Office Hysteroscopy and Power Doppler Sonography using the International Endometrial Tumor Analysis Group Nomenclature in the Evaluation of Postmenopausal Bleeding

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Abstract: To evaluate the role of office hysteroscopy and power Doppler sonography of the endometrium via the international endometrial tumor analysis group nomenclature in the assessment of postmenopausal bleeding and compare their findings with histopathological examination. One hundred females with postmenopausal bleeding underwent the following, grey scale ultrasound to assess endometrial thickness and echogenicity, power Doppler sonography to assess vascular patterns and office hysteroscopy with biopsy for histopathological diagnosis. The results indicated that Endometrial thickness and endometrial echogenicity showed significant difference between pathologies. In power Doppler analysis, there was a significant relation between the single dominant with or without branching pattern and endometrial polyps; multiple vessels with multifocal origin at myometrial endometrial junction pattern was greatly detected in atrophic cases with statistically significant relationship; scattered pattern showed an apparent relation with endometrial hyperplasia; while circular pattern had an exclusive significant relation with myomas. Hysteroscopic findings were also significantly related to the pathological diagnoses. It can be concluded that Power Doppler sonography with the proposed terminology is a valuable non-invasive tool in assessment and diagnosis of endometrial pathology in postmenopausal cases. The utilization of standardization of nomenclature between sonographers would allow more consistent communication, better lesion-description and aid further studies on this technology.

Key words: Abnormal uterine bleeding colour Doppler · Histopathology · IETA group · Office hysteroscopy · Power Doppler

INTRODUCTION

Abnormal uterine bleeding (AUB) is the most common problem which brings the woman to a gynecologist during the postmenopausal period [1]. Most women with postmenopausal bleeding have no organic cause. Dilatation and curettage was utilized as the ''gold standard'' for differentiating between normal and abnormal endometrium, however lately hysteroscopic guided biopsy is considered the new gold standard for diagnosing endometrial pathology, as dilatation and curettage had a great number of false negative diagnosis ranging between 2% and 10%, mainly as a result of being a blind technique [2,3]. Hysteroscopy has become of increasing importance in the diagnosis of AUB, because of its clinical applicability, suitability as an out-patient procedure, lack of need for anaesthesia in cases of office hysteroscopy and the reduction of costs compared with dilatation and curettage [4, 5]. Recently, colour and power Doppler images were utilized to diagnose endometrial pathologies. Power Doppler sonography (PDS) is rather a novel technique that can demonstrate the vasculature of

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a lesion based on the amplitude of the Doppler signal but not on the Doppler frequency shift. The frequency is determined by the velocity of the red blood cells, while the power depends on the amount of blood present. It is not reliant on the insonation angle and is perceptive of low-velocity blood vessels. It can depict flow which was previously undetectable and thus permits an easier and more confident diagnosis where the ultrasound signal is weak because blood vessels are small. It might be valuable in diagnosing endometrial pathology and assist gynaecologists in choosing the most appropriate invasive method to proceed with if needed [6].

Comparing results of different studies on endometrial sonography is difficult, as each study group use their own terminology when analyzing the sonographic features they detect. The International endometrial tumor analysis group (IETA) described the sonographic features of the endometrium to make a consensus on terms and definitions on ultrasound findings. They described transvaginal scan of the endometrium and uterine cavity. First using unenhanced ultrasound examination, assessing endometrial thickness, echogenicity, endometrial midline, the interface between intracavitary lesion and the endometrium, the endometrial-myometrial junction, synechia and intracavitary fluid. Then color and power Doppler assessment, the color score was described as a score 1 (no color flow) to 4 (abundant color). The vascular patterns on PDS they described were as follows: single dominant vessel without branching, with branching, multiple vessels with focal origin, with multifocal origin at the myometrial–endometrial junction, scattered vessels and circular flow. Then they used enhanced ultrasound examination which involved assessing the cavity with either sonohysterography or pre-existing fluid in the cavity [7].

The present work aimed to assess whether PDS is as accurate as hysteroscopy with biopsy to diagnose intrauterine lesions. The endometrium of 100 cases with postmenopausal bleeding was studied by several modalities including 2D transvaginal ultrasonography, transvaginal power Doppler, using the IETA group nomenclature and office hysteroscopy with biopsy.

MATERIALS AND METHODS

This was a cross-sectional study conducted in Cairo University hospitals from June 2013 to December 2014. Approval of the institutional review board of Cairo University was obtained before conducting this study. All included women were informed clearly about the aim of the study, the required procedures and the follow up plan and they gave a written informed consent before inclusion. The study included 100 patients complaining of postmenopausal bleeding. Postmenopausal bleeding was defined as vaginal bleeding that occurred after at least 12 months of amenorrhea. Exclusion criteria included any history of hormone administration in the last 6 months, any medical condition that might cause abnormal uterine bleeding like coagulation disorders, hypertension, cardiac disease, thyroid disorders or hepatic condition. All patients underwent full history taking, physical examination and laboratory tests in the form of complete blood picture, liver and kidney function tests, & coagulation profile (PT, PC and INR).

This was followed by 2D grey scale ultrasound to assess endometrial thickness and echogenicity (whether the endometrium is uniform or non-uniform). Endometrial PDS was then done using a GE Voluson 730 Expert ultrasound system (GE Healthcare, Zipf, Austria) with transvaginal 5- to 9-MHz volume transducer and the features were classified using the six different vascular patterns described by IETA group including; single dominant vessel without branching, with branching, multiple vessels with focal origin, with multifocal origin at the myometrium–endometrium junction, scattered vessels or circular flow [6]. The 2D grey scale and PDS was done by the first author to nullify inter-observer bias. All patients then had Office hysteroscopy carried out in the outpatient clinic using vaginoscopic approach [8]. The hysteroscopy used was *Karl Storz (Germany)*. It is a rigid continuous flow panoramic hysteroscopy by 25 cm in length, 4 mm diameter of an outer sheath and 30° fiberoptic lens. The light source used was a metal halide automatic light source from *Circon Acmi G71A/ Germany* with a 150 Watt lamp. A fibroptic cable is connected to the light source and to the hysteroscope.

Attaching plastic bags of saline solution was used to provide constant uterine distention and the infusion pressure was kept at 100-120 mmHG by pneumatic cuff under manometric control. The procedure was recorded using a single video clip and the image was shown on a monitor seen by the operator. The camera was *Karl Storz Germany* with a focal length varying from f 70 to f 140. Office hysteroscopy was done to visualize the uterine cavity and endometrial biopsy of focal areas of pathologic endometrium was done and sent for histopathological

study. If no areas of pathologic endometrium were seen, five biopsy specimens of tissue were obtained from the endometrium for histopathological examination [9]. Finally, endometrial samples were fixed in neutral formalin and later embedded in paraffin for histological analysis. The office hysteroscopy was done by two operators having the same experience and training (Ayman A Hassan and Hisham M Haggag) and videos was checked by both and consensus on diagnoses was recorded.

The 2D grey scale ultrasound and PDS were first done and data recorded, then the office hysteroscopy was done and result recorded. The biopsies were then sent for pathology and the result returned after 4 days. Authors were not allowed to change any recorded data according to the histopathological result. So they were chronologically blinded to the histopathological diagnosis. Pre-coded data was entered into the Statistical Package of Social Science Software program, version 21 (SPSS) to be statistically analyzed. Data was summarized using mean and standard deviation for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using Mann Whitney test and Kruskal Wallis test for quantitative variables and Chi square and Fisher's exact test for qualitative ones. Sensitivity, Specificity, positive predictive value, negative predictive value and accuracy were calculated for all procedures.

RESULTS

Two hundred and forty women with postmenopausal bleeding were invited to enrol in the study, 25 refused for fear from the office hysteroscopy procedure; 28 had used hormone therapy in the past 6 months; 76 were hypertensive, 5 had a hepatic disorder, 3 had a coagulation disorder associated with a hepatic disease, 2 were on thyroid disorder medication and 1 was cardiac. This resulted in a total of 140 patients excluded from the study (the 87 excluded due to medical disorders were managed normally according to their case and hospital protocols), leaving 100 postmenopausal women who proceeded with the study and their data was analysed. The mean age of the studied group was 54.3±3 and their average age of menopause was 50.3±2.6. The histopathological diagnoses were as follows: atrophy 45 cases (45%), endometrial carcinoma 4 cases (4%), endometritis 2 cases (2%), endometrial hyperplasia 18 cases (18%), myoma 8 cases (8%) and endometrial polyp 23 cases (23%). The mean endometrial thickness of the patients was 7.6±4.7 mm, 45 (45%) patients had uniform endometrium, whereas 55 (55%) had non-uniform echogenicity. Table 1 and 2 show the different endometrial thickness and endometrial echogenicity according to the diagnosed pathologies, they show significant between different pathologies.

Table 1: Endometrial thicknesses on gray scale sonography in different pathologies

Pathology	Endometrial thickness (mm)	P value
Atrophy (n=45)	4.1 ± 1.6	<0.001[a]
Carcinoma (n=4)	16.8 ± 10.8	
Endometritis (n=2)	3.0 ± 0.0	
Hyperplasia (n=18)	9.7 ± 2.6	
Myoma (n=8)	7.1 ± 3.9	
Polyp (n=23)	11.7 ± 2.7	

[a]P value <0.05 is considered statistically significant, all values presented as mean and standard deviation. P value calculated by Kruskal Wallis test.

Table 2: Endometrial echogenicity in different pathologies

Pathology	Endometrial echogenicity (n)		P value
	Uniform	Non-uniform	
Atrophy	28	17	0.003[a]
Carcinoma	1	3	
Endometritis	2	0	
Hyperplasia	2	16	
Myoma	2	6	
Polyp	10	13	

[a]P value < 0.05 is considered statistically significant. P value calculated by Chi square test.

Table 3: The relationship between hysteroscopic findings and pathological diagnoses

Hysteroscope	Endometrial pathology (n)						P value
	Atrophy	Carcinoma	Endometritis	Hyperplasia	Myoma	Polyp	
Atrophy	40	1	2	1	0	0	<0.001[a]
Carcinoma	0	3	0	0	0	0	<0.001[a]
Hyperplasia	5	0	0	17	0	0	<0.001[a]
Myoma	0	0	0	0	7	3	<0.001[a]
Polyp	0	0	0	0	1	20	<0.001[a]

[a]P value < 0.05 is considered statistically significant. P value calculated by Chi square test.

Table 4: The sensitivity, specificity, PPV, NPV and accuracy of hysteroscopy to detect different pathologic findings

Pathology	Sensitivity	Specificity	PPV	NPV	Accuracy
Atrophy	88.9%	92.7%	90.9%	91.1%	91.0%
Carcinoma	75.0%	100.0%	100.0%	99.0%	99.0%
Endometritis	0.0%	100.0%	--	98.0%	98.0%
Hyperplasia	94.4%	93.9%	77.3%	98.7%	94.0%
Myoma	87.5%	96.7%	70.0%	98.9%	96.0%
Polyp	87.0%	98.7%	95.2%	96.2%	96.0%

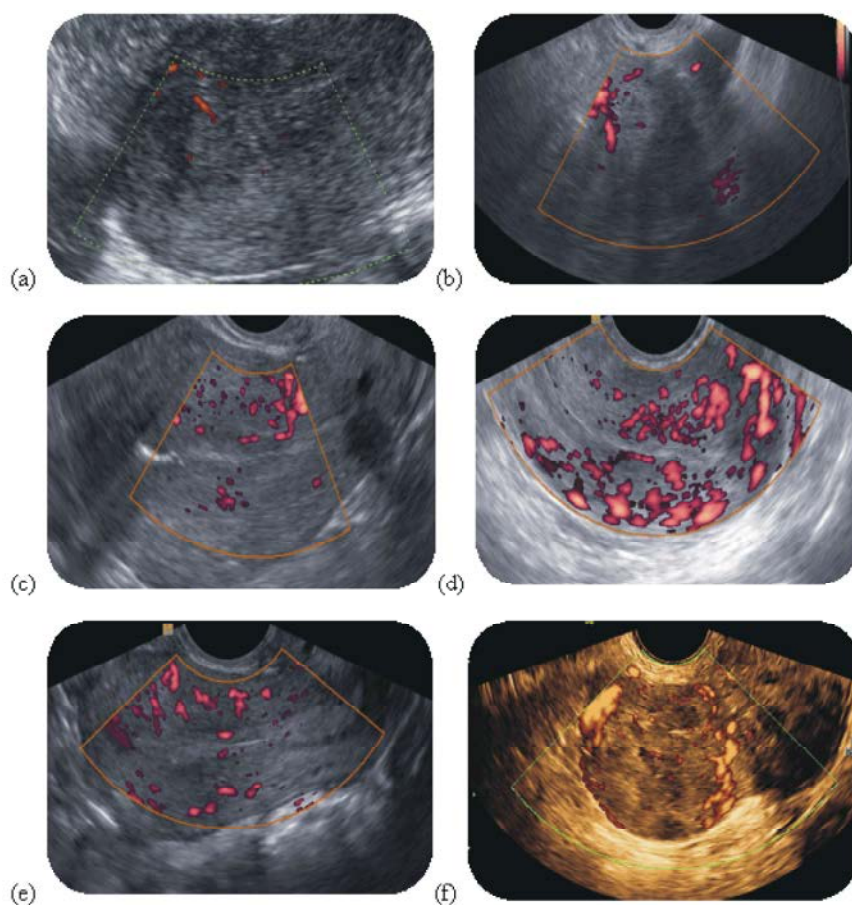NPV: negative predictive value; PPV: positive predictive value

Fig. 1: Power Doppler sonography vascular patterns according to IETA group: (a) Single dominant vessel without branching (endometrial polyp) (b) Branching single dominant vessel (endometrial polyp) (c) Multiple vessels with focal origin (endometrial atrophy) (d) Multiple vessels with multifocal origin at myometrial-endometrial junction (endometrial atrophy) (e) Scattered pattern (endometrial hyperplasia) (f) Circular pattern (submucous to interstitial myoma)
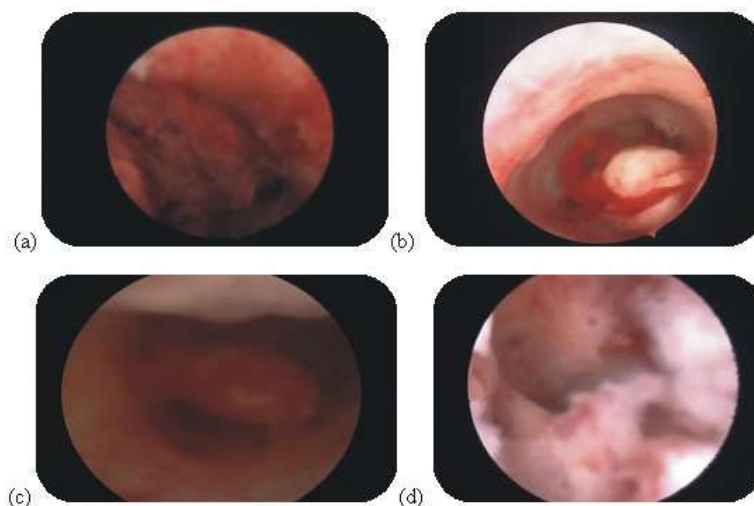
Fig. 2: Hysteroscopic picture suggestive of (a) carcinoma (b) submucous myoma (c) endometrial polyp (d) endometrial hyperplasia

PDS according to the IETA nomenclature showed the following; single dominant vessel without branching 11 cases (11%); with branching 6 cases (6 %); multiple vessels with focal origin 9 cases (9%); multifocal origin at the myometrial–endometrial junction 41 cases (41 %); scattered vessels 25 cases (25%); circular flow 8 cases (8%) (Fig. 1). The single dominant with or without branching pattern had a significant relation with endometrial polyps; multiple vessels with focal origin vascular pattern was not significant with any pathology; multiple vessels with multifocal origin at myometrial endometrial junction pattern was greatly detected in atrophic cases with statistically significant relationship, but was also detected in 3 out of 4 cases of endometrial carcinoma,. In this study we did not find a specific IETA vascular pattern associated with carcinoma. Scattered pattern showed an apparent relation with endometrial hyperplasia; while circular pattern has an exclusive significant relation with myomas.

The sensitivity, specificity, positive and negative predictive values and accuracy for single dominant vessel in diagnosing endometrial polyps were 47.8, 100, 100, 86.5 and 88%; branching single dominant vessel pattern in diagnosing endometrial polyps were 21.7, 98.7, 83.3, 80.9 and 81%; for multifocal origin at the myometrial-endometrial junction in diagnosing atrophy they were 71.1, 83.6, 78, 78 and 78%; for scattered vessel pattern in diagnosing endometrial hyperplasia they were 88.9, 89, 64, 97.3 and 89 % and for circular flow pattern in diagnosing submucosal fibroids, they were 100, 100, 100, 100 and 100 %, respectively. The hysteroscopic findings were also highly significant to the pathological diagnoses (Table 3).

The sensitivity, specificity, positive and negative predictive values and accuracy of hysteroscopy to detect abnormal endometrial pathology in the patients with postmenopausal bleeding is shown in Table 4. Examples of the different pathologies encountered by hysteroscopy in this study are shown in Fig. 2.

DISCUSSION

In this study we aimed to assess whether non-invasive assessment of the endometrium in women with postmenopausal bleeding via grey-scale transvaginal ultrasonography and PDS using the IETA group nomenclature was as accurate as hysteroscopy with biopsy to diagnose intrauterine lesions making it a useful tool for selection of cases requiring this invasive diagnostic procedure. To our knowledge this is the second study assessing the IETA group nomenclature usefulness and practicality. The endometrial thickness still remains the first thing to be assessed in postmenopausal bleeding cases. Our findings go in line with those obtained by Kabil Kucur *et al.* [6], who showed the endometrial thickness to be significantly more in females with endometrial hyperplasia and cancer than in those with nonspecific pathologies (P=0.012, P=0.033). In another study the mean endometrial thickness was significantly greater in patients with endometrial cancer than those without endometrial cancer (16.6 ± 6.1 mm vs. 9.5±4.7 mm, P<0.05) [10].

The endometrial echogenicity is also considered an important variable in endometrial assessment. In a study by Opolskiene *et al.* [11], they concluded that the most

important ultrasound variables to predict malignancy were non uniform endometrium, endometrial thickness and irregular branching of endometrial vasculature. While, Kabil Kucur *et al.* [6] stated that all endometrial cancer cases had heterogeneous endometrium. There are few studies that used the IETA nomenclature in describing the vascular endometrial patterns. Before the IETA nomenclature, Alcázar *et al.* [12] described three different endometrial vascular patterns by utilising PDS (multiple-vessel pattern, single-vessel pattern and scattered-vessel pattern). They found PDS flow valuable in differentiating benign from malignant endometrial pathologies in postmenopausal females. They found a total of 81.3% of vascularized endometrial cancers showed multiple-vessel pattern, 97.1% of vascularized polyps showed single-vessel pattern and 72.7% of vascularized hyperplasia exhibited scattered-vessel pattern.

Sensitivity and specificity for endometrial cancer were 78.8% and 100%. For endometrial polyp the corresponding values were 89.2% and 87% and for hyperplasia they were 57.1% and 88.3%. Timmerman *et al.* [13] described pedicle artery sign, which is equivalent to single dominant artery in the IETA terms, with an 81.3 % PPV for endometrial polyps. A rim-like Doppler pattern, equivalent to circular flow pattern in the IETA nomenclature, was reported by Cil *et al.* [14] for submucosal myomas. While, Kabil Kucur *et al.* [6] stated that single dominant artery with or without branching was a credible finding for endometrial polyps (P=0.001). Multiple vessels with focal origin pattern were significantly correlated with endometrial cancer (P 0.026). Scattered vessel pattern was an apparent finding for endometrial hyperplasia (P=0.001) and a circular flow pattern was almost exclusive to submucous fibroids (P=0.001) [6].

Our study goes in line with all these studies, except that there was no specific vascular pattern with a statistically significant association with endometrial cancer. This might be attributed to the small sample size (only 4 cases of endometrial carcinoma in our cohort). This may be also due to the fact that our hospital was not an oncology tertiary center and women with postmenopausal bleeding come to our general gynaecology clinics for their initial assessment and treatment. We also acknowledge the limitation of the IETA group nomenclature regarding the diagnosis of congenital uterine anomalies and the neglect to recent advancement in three-dimensional ultrasound which has been endorsed by the vast gynecological community as a useful tool for assessment of the uterine morphology [15]. Hysteroscopy on the other hand is a superior method with high sensitivity and specificity in diagnosing the cause of postmenopausal bleeding thanks to the fact that the uterine cavity and intrauterine pathology are directly visualized [16]. We found hysteroscopy to be an accurate method for diagnosing different pathologies in cases with postmenopausal bleeding. This is in accordance to Tinelli *et al.* [9] stated that hysteroscopy was a significantly accurate diagnostic method for the detection of endometrial pathology which revealed sensitivity of 98%, specificity of 91%, PPV of 88%, NPV of 98% and diagnostic accuracy of 94%. Also, Pop-Trajkoviæ-Diniæ *et al.* [4] found a high sensitivity and specificity for hysteroscopy in detection of intrauterine pathology (100% and 81%). The study by Allameh and Mohammadizadeh [17] presented the results of 100% sensitivity for hysteroscopy, specificity of 80.5%, PPV of 88.9% and NPV of 100%. Similarly the study by Tandulwadkar *et al.* [18] showed sensitivity of 97% and specificity of 98% and finally Barati *et al.* [19] found sensitivity of 98.7% and specificity of 99%. In a retrospective study by Loiacono *et al.* [20] they stated that in patients with AUB hysteroscopy had sensitivity, specificity, PPV and NPV of 100% for polyps and myomas; for endometrial hyperplasia these were 81, 96, 87 and 93%, as for endometrial carcinoma they were 63, 97, 77 and 95%, respectively.

In conclusion, PDS of the uterine cavity is a helpful non-invasive tool in assessment of postmenopausal bleeding. The IETA group nomenclature is clinically valuable and reasonable; the utilization of standardization of nomenclature between sonographers would allow more consistent communication, better-described lesions and aid further studies on this technology.

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