HJOG An Obstetrics and Gynecology International Journal

Research Article

HJOG 2017, 16 (2), 13-22

Comparative study of endometrial imaging and cytologic evaluation in perimenopause for the timely diagnosis of endometrial cancer

Vaitsi V.[1,2,4], Moschaki V.[2,3,4], Chatzistamatiou K.[2,4], Tsertanidou A.[4], Athanatos D.[1], Athanasiou E.[5], Loufopoulos A.[2], Tarlatzis B.[1], Agorastos T.[4]

[1] 1st Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Papageorgiou Hospital, Thessaloniki, Greece

[2] 2nd Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Hippokratio Hospital, Thessaloniki, Greece

[3] 3rd Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Hippokratio Hospital, Thessaloniki, Greece

[4] 4th Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Hippokratio Hospital, Thessaloniki, Greece

[5] Laboratory of Cytology, Papageorgiou Hospital, Thessaloniki, Greece

Correspondence

Kimon Chatzistamatiou, 27 Tsimiski st, 54624, Thessaloniki, Greece Tel: 0030 6973321162, E - mail: kimon.chatzistamatiou@gmail.com

Abstract

Introduction: The aim of the present study was to determine the diagnostic accuracy of sono - hysterography alone or combined with liquid-based cytology (LBC) of endometrium for endometrial lesions detection in perimenopausal women with abnormal uterine bleeding (AUB). **Material and Methods:** Eighty - one perimenopausal women with AUB were recruited. Each woman underwent transvaginal sonography (TVS), sono - hysterography, LBC and histologic endometrial examination. The ndings of TVS and sono - hysterography, were compared with histology. Furthermore, the combined ndings of sono - hysterography and LBC were assessed in comparison to histology concerning diagnostic accuracy for detecting endometrial cancer. **Results:** TVS versus sono - hysterography presented endometrial thickening without other lesions, focal, and di use lesions in 71.6% versus 54.3%, 19.7% versus 32% and 6.2% versus 9.9% respectively. Endometrial cancer, both for TVS and sono - hysterography, was associated with increased endometrial thickness with di use lesions of mixed echogenicity (p= 0.013, p= 0.003 respectively). Sensitivity, speci city and positive predictive value (PPV) of LBC for endometrial cancer was 100%, 92.3%, and 63.6% respectively. The combination of LBC and sono - hysterography increased speci city and PPV for cancer detection to 100%. **Conclusion:** Sono - hysterography presented better diagnostic accuracy than TVS for detecting endometrial lesions. The combination of sono - hysterography and LBC increased diagnostic accuracy for cancer detection.

Key words: endometrial cancer; sonohysterography; transvaginal ultrasound; endometrial cytology

Introduction

World Health Organization (WHO) has determined perimenopause as the period between 2 to 8 years before menopause and a year after the last menstruation. Quite a few women during this period present with abnormal uterine bleeding (AUB)[1]. During perimenopause the menstrual cycle changes by loosing its periodical occurrence[2]. Women can present with any of the probable manifestations of uterine bleeding, mainly caused by anovulation. It is also known, that during this period the occurrence of endometrial cancer is more common[2].

The diagnostic evaluation of women with AUB in the perimenopausal period is mainly based on the transvaginal sonography (TVS), which is the most common non - invasive method in order to detect abnormalities of the uterus and ovaries. In a meta-analysis of studies on women with perimenopausal bleeding, it was confirmed that TVS using measuring of endometrial thickness (>5mm) could detect endometrial cancer with a sensitivity of 96% and also could distinguish abnormalities of the endometrium such as atypical hyperplasia, polyps or cancer with 92% sensitivity and 92% specificity in women without hormonal replacement therapy (HRT). In case of HRT specificity was reduced to 77%[3].

A relatively new method in comparison to TVS, is sonohysterography (SHG), a method during which saline is infused in the uterine cavity in order to improve the accuracy of endometrial imaging with TVS. This technique was first used by Deichert[4]. Since then many research groups used it in order to detect lesions of the uterine cavity and to determine proper fallopian tube function in infertile women. Other tests that can be performed on endometrium are cytology and biopsy of endometrial tissue taken during hysteroscopy or curettage[5].

The aim of the present prospective study, is to identify the diagnostic accuracy of SHG combined with liquid based endometrial cytology (LBC), in comparison to endometrial biopsy, for the detection of focal and diffuse lesions in perimenopausal women with AUB, and also to investigate the distinctive capacity and reliability of the combination of these methods for the detection of endometrial cancer.

Material and methods

Study protocol

The presented prospective study was conducted at the 1st Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, "Papageorgiou" University Hospital, Thessaloniki, Greece. Women recruited were perimenopausal Indo - European, in good health who hadn't received HRT for at least the last 6 months, with normal coagulation tests and normal cervical cytology and reported AUB. The aim and method of the study was explained to all women and their informed consent was given prior to recruitment.

After a detailed history of each patient, and the exclusion of pregnancy, a clinical and ultrasound examination was performed. Then, each woman was subjected to sonohysterography (SHG), endometrial sampling for cytologic endometrial evaluation using LBC, and, finally, dilatation and curettage (D&C) followed by endometrial histological assessment. The exclusion criteria for the participation of women were apart from pregnancy, pelvic infection and persistent cervical stenosis.

Ethics

The research protocol was conducted according to the principles as have set forth by the Helsinki Declaration of 1975. The study protocol was approved by the bioethics Committee of the Aristotle University of Thessaloniki, Greece

Ultrasound examination

All women participating in the study had a TVS ex- amination after bladder evacuation and prior to SHG. Focal or diffuse lesions of the myometrium and endometrium, such as increased thickness of the endometrium, polyps, leiomyomas, hyper - or hypo - echogenic areas were recorded.

TVS Technique

The ultrasound equipment used was General Electric Pro 200 with a 7.5 MHz probe. Initially, a sagittal and a transverse imaging of the endometrium as a whole was obtained and the thickness of the endometrium was measured using the thicker part on the sagittal plane. The endometrial thickness was estimated as the thicker part of the double layer and any hypo - echogenic areola was excluded. At least three measurements were made and the average was calculated. This procedure was followed by the overall evaluation of the uterus so that focal or diffuse lesions could be detected. The ultrasound images were digitally recorded in DICOM format, in pixel depth 8 bits and pixel size 768x576 and stored on optical disc.

SHG technique

For SHG, a special COOK silicone balloon catheter (COOK ob/GYN 1100 West Morgan Street, Spencer IN 47460 USA) was used. The catheter has a double canal and is made of polyurethane. The canal ends up to an open edge and is used for the infu- sion of liquid inside the uterine cavity, so that it can be distended. The second canal is closed and has at its end a small balloon made of silicone. The spout of this balloon - canal, to which a syringe with sa- line is adjusted, has a special valve so that saline that is infused cannot be poured out. The diameter of the catheter is small, just 5.0 Fr and its length is 30 cm which allows it to pass through the endocervical canal.

For SHG, the patient was placed in dorsal lithotomy position so that disinfection and a suitable vaginal exposure (with a vaginal speculum) could be achieved. Then the COOK silicone balloon catheter was advanced into the uterine cavity through the endocervical canal and filled with normal saline. Afterwards the vaginal speculum was removed. If the lesion that should be examined was located near the internal cervical os, the balloon was filled inside the endocervix. This variation of the technique usually caused pain and inconvenience to the patient. Therefore in all these cases an analgesic was provided to the patients before the examination. Technical difficulties were observed in cases with dorsal flexion of the uterus. In these cases a proper traction of the cervix was made using a single - tooth tenaculum.

The vaginal probe was placed along with a 20ml syringe adjusted to the free edge of the catheter, containing saline that was already warmed up. In order to avoid artifacts, the prefilling of the catheter with saline was necessary. Then 15 - 20ml was infused in the uterine cavity prior to scanning.

Liquid based cytology

For endometrial cytologic evaluation the LBC method was used. Sampling was performed using a TAO brush (COOK urological INC. COOK OB/GYN, Indiana, USA) which consists of a stainless steely shaft, 20cm long, a nylon brush, a plastic grip, with reference index and a vinyl cap 9.0 Fr 16 cm long and is a certified device, suitable for taking endometrial cells (www.cookmedical.com).

The brush was used according to the manufacturer's instructions. After sampling the brush was placed in cell - preserving liquid (Cytorich, COOK OB GYN) and the sample was evaluated in terms of cytology by a specialized cytologist.

Endometrial biopsy

The final diagnosis of the cause of the AUB was set by endometrial biopsy. The method of dilatation

and curettage (D&C) was used for endometrial tissue sampling. The sample was placed into formaldehyde solution and sent for histological examination by experienced histopathologists.

Statistical analysis

Descriptive statistics was applied. For quantitative variables, measures of central trend (mean, median) and measures of dispersion [standard de- viation (SD), Interquartile range (IQR)] were estimated, while for the qualitative variables, frequencies in the form of absolute values and percentages were calculated.

The Kolmogorov - Smirnov test was used for the assessment of the normality of the distribution for quantitative variables (due to n <50). Normally distributed, were described by the median, the IQR and range. In order to compare the quantitative variables between two different groups, the Student's t- test was used for variables with normal distribution and the Mann - Whitney test was used for variables that were not distributed normally.

For the comparison between qualitative variables, the x2 test was used. The level of statistical significance was p <0.05.

Results

Eighty - one peri - menopausal women with average age of 44 years (40 - 58) were recruited. AUB was the main symptom in 70 women (86.4%). Sixty two women had continuous bleeding (76.5%), while 19 women had intermittent bleeding (23.5%).

The average bleeding duration was 10 days (1 - 31 days). Gynecological personal history was free from disease for 7 women (8.6%), 66 women reported AUB for the last two years (81.5%), 3 women had polyps (3.7%), 2 women had endometrial hyperplasia (2.5%) and 3 women had leiomyomas (3.7%). According to the medical personal history of these patients, 64 women didn't have any other diseases (79.0%), 9 had hypothyroidism (11.1%), 2 women had rheumatoid arthritis and osteoporo- sis (2.5%), 2 had obesity and hypertension (meta- bolic syndrome) (2.5%) and 1 woman had hydro- nephrosis (1.2%). Table 1 presents most important demographic data of these patients.

TVS

Fifty eight out of 81 women (71.6%) had increased endometrial thickness, without obvious lesions within the endometrium, 16 women (19.7%) had focal lesions [endometrial, subendometrial (submucosal) or defective imaging of the uterine cavity] and 5 women (6.2%) had diffuse lesions. Moreover, considerably increased thickness of the endometrium (> 10mm) without focal abnormalities was reported for 34 women (42%). Regarding the de- tection of focal lesions, 7 out of 16 women (8.6%) had submucosal lesions that protruded in the uter- ine

Table 1. Demographic characteristics of the women participating in the study

Demographics	**Total n=81**
Age (median - range)	44 years (40-58)
Symptoms	
Continuous bleeding	62 (76.5%)
Intermittent bleeding	19 (23.5%)
Bleeding duration (mean - range)	10 days (10 - 31)
Gynecological history	
Endometrial hyperplasia	2 (2.5%)
Menstrual cycle irregularities66 (81.5%)	
Polyps	3 (3.7%)
Leiomyomas	3 (3.7%)
Unremarkable	7 (8.6%)
General medical history	
Hypothyroidism	9 (11.1%)
Hashimoto's thyroiditis	3 (3.7%)
Rheymatoid arthritis	2 (2.5%)
Metabolic syndrome	2 (2.5%)
Hydronephrosis	1 (1.2%)
Unremarkable	64 (79%)

cavity (probable leiomyomas). The presence of focal endometrial lesions (probable polyps) was detected in another 7 women (8.6%), and inconclusive imaging of the uterine cavity due to leiomyomas was reported for the rest 2 (2.5%). Finally, the echogenicity of the lesions was homogenous in 71 women (87.7%) and heterogeneous in 10 (12.3%) (Table 2).

Table 2. Findings from the evaluation of the patients participating in the study with the two different imaging procedures examined, i.e. TVS and SHG

	TVS		SHG	
Abnormal findings	**N**	**%**	**N**	**%**
Submucosal lesions	7	8.6	8	9.9
Endometrial lesions	7	8.6	16	19.8
Inadequate imaging of the endometrial Cavity	2	2.5	2	2.5
Increased endometrial thickness with diffuse lesions	5	6.2	8	9.9
Evenly Increased endometrial thickness without lesions	58	71.6	44	54.3
Unevenly Increased endometrial thickness without lesions	2	2.5	3	3.7
Total	81	100	81	100

N= number of patients, TVS: Transvaginal Sonography, SHG: Sono - hysterography

SHG

SHG evaluation of the uterine cavity revealed no abnormalities in 44 women (54.3%) while focal lesions were observed in 26 (32%) and increased endometrial thickness with diffuse lesions was reported for 8 women (9.9%). Considerably increased thickness of the endometrium (> 10mm) was reported for 24 women (38.7%). Focal lesions reported were: submucosal lesions (probable leiomyomas) in 8 cases (9.9%), endometrial lesions (probable polyps) in 16 cases (19.8%) and finally there were 2 cases (2.5%) with inconclusive imaging of the uterine cavity. The echogenicity of the lesions was homogenous in 67 women (82.7%) and heterogeneous in 14 women (17.3%) (Table 2).

Cytological evaluation

The cytological evaluation on the 81 women enrolled resulted in 7 cases of women with cytology sample suspicious for malignancy. Endometrial cells, in all these cases, were reported to have atypia. In cases of simple hyperplasia the main finding was medium grade cellularity along with an increase in stromal cells, while in complex hyperplasia the cytological examination revealed mixed findings (Table 3).

Histopathology results

Hyperplasia was detected in 14 women (17.3%). Simple hyperplasia was found in 3 women (3.7%), complex hyperplasia in 8 (9.9%) and atypical hyperplasia in 3 (3.7%). Focal lesions such as polyps were identified in 19 women (23.4%). Abnormalendometrial maturation was observed in 59 women (67.9%). From this group, 42 women (52.5%) presented with no other finding, and 18 women (22.2%) with polyps. Finally, 7 women (8.6%) were diagnosed with endometrial carcinoma, 6 cases of endometrioid carcinoma and one case of papillary adenocarcinoma with squamous differentiation (G1 - G2) (Tables 3 and 4).

Comparison of the different endometrium assessment methods for the diagnosis of endometrial cancer

According to histology 7 women were diagnosed

Table 3. TVS, SHG and cytology reports concerning the seven cases with endometrial cancer identified during the study

Carcinoma cases	TVS*	SHG	Diffuse lesion*	Cytology
1. Adenocarcinoma	Significantly increased endometrial thickness with hypo and hyper - echogenic areas	Significantly increased endometrial thickness with hypo and hyper echogenic areas	Yes/Yes	Endometrial cells with abnormal orientation possible malignancy
2. Endometrioid adenocarcinoma	Significantly increased endometrial thickness with hypo echogenic areas	Significantly increased endometrial thickness with hypo echogenic areas	Yes/Yes	Endometrial cells with abnormal orientation possible malignancy
3. Adenocarcinoma	Significantly increased endometrial thickness with hypo echogenic areas	Significantly increased endometrial thickness with hypo and hyper echogenic areas	Yes/Yes	Endometrial cells with abnormal orientation possible malignancy
4. Endometrioid adenocarcinoma	Significantly increased endometrial thickness with hypo and hyper echogenic areas	Significantly increased endometrial thickness with hypo and hyper echogenic areas	Yes/Yes	Endometrial cells with abnormal orientation possible malignancy
5. Papillary adenocarcinoma	Significantly increased endometrial thickness with hypo echogenic areas	Significantly increased endometrial thickness with hypo and hyper areas	No/Yes	Endometrial cells with abnormal orientation possible malignancy
6. Well-differentiated adenocarcinoma	Significantly increased endometrial thickness with hypo and hyper areas	Significantly increased endometrial thickness with hypo and hyper areas	Yes/Yes	Endometrial cells with abnormal orientation possible malignancy
7. Moderately-differentiated adenocarcinoma	Significantly increased endometrial thickness with hypo echogenic areas	Significantly increased endometrial thickness with hypo echogenic areas	No/Yes	Endometrial cells with abnormal orientation possible malignancy

TVS: Transvaginal Sonography, SHG: Sono - hysterography.

* The column shows whether diffuse lesions were visible using TVS/SHG respectively

with endometrial cancer. The mean age of these women was 46 years (42 - 51), while the mean age of the women without malignancy was 47.5 years (40 - 58) ($p > 0.05$). The majority of women with malignancy reported prolonged uterine bleeding as the main symptom (6/7). None of these women reported intermittent bleeding as the main symptom. Regarding the duration of the symptoms, the average duration of the bleeding in women with malignancy was 11 days (4 - 19), while in women with- out malignancy was 10 days (11 - 31).

Regarding personal history of women with malignancy, a significant percentage 57.1% (4/7) had nothing to report, while 28.5% (3/7) had hypothy- roidism. The majority of these women 71.4% (5/7) reported abnormal menstrual bleeding during the last 5 years, one reported endometrial hyperplasia (14.2%) and the last one had nothing to report (Table 3).

Concerning TVS and SHG findings it was shown that the detection of diffuse lesions, of mixed - heterogeneous echogenicity, accompanied with increased endometrial thickness were statistically re-

Table 4. Findings from the evaluation of the patients participating in the study according to their histopathological findings

Abnormal findings	N	%
Abnormal endometrial maturation without other lesions	42	52.5
Abnormal endometrial maturation with polyps	18	22.2
Endometrial hyperplasia (including one case with polyps)	14	17.3
Simle hyperplasia	3	3.7
Complex hyperplasia	8	9.9
Atypical hyperplasia	3	3.7
Carcinoma	7	8.6
Total	81	100

lated to endometrial cancer diagnosis (p= 0.013 and p= 0.003 respectively). On the other hand, increased endometrial thickness (>10mm) without other sonographic findings was not associated to cancer (p> 0.05).

Endometrial LBC was indicative of cancer as it is shown in Table 3. Specifically, in all cases of endometrial cancer, and only in these cases, the cyto- logic evaluation raised suspicions for malignancy. Sensitivity of cytological examination for the diag- nosis of endometrial cancer was 100% and spec- ificity was 92,3%, while positive predictive value (PPV) was 63,6%. Moreover, the diagnostic accu- racy was increased if SHG was combined with cy- tology for the diagnosis of endometrial cancer and in that case the specificity and the PPV approached 100%.

Discussion

AUB is a common symptom in perimenopausal women[6]. Epidemiological studies show that 33% of women visiting an outpatient gynecology clinic worldwide and 69% of women in menopause report as prominent symptom uterine bleeding[7-9]. The causes of AUB include a broad spectrum of endometrial pathology ranging from functional irregularities of the endometrium to endometrial cancer[7-9]. It is estimated that the cause of AUB in 5 - 15% of perimenopausal women is endometrial cancer[10]. Moreover, it is reported that abnormal endometrium is strongly related to its thick- ness assessed during TVS. Endometrial thickness larger than 5mm is associated to focal endometrial lesions in 80% of women with postmenopausal uterine bleeding[11].

Consequently, the diagnostic assessment in cases with AUB in the perimenopause, is of great importance. Until today, the diagnostic method mainly used is hysteroscopy combined with direct biopsy. However, this is an invasive and expensive method. For these reasons it could be advocated that it should not be used in all cases of AUB but only in cases of suspected uterine pathology. The second most reliable method is D&C. This method combined with histological assessment has been widely used in Greece because of its low cost compared to hysteroscopy. The diagnostic accuracy of D&C is optimal (94%) in patients without focal lesions, however, in case of such lesions D&C is inferior to hysteroscopy since it fails to remove (up to 58%) focal lesions such as polyps[12].

Regarding the rest available diagnostic modalities, TVS is the most important in case of AUB. It is a simple, noninvasive method with increased accuracy regarding endometrial imaging but cannot easily detect small or focal endometrial lesions. On the contrary, this limitation is less important in case of SHG, which can detect focal as well as diffuse lesions of the endometrium. During the last years

there have been significant reports on the possibility that SHG could be used as a triage method for perimenopausal women with uterine bleeding due to the following reasons[10, 11, 13 - 19]:

1. Better contrast inside the uterine cavity.
2. Highly safe, tolerable by patients, easy to perform.
3. Real time noninvasive method.
4. Can be combined with other diagnostic methods.

In the presented study the abovementioned modalities were compared as methods of diagnostic accuracy for endometrial abnormalities. SHG was well tolerated and easy to perform. All of the 81 women who participated were able to complete the examination. However, under certain circumstances like stenosis of the cervix and extreme obesity, the examination cannot be successfully completed[20]. Stenosis of the cervix in fact seems to be the most common factor for unsuccessful examination accounting for 14.9% of such cases[17]. A recent study by Allison et al reports that there are ways to improve acceptability of the procedure including the correct position of the body during the ex- amination. It is also mentioned that pain or patient discomfort leading to unsuccessful SHG examination can be caused by pathological problems such as pelvic inflammatory disease[21]. The method, in general, is also safe, however, complications such as endometrial injury, bleeding and infection have been reported[10 - 19]. Concerning the presented study no complications were observed.

Simple TVS is widely used for the initial evalua- tion of AUB and is considered to be reliable in cases of perimenopausal women. The diagnostic accuracy varies significantly. The sensitivity of the method is 87% (24 - 96%) and the specificity 82% (29 - 93%)[19,24,25]. A recent study reports that sen- sitivity, specificity, positive and negative predictive value of the method is 71.4%, 67.7%, 54.4% and 81.5% respectively[28]. Although TVS is widely used there are certain drawbacks of the technique like the lack of the ability to detect small endometrial lesions or lesions iso - echogenic to the endometrium and to distinguish diffuse endometrial lesions from normal endometrium[28 - 29]. On the other hand, during SHG it is much easier to detect small lesions and to distinguish focal from diffuse endometrial lesions. According to the literature the sensitivity, and specificity of SHG is 85 - 91%, and 83 - 100% respectively[18,19,30]. The positive and negative pre- dictive value has been reported to be 86.7% and 94.5% respectively for the diagnosis of lesions of the uterine cavity[30].

The contribution of SHG in case of endometrial cancer is quite important. In our study it detected the presence of diffuse lesions of endometrium in all 7 cases of cancer, while TVS in 5 of them.

Both methods, of course, cannot substitute histologic evaluation, but they can determine women at greater risk for endometrial cancer who could benefit from more thorough investigation. In both methods the presence of cancer was related to the presence of the diffuse lesions.

Finally, the present study attempted to evaluate the diagnostic accuracy of the combination of SHG and cytology for the diagnosis of endometrial cancer. It was observed that the specificity and the PPV reached 100%. Although cytology alone presents relatively high sensitivity and specificity, the combination of the methods reduces furthermore the possibility of false positive or negative results.

Conclusions

In conclusion, SHG is an alternative to TVS for the evaluation of perimenopausal women with AUB. SHG surpasses TVS mainly concerning the iden- tification of focal and diffuse lesions of the endometrium as well as of submucosal structures. It is also safe and cheap without significant complications. However, it should be underlined that SHG cannot substitute histology, but it can be used in combination with en-

dometrial cytology as triage method for referring women with AUB to a more invasive method that can provide histological assessment.

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Received 12-4-2017
Revised 26-4-2017
Accepted 10-5-2017