.6 $\pm$ 8.7; therefore no correlation were present between age and years since menopause for endometrial cancer and atrophy (P = NS).

Each patient, one year after hysteroscopy underwent a follow-up trans-vaginal ultrasonography and hysteroscopy with endometrial biopsy. No new cases of endometrial cancers were observed among this series.

4. Discussion

As reported in literature [2,22], also in our department, 6% of menopausal women with AUB (36% of all postmenopausal women) reported a malignant lesions.

Hormonal replacement therapy (HRT), does not affect cut-off value for further diagnostic procedures [11]. Our results confirm that no statistically significant differences are evident comparing women with AUB in HRT and those not undergoing therapy, concerning endometrial thickness and benign endometrial pathology (polyps and myomas). Moreover, no endometrial cancer has been diagnosed in women not on HRT for a long time (120 months), and this result is likely related with the accurate selection of patients eligible for HRT. In our study only 81 out of 220 (36.8%) patients, underwent HRT. This small sample size, the different population considered (Italian postmenopausal women) could explain, why we did not observe difference in thickness between HRT users and not users in opposition to what has been reported in the postmenopausal estrogen–progestin interventions (PEPI) trial [23].

Trans-vaginal ultrasound with a cut-off value $<$4 mm can exclude endometrial cancer in postmenopausal women with AUB with a sensibility up to 98% [10]. A Nordic Multicenter study [9] reported, no cases of endometrial cancer using 4 mm as cut-off limit; trans-vaginal ultrasound revealed an overall sensitivity of 96% considering benign organic lesions. Indeed, Gull et al. [24], who evaluated medical records of 339 women with postmenopausal bleeding, reported that no endometrial cancers were missed (using a cut-off level $\leq$4 mm), if trans-vaginal ultrasound measurement of endometrial thickness was performed. Furthermore, the meta-analysis of Smith-Bindman et al. [25], showed that the probability of endometrial cancer in postmenopausal women with vaginal bleeding following a normal trans-vaginal ultrasound (using a 5 mm threshold to define abnormal endometrial thickening) is 1%; thus they concluded that trans-vaginal ultrasound because of its high

sensitivity for detecting endometrial cancer can reliably identify postmenopausal women with vaginal bleeding who are highly unlikely to have significant endometrial disease so that endometrial sampling may be unnecessary. According to ecographists, endometrial thickness ≥4 mm is an indication to endometrial sampling [26].

On the contrary, in our study, trans-vaginal ultrasonography had a low sensibility (55.6%); according to ultrasonographic indication [26] only 66.4% of women with endometrial thickness ≥4 mm should undergo biopsy, while in 33.6% (endometrial thickness <4 mm) trans-vaginal ultrasound would be sufficient to exclude intrauterine pathology. But in this second group of patients (74 cases), diagnostic hysteroscopy with biopsy revealed two endometrial cancers (2.7%) and six (8.1%) benign organic lesions such as polyps and myomas. As a result of our findings, trans-vaginal ultrasonography alone is inadequate to rule out endometrial carcinoma in postmenopausal women with AUB. Furthermore, a recent meta-analysis concluded that ultrasonic measurement of endometrial thickness had limited diagnostic prediction for endometrial hyperplasia or carcinoma, however, it was a good test for exclusion of endometrial pathology [27].

Arslan et al. [28] reported that Doppler's velocity waveforms of uterine vessels coupled with transvaginal ultrasonography were not valuable enough to replace histopathological examination in the diagnosis of a neoplastic endometrial pathology in women with abnormal uterine bleeding. They concluded that non-invasive methods (trans-vaginal ultrasonography and/or Doppler flow velocity waveforms), cannot replace invasive procedures in the evaluation of patients with abnormal uterine bleeding.

In a recent meta-analysis of nine studies representing almost 4000 symptomatic women, Tabor et al. [29] showed that the measurement of the endometrial thickness in women with postmenopausal vaginal bleeding did not reduce the need for invasive diagnostic testing because 4% of cases of endometrial cancer would still be missed with a false-positive rate as high as 50%. The authors noted statistically significant differences in endometrial thickness between centers and they stated that this could reflect differences in population studied or in the method of measuring endometrial thickness [30].

According to our series, in postmenopausal women with AUB, outpatient hysteroscopy by vaginoscopy with normal saline showed a high diagnostic accuracy with a sensibility of 100%, specificity of 49.6%, positive predictive value 81.3%; moreover, it was a simple and safe procedure with a good compliance for the patient. In literature, the use of hysteroscopy alone is reported to have different sensibilities (from 65.52% to 100%) [14,31]. Our results agree with those of a recent review of Clark et al. [12] who, considering data from 26 346 women undergoing hysteroscopy, reported that a positive hysteroscopy result increased the probability of cancer to 71.8% whereas, a negative hysteroscopy result reduced the probability of cancer to 0.6%. Thus, they concluded that diagnostic accuracy of hysteroscopy was high for endometrial cancer. Similar results were recently reported by Guida et al. [32] in women with postmenopausal bleeding.

In our series, ROC curve of hysteroscopy was 0.993, just higher than results of Bachmann et al. [33], who generated an area of 0.910 and concluded that combining ultrasound results with hysteroscopy did not meaningfully alter the diagnostic probability of endometrial cancer in women with postmenopausal bleeding.

According to our experience, sensibility of hysteroscopy increased in relation to operator's skills and use of normal saline as distension medium in presence of AUB. Hysteroscopy allowed differential diagnosis of intrauterine polyps and myomas; in most cases it detected malignant pathologies and should be always followed by endometrial sampling or lesion's removal.

Age and years since menopause, did not provide an added value to diagnostic procedures considered in the study.

In our series, all endometrial cancer were detected by hysteroscopy; further studies using larger sample size are needed to confirm this high sensitivity of hysteroscopy in diagnosing endometrial cancer in postmenopausal women with abnormal uterine bleeding. However, hysteroscopy is an invasive procedure and its risks and cost/benefit should be carefully considered. Trans-vaginal ultrasound remains a non-invasive diagnostic test that may help to determine which women should undergo endometrial biopsy. In fact the high sensitivity of trans-vaginal ultrasound makes it an excellent non-invasive test for determining which women with vaginal bleeding do not require endometrial biopsy [25]. Thus, because its specificity is low,

an abnormal endometrial thickness ($\geq$5 mm) should be followed by a histological biopsy.

Recently, a systematic review and meta-analysis of De Kroon et al. [34] concluded that saline contrast hysterosonography, in combination with an aspiration biopsy in selected cases, can become the standard diagnostic procedure in pre- and postmenopausal women complaining of abnormal uterine bleeding. In fact, saline contrast hysterosonography is a both feasible and accurate and a fair reduction in cost will be achieved, if diagnostic hysteroscopy in an outpatient setting is replaced by this technique [34].

In our experience, the risks of errors during trans-vaginal ultrasound and office hysteroscopy depend on operator's skill and experience. In our department office hysteroscopy has been introduced a long time ago, with easy access for patients; narrow-diameter hysteroscopes can be used for office procedures, without anesthesia; thanks to these aspects, patients' compliance is increased and costs are reduced.

In conclusion, endometrial thickness <4 mm can miss malignancies but trans-vaginal ultrasound remains the first line diagnostic procedure in postmenopausal women without AUB because it is not invasive and has high sensitivity for detecting endometrial cancer and other endometrial disease; according to our experience, outpatient hysteroscopy with biopsy is mandatory in all postmenopausal women with AUB.

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