ACCURACY OF TRANSVAGINAL ULTRASONOGRAPHY COMPARED TO ENDOMETRIAL BIOPSY FOR THE ETIOLOGICAL DIAGNOSIS OF ABNORMAL PERIMENOPAUSAL BLEEDING

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Abstract

Background and aims. *Perimenopause is marked by clinical manifestations which disturb everyday life and which may also hide a pathomorphological, more precisely endometrial, substrate. An accurate early diagnosis established by accessible, non-invasive methods is very important for the therapeutic management.*

Method. *The study included 103 patients aged between 41.5–55.11 years, divided into 3 age groups: 40-44 years (n=10), 45-49 years (n=54) and ≥50 years (n=39).*

Results. *Certain risk factors of endometrial neoplasm or premalignant conditions were evidenced, their accurate identification being useful in limiting the number of patients with abnormal uterine bleeding (AUB) submitted to diagnostic screening. The most common cause of AUB in our study was fibroma, followed by functional causes.*

Conclusions. *Transvaginal ultrasound (TVUS) represents a minimally invasive method for the screening of perimenopausal patients with AUB, especially to rule out endometrial adenocarcinoma (EAC). TVUS sensitivity was higher than clinical diagnosis in case of leiomioma, polypi and EAC. TVUS was more accurate in the diagnosis of EAC, polypi and leiomioma.*

Keywords*:* endometrial neoplasms, uterine hemorrhage, perimenopause, transvaginal ultrasound

Introduction

Abnormal uterine bleeding (AUB) is the main reason why women refer to the gynecologist; it is a well defined condition, bleeding that is unlike normal menstrual flow in terms of frequency, duration and quantity. It includes oligomenorrhea, polymenorrhea, menorrhagia, metrorrhagia, menometrorrhagia and spotting [1].

Perimenopause includes the last 2-8 years prior to menopause and one year after its onset. Menorrhagia represents bleeding at regular intervals in larger amounts and longer duration and it may be associated with fibroma, adenomyosis or endometrial polyps. Polymenorrhagia and metrorrhagia represent other types of AUB, their underlying cause being other endometrial alterations.

The accuracy of the etiological diagnosis of AUB in perimenopausal patients is important for the subsequent therapeutic management. In time the diagnostic techniques have progressed from the classical uterine curettage to immunohistochemical markers, transvaginal ultrasound (TVUS). The latter remains a reliable, accessible and well accepted method [2,3].

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Methods

Between January 2013 – 31 December 2014 a number of 103 patients were investigated at the private ward of the Dominic Stanca Hospital of Gynecology. The study was performed based on the patients' informed consent and was approved by the Ethics Committees of the Cluj-Napoca County Hospital and the Iuliu Hatieganu University of Medicine and Pharmacy.

The study group included 103 patients aged between 41.5–55.11 years. They were divided into 3 age subgroups: 40-44 years (n=10), 45-49 years (n=54) and ≥50 years (n=39).

Patients with pregnancy suspicion (uncertain βhCG), under hormonal treatment in the past 6 months, AUB of other causes (drug-induced, iatrogenic), cervical conditions or history of abnormal Pap smear test were excluded.

All the patients had a case sheet that included anamnestic data, age, number of births, menstrual manifestations, as well as the signed informed consent.

Examinations

TV ultrasound was performed with a vaginal transducer of 7-10 MHz of a Medisan R7 US device. The endometrial thickness was measured on days 8-11 post-menstruation at 1 cm from the uterus fundus, and described in longitudinal section [4,5].

The endometrial bioptic sample for the histopathological examination was collected with Pipelle or D&C curettes, then fixed in 10% formalin, included in paraffin and stained with Hematoxillin eosin. Histopathological examination was performed in the Pathological Laboratory of the Railway University Hospital using a ZEISS microscope, Axioscope 2 plus, Achroplan Objective 4x, 10x si 20x, NEOFLUAR plane 40x and APOCHROMAT plane 100x.

Histopathology was also correlated with clinical symptoms and ultrasound results.

Statistics

Indicators

Elements of descriptive statistics were calculated, data being presented based on centrality, location and distribution indicators. The Shapiro-Wilk test was used for normal distribution testing, while for variance F or Levene and/or Bartlett tests were used.

The analysis of three or more samples was done with ANOVA or non-parametric Kruskal-Wallis test. In certain cases the ÷2test, concordance, non-parametric, was used. The threshold of significance was $\alpha=0.05$ (5%). $\alpha=0.01$ (1%) or $\alpha=0.001$.

- $0.01<p<0.05$ – statistically significant difference;
- $0.001<p<0.01$ – strong statistically significant difference;
- $p<0.001$ – highly statistically significant difference;
- $p>0.05$ – statistically insignificant difference;

In order to establish correlation between two continuous quantitative variables with uniform distribution, Bravais-Pearson's correlation test (r) was used.

Statistical processing was with StatsDirect v.2.7.2 package, OpenEpi v.3.03 and Microsoft Excel spreadsheet. The latter was also used for the graphical output of results.

Assessment of the diagnostic test

The test quality was assessed using a contingency table:

- sensitivity (Sn), specificity (Sp)
- positive predictive value (PPV), negative predictive value (NPV)
- accuracy (Acc)
- likelihood ratio (LR)
  - generates big changes, often decisive, between pre- and post-test probabilities
  - generates moderate changes of probability
  - generates small changes of probability
  - generates very small changes of probability

However, in certain cases, the comparison of a new test with a gold standard is impossible. In such cases the comparison may be done against another test, an "imperfect standard", seeing to what extent the two tests yield similar results.

The quality of the test is calculated using a contingency table:

- positive concordance (pC) – equivalent of sensitivity
- negative concordance (nC) – equivalent of specificity
- absolute concordance (aC) – equivalent of accuracy

Results

The statistical analysis of the patients' age, considering all three age groups, evidenced strong statistically significant differences between at least two age groups ($p<0.0001$), while unpaired tests revealed strong statistically significant differences between all groups, taken in pairs ($p<0.0001$). The study of age correlated with the living background, considering all age groups, evidenced strong differences between at least two age groups, both in the urban ($p=3.23$ x 10-24), and rural ($p<0.0001$) environment.

Analyzing the number of pregnancies correlated with the living background, considering all age groups, there were no statistically significant differences between age groups, neither urban ($p=0.0735$) nor rural ($p=0.4852$).

Regarding the patients' number of births, considering all age groups, there were no statistically significant differences between any age groups, and not in the whole group ($p=0.2348$), neither urban ($p=0.0735$) nor rural ($p=0.852$). The types of bleeding were all at endometrial level: menorrhagia (n=16), metrorrhagia (n=57), or menometrorrhagia (n=30).

Scores were given to the degree of bleeding severity: menorrhagia (MN)=1, metrorrhagia (MT)=2, menometrorrhagia (MM)=3.

The statistical analysis of endometrial bleeding severity scores, considering all age groups, there were no statistically significant differences between any age

groups, and not in the whole group, neither by background (p>0.05).

The assessment of severity of the associated risk factors evidenced no associated pathology in 59.22% of the patients. The other patients had liver steatosis (LS), diabetes mellitus (DM), arterial hypertension (AHT) or obesity (OB), either as a single condition (29.13%), or in 2-3 associations (11.65%).

We staged the associated risk factors in relation to their severity in the context of our investigation and the existence of one or several risk factors. The scores associated to risk factors ranged from 1 (no risk factors) to 9 (association considered the highest risk factor). The following scores were given: no RF=1, LS=2, DZ=3, AHT=4, OB=5, AHT+LS=6, OB+AHT=7, OB+DM=8 and OB+AHT+DM=9. Considering all three age groups, statistically significant differences were found between at least two age groups (p=0.029). In relation to the living background no statistically significant differences were found between urban p=0.2469) or rural (p=0.1124).

Taking the age of 50 as "threshold", we attempted to find whether there was a link between the two age groups resulted and the presence of one or several risk factors. The statistical analysis of the study group could not establish a statistically significant relation (p>0.05) in this respect.

The study of the histopathological endometrial type evidenced that 50.49% of patients had secretory, proliferative or atrophic endometrium, physiological changes characteristic of certain periods of the menstrual cycle, while the other 49.51% of the patients presented various pathological alterations of the endometrium (Table I).

In relation to the threshold age of 50, the proliferative endometrium was found in the maximum number of patients of both groups, though there were other major differences between the two age groups, before and after 50 years. The statistical analysis could not establish a significant correlation (p>0.05) between pathological endometrial alterations and the two age groups.

The endometrium thickness (mm) was assessed by ultrasonography in the patients with leiomyoma (n=63), polyp (n=21), adenomyosis (n=12) and EAC (endometrial adenocarcinoma) (n=6) and considering all three age groups no statistically significant differences were found (p=108). Only for unpaired tests there were statistically significant differences regarding endometrial thickness in patients with leiomyoma vs. EAC, and in those with polyp vs. EAC (p<0.05) (Figure 1).

Table I. Type of endometrium in the study patients.

Type	Total			40-44 yrs			45-49 yrs			≥ 50 yrs		
	U	**R**	**Total**	**U**	**R**	**Total**	**U**	**R**	**Total**	**U**	**R**	**Total**
Secretory	10	2	**12**	1	0	**1**	4	2	**6**	5	0	**5**
Proliferative	20	17	**37**	3	2	**5**	1	8	**19**	6	7	**13**
Atrophic	2	1	**3**	0	0	**0**	1	1	**2**	1	0	**1**
Adenomyosis	3	1	**4**	0	0	**0**	0	1	**1**	3	0	**3**
Adenocarcinoma	1	0	**1**	0	0	**0**	0	0	**0**	1	0	**1**
Endometritis	0	2	**2**	0	2	**2**	0	0	**0**	0	0	**0**
Fibroma	1	1	**2**	0	0	**0**	1	1	**2**	0	0	**0**
Fibroma + polyp	3	3	**6**	0	0	**0**	2	2	**4**	1	1	**2**
Fibroma+squamous metaplasia	2	1	**3**	0	1	**1**	1	0	**1**	1	0	**1**
Simple hyperplasia	8	5	**13**	0	0	**0**	5	4	**9**	3	1	**4**
Complex hyperplasia without atypical features	0	1	**1**	0	0	**0**	0	1	**1**	0	0	**0**
Complex hyperplasia with atypical features	7	3	**10**	0	0	**0**	3	1	**4**	4	2	**6**
Squamous metaplasia	5	0	**5**	0	0	**0**	5	0	**5**	0	0	**0**
Fallopian tube metaplasia	1	1	**2**	0	0	**0**	0	1	**1**	1	0	**1**
Polyp	1	0	**1**	1	0	**1**	0	0	**0**	0	0	**0**
Polyp + tube metaplasia	1	0	**1**	0	0	**0**	0	0	**0**	1	0	**1**

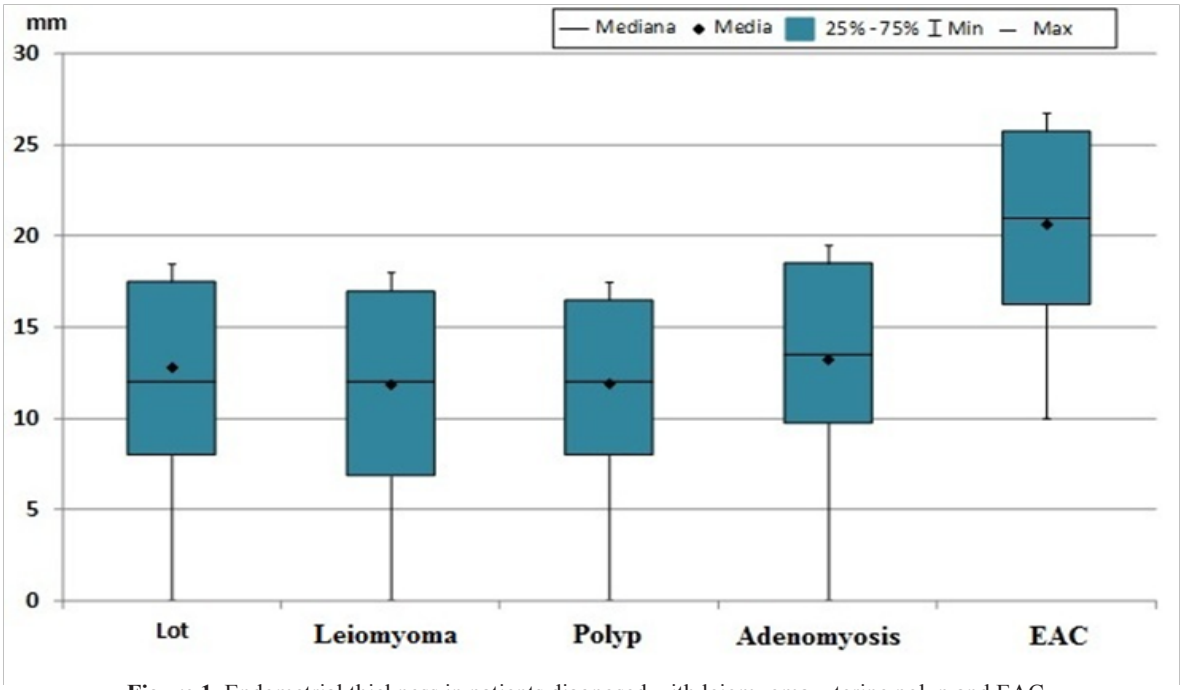

Figure 1. Endometrial thickness in patients diagnosed with leiomyoma, uterine polyp and EAC.

The diagnostic process of these patients included, besides clinical examination (CE), transvaginal US and histopathology (HP). The latter, a certainty diagnosis, was considered the gold standard, while clinical diagnosis and TVUS were considered imperfect standards.

In the case of patients with leiomyoma, the comparison against HP evidenced that TVUS had a better sensitivity (94%) than CE (90%), and also a higher diagnostic accuracy (77.78% vs. 37.5%). The likelihood ratio (LR) was above 1 in the case of TVUS and below 1 for the CE.

In the case of the patients with polyps, TVUS sensitivity was 67%, higher than of CE (48%), and so was diagnostic accuracy (66.67% vs. 47.62%). The likelihood ratio (LR) could not be calculated as the test specificity could not be determined.

In the case of patients with adenomyosis, after comparison with HP, the TVUS sensitivity was smaller (8%) than of CE (25%), and so was diagnostic accuracy (8.33 vs. 25%). The likelihood ration (LR) could not be calculated as the test specificity could not be determined.

In patients with EAC, TVUS sensitivity was 100%, higher than CE (67%), and so was diagnostic accuracy (100% vs. 66.67%). The likelihood ration (LR) could not be calculated as the test specificity could not be determined.

Discussion

Given that perimenopause, clinically manifested by AUB, may be associated with EAC in about 10% of cases [6], each patient should be investigated for risk factors of endometrial neoplasm and should receive an accurate diagnosis based on ultrasonography, histeroscopy and endometrial biopsy [7].

An ideal diagnostic test should be minimally invasive or non-invasive, easy to perform, well accepted and tolerated by the patient, inexpensive and with high sensitivity and specificity [8]. Unfortunately, no one method meets all these criteria, some of them being unacceptable for focal injuries, others being too invasive and not easily accepted by the patients. There is no consensus regarding these methods for the diagnostic evaluation of perimenopausal patients with AUB [9].

The aim of this study was to check the diagnostic performance of TVUS in the diagnosis of endometrial pathology and in the detection and quantification of risk factors of endometrial neoplasia in patients with AUB, all leading to documented clinical and therapeutic decisions. Patient history should be recorded in detail, identifying risk factors of endometrial hyperplasia and EAC [10].

Since there is a considerable number of known risk factors of endometrial neoplasia, they could be grouped in a predictable clinical model in perimenopausal patients with AUB [11].

Older ages may be considered as one of the factors, about 90% of the EAC cases being in women over 50 [12] and only 5% in younger patients under the age of 45. In our study we did not find EAC in patients under the threshold age of 50, all the diagnosed cases being in the group ≥50

years. In accordance with our findings, a recent study by Burbos et al. [13] on a high number of patients under the age of 50 years did not find any case of EAC.

Obesity is the main cause of hyper-estrogenism and is a risk factor for multiple forms of hormone-related cancer [14,15]. EAC is the most frequently associated with obesity, and an increase of 5 kg/sq.m. of the BMI means a higher risk of developing EAC [16,17]. During the perimenopause overweight leads to insulin resistance, excess of ovarian androgens, anovulation and luteal insufficiency [18]. In our study obesity was associated to every case of EAC, determining a significant increase in endometrial thickness, as measured by TVUS.

The co-existing conditions, such as diabetes mellitus, arterial hypertension and liver steatosis are often mentioned in literature as being associated with EAC [19,20]. Some studies have reported diabetes mellitus as a risk factor for EAC in perimenopausal and postmenopausal women [21], while other authors do not confirm this fact [22]. The association of at least two risk factors, such as DM and obesity, was more frequent in our patients with AUB and EAC. In our study DM was found as associated risk factor in 9 patients, AHT in 27, and LS in 5 patients, being often associated with overweight and thus raising the risk factors severity score.

The relation between AHT and endometrial alterations is still unclear. Some studies report AHT and obesity as risk factors, while others have found no correlation between AHT and EAC [23]. In our study we found AHT to be a risk factor in 26.2% of the patients with AUB, but without statistically significant correlation with severe endometrial changes, unless associated with obesity.

A history of fibromas seemed the only condition significantly associated with endometrial alterations in perimenopausal patients with AUB [24]. In our study the presence of fibroma evidenced by ultrasound did not represent a risk factor for premalignant or malignant endometrial injuries.

Regarding clinical manifestations, most of the study patients had metrorhhagia (55.34%), a predominant symptom reported in literature [25]. There was no statisticall significant difference between the AUB severity score and age or number of births.

Transvaginal US represents a valuable method of diagnosing women over the age of 40 [26]. An optimal diagnosis generally requires TVUS, which yields high resolution images [27]. The endometrium thickness in perimenopausal women has a minimal value, the differentiation between endometrial morphological features being impossible in case of hyperplasia or EAC [28]. The optimal threshold value of endometrial thickness, beyond which further investigation is necessary, is still under debate. Thickness over 8 mm confers high sensitivity – 83.6%, but less specificity – 56.4% to TVUS [29], while a thickness over 16 mm confers 67% sensitivity and 75% specificity.

TVUS remains a very reliable diagnostic method, being generally accepted that in perimenopause an endometrium >8 mm raises the suspicion of endometrial damage in patients with AUB [30,31]. Like in our study, other studies also reported a good correlation between TVUS and histopathology.

The likelihood ration (LR) reflects the degree in which a paraclinical method may increase or lower the probability of diagnosing a certain disease. Thus, an increased positiv LR associated with a low negative LR reflects the method performance.

In our study 73 patients had abnormal histopathology findings (EH, EAC) on an average endometrial thickness of 13.03 mm. Also the TVUS accuracy in diagnosing the general causes of AUB, confirmed by pathology, was 63.9% [32], and all the EAC cases were diagnosed (100%); however, it was less accurate in diagnosing adenomyosis (8.33%). Not only endometrial thickness is important in the TVUS assessment, but also changes in texture may indicate endometrial injury. The focal or diffuse heterogeneous aspect evidenced by TVUS requires further investigation [33]. The TVUS sensitivity and specificity in detecting adenomyosis are 53%-89% and 65%-98% respectively [34,35], which is in disagreement with our results.

Dasgupta et al. in a study of 252 patients found a low positive LR (2.8-3.8) for TVUS, and because of the false positive results it was considered low acceptance for the diagnosis of uterine pathology. However, due to the 2.2 negative LR, TVUS may be considered useful for screening, while classical curettage is unacceptable (negative LR 0.46) [36]. According to another study by Bakos [37], TVUS was as precise as D&C in patients with AUB, while Doppler TVUS may detect 76% of abnormal endometrial injuries [38].

A major drawbakc of TVUS is the high rate of false negative results in the diagnosis of focal uterine pathology. The cases evidenced by TVUS with doubtful alterations are then submitted to sono-histerography with saline (SIS) or histeroscopy [39,40]. Related to histopathological aspects, our study found 13 cases of simple hyperplasia (13.39%), in accordance with findings reported by Bombay Hospital and DHQ Hospital in India [41].

Compared to other studies, our results concord, the predominant histopathological pattern being proliferative endometrium.

The metaanalysis of various studies showed that US determination of endometrial thickness and its qualitative assessment (homogenenous / non-homogeneous) is accepted as a predictor for endometrial injury, but limited regarding the histopathological type (EH, polyp, submucosal fibroma), the minimal thickness accepted as normal being 5 mm.

Our results by age groups evidenced the following:

The 40-44 age group included the smallest number

of patients, the majority of urban background, low number of births and early last menstruation; endometrial changes were predominantly proliferative.

The 45-49 age group was the most numerous, high urban incidence, 1-2 births, also presenting proliferative changes.

The age group >50 was characterized by over 3 births, late last menstruation, mostly of urban background.

The relatively small number of patients did not allow for a conclusive statistical processing in order to establish the likelihood ratio (LR). The TVUS examination had a higher sensitivity than the clinical diagnosis in establishing AUB etiology, subsequently confirmed by histopathology

Conclusions

The diagnosis of uterine bleeding is very important in perimenopause, the prognosis and response to therapy directly depending on the histopathological examination of the bioptic sample. The most common cause was represented by fibroma, followed by functional causes. A correlation is obviously established between clinical ultrasound and pathological examinations in the etiological diagnosis of AUB. TV ultrasonography represents a valuable minimally invasive method for first intention screening for endometrial alterations in perimenopausal patients with AUB, especially for excluding endometrial adenocarcinoma.

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