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Original article

Role of Uterine Artery Doppler Indices in Patients with Perimenopausal Bleeding for Diagnosis of Endometrial Pathologies: A Prospective Study

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ABSTRACT

Background: Abnormal uterine bleeding is nearly a daily challenge in gynecological practice. In addition, it responsible for a respected percentage of hysterectomies. Early diagnosis is crucial, especially if noninvasive, readily available method is used.

The aim of the work: To investigate the usefulness of Doppler transvaginal ultrasound in diagnosis of uterine pathology responsible for abnormal uterine bleeding in the perimenopausal women.

Patients and Methods: The study included 156 patients [106 with AUB and 50 healthy controls]. The study was carried out during the duration between February to September 2020. For all females, full history taking, clinical and laboratory investigations were carried out. In addition, transvaginal ultrasonic uterine artery Doppler was done and its indices [Pulsatility index [PI] and resistance index [RI]] were documented. After histopathological results from endometrial biopsy, females were subdivided into two groups [A and B]: **Group A** included 52 patients with non-significant [dysfunctional] causes of AUB. **Group B** included 54 patients with significant [pathological] causes of AUB as endometrial hyperplasia and carcinoma.

Results: Both groups of AUB were comparable regarding patient age, BMI, pattern of bleeding, number of used vulval pads, and preoperative hemoglobin concentration. However, pathological ABU was associated with high parity, long duration of bleeding, increased number of bleeding days/last month, and significantly lower values of uterine artery PI and RI. Endometrial thickness was significantly increased in ABU when compared to control group. Finally, RI was sensitive than PI in diagnosis of pathological AUB. [area under the curve was 0.998 and 0.834 respectively]. PI had a sensitivity of 70.8%, specificity of 92% at a cut-off value of 1.82; while RI had sensitivity of 96.2% and specificity of 100.0% at a cutoff value of 0.575.

Conclusion: Transvaginal Doppler ultrasound seems to sensitive and specific modality for diagnosis of endometrial abnormalities in females with perimenopausal AUB.

* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

The term Abnormal Uterine Bleeding [AUB] usually describes any abnormal type of uterine bleeding [abnormality indicate that, the type is not within normal amount, duration, frequency and cyclicity ranges] [1].

AUB is a symptom and not a disease. It is commonest complaints in daily gynecologic practice. It represents > 70% of all consultations of females in the perimenopause age [2].

In response to challenges related to AUB clinical investigation, a specific system had been developed. It had been based on the acronym [Polyps, adeno-myosis, leiomyoma, malignancy and hyperplasia – coagulopathy ovulatory disorders, endometrial factors, iatrogenic, and not classified [3].

Perimenopausal AUB, could represent an emergency, especially in post-menopausal period, as it could develop as a result of endometrial pathological lesions. In such situations, it needs urgent and invasive intervention for diagnosis and determination of the optimal therapeutic intervention. The prevalence of endometrial cancer in females with AUB is about 8-20%, and is the most frequent cause of pathological changes in females > 60% of age [1].

Clinical and laboratory evaluations are critical to determine the etiology of AUB in the perimenopausal age group. Ultrasound [US] could play a role in the exclusion of organic lesions for AUB. This is important because AUB is the main etiology for hysterectomy and represents two-thirds of all hysterectomies [4].

The endometrium biopsy remains the gold standard and definitive diagnostic modality for endometrial pa-thologies. However, introduction of high-resolution ultrasound [US] studies, as a noninvasive method for the uterine cavity has increased. Many trials showed a thicker endometrium [on gray-scale ultrasound] in neoplastic endometrium [5].

The transvaginal ultrasound [TVUS] is recommended to study endometrium changes and thickness, as it is a noninvasive and simple procedure. It is able to exclude any organic endometrial lesions in cases of AUB. The use of transducers with high frequency, which could be placed near to the region of interest, permits better visualization of endometrium and the uterus as a whole [6].

Transvaginal color Doppler sonography permits the analysis of vascular abnormalities of uterine vasculature for both larger and smaller vessels, with color representation of angiogenic myometrial changes. Thus, it could be considered as a crucial diagnostic tool in the assessment of AUB, especially for females older than 40 years. Color Doppler investigation was found to be valid for diagnosis and prognosis of suspicious endometrial pathologies, through analysis of hemodynamic data of large uterine vessels and by determination of the characteristics of vascularization for endo- and myometrium levels, but there is a need for long-term follow-up [7].

Lower impedance to blood flow in tumor tissues has led authors to consider the usage of Doppler indices of uterine vessels to distinguish between malignant and benign pathologies. Some researchers have investigated the diagnostic role Doppler ultrasound of uterine vessels to differentiate premalignant from malignant endometrial lesions. Others reported Doppler ultrasound to be of limited values [8]. Thus, searches were conducted to determine the characteristics of endometrial and myometrial vessels on Doppler ultrasound, and a few discriminatory patterns have been defined to polyps, fibroids and endometrial carcinoma [9].

Research Question

What is the role of uterine artery resistance index & pulsatility index in the evaluation of endometrial abnormality?

THE AIM OF THE WORK

This current work aimed to use color Doppler to study the uterine artery blood flow indices in patients with AUB to find the relationship between endometrial thickness, uterine blood flow and histopathology of endometrium.

PATIENTS AND METHODS

This is a prospective study. It included 156 patients, who were selected from those attending the Department of Obstetrics and Gynecology at Al-Azhar

University [Damietta]. The study was carried out during the duration between February to September 2020. Patient was eligible for inclusion in the study if she suffered from AUB, aged between 40 and 51 years, with no hormonal treatment at least, three months before the study.

In addition, no administration of non-steroidal anti-inflammatory drugs [NSAIDs] 24 hours before examination. On the other side, the patient was excluded if bleeding is due to complications of pregnancy, the presence of systemic cause of abnormal bleeding [e.g. hypertension, thrombo-cytopenia and thrombophilia], a history of pelvic inflammatory disease [PID], presence of any pelvic lesion as ovarian cysts, fibroids, adenomyomas, polyps or pelvic endometriosis, patients receiving hormonal treatment, patients received anticoagulant drugs, or female using intrauterine device [IUD] [either hormonal or non-hormonal].

The sample size was calculated by the use of Epi Info program version 7 and calculation was based on the prevalence of endometrial pathology [outcome] in peri-menopausal women [Exposed group] is 34% as described by Farhat *et al*. [10].

The precision of 2%, 95% confidence level, a study power of 80%. The study included 106 women with perimenopausal bleeding and 50 women without vaginal bleeding as controls. For all patients, full history taking, clinical and laboratory investigations [complete blood count, coagulation profile, fasting and post-prandial blood sugar, liver and kidney functions tests] were performed. In addition, transvaginal ultrasonic uterine artery Doppler was performed and its indices [Pulsatility index [PI] and resistance index [RI]] were documented. Then, endometrial sampling was carried out by a curette for patients with AUB.

After histopathological result, patients in the AUB group were subdivided into two groups [A and B]: Group A included 52 patients with non-significant [dysfunctional] causes of AUB as disordered endometrium, secretory endometrium and atrophic endometrium. Group B included 54 patients with significant [pathological] causes of AUB as endometrial hyperplasia [all subtypes] and endometrial carcinoma. Uterine vessels were scanned by a color Doppler technique, and the ascending branch was recognized lateral to the cervix, at the level of the internal os. The gate of the Doppler was positioned when the vessel with good color signals was identified on the screen. Pulsed wave Doppler was applied at a sampling gate of 2 mm with the angle of insonation at less than 30°. Pulsatility index [PI] and resistance index [RI] were automatically calculated after three similar waveforms. Both right and left uterine arteries were examined with the mean of both recorded.

The following figures represented samples of ultrasound findings.

Figure [1]: Ultrasound image showing thickened endometrium

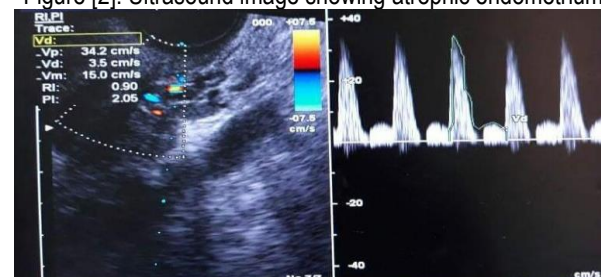Figure [2]: Ultrasound image showing atrophic endometrium

Figure [3]: Doppler waves of uterine artery

Ethical Consideration:

The study protocol was submitted and approved by the Institution Research Board [IRB] of the Faculty of Medicine Al-Azhar University Damietta [IRP number: 00012362-12-19-003]. In addition, informed consent was obtained from each participant before inclusion in the study. Confidentiality and personal privacy were respected in all stages of the study.

Statistical methodology:

Data were collected, documented and coded. Then, fed to the computer software program known as statistical package for social science [SPSS], version 20 [IBM®SPSS® Inc., Chicago. IL, USA]. Measures for data representation were mean and standard deviations for normally distributed quantitative data, frequency and percentages for qualitative data. Chi-square test was used to measure the association between qualitative variables. However, Fisher exact test will be used for 2x2 qualitative variables when more than 25% of the cells have expected count <5. In addition, Student [t]-test was used to compare two sets of quantitative normally distributed data, while Mann Whitney test was used when these data is abnormally distributed. One-way analysis of variance [ANOVA] test will be used for comparison between three or more groups having quantitative normally distributed data, while Kruskal-Wallis test was used when these data is not normally distributed. The ROC [Receiver Operating Characteristic] curve was done to detect the cutoff value with the highest sensitivity and specificity

RESULTS

In the current work, no significant difference was found between groups regarding patient age or body mass index [BMI]. The mean age was 46.32±2.77, 45.67±2.39 and 45.33±2.18 years, in control, group A and group B, respectively. However, females with abnormal uterine bleeding [either dysfunctional or pathological] had significantly higher parity when compared to control group [3.96±1.66, 3.63±1.41 versus 3.24±1.3 respectively] [Table 1].

The duration of ABU was significantly longer in patients with pathological when compared to those with functional uterine bleeding [6.45±2.1 vs 4.66±2.3 months respectively]. In addition, the number of bleeding days in the last month was significantly increased in group B when compared to group A [14.0±2.1 vs 12.6±2.4 days, respectively]. Otherwise, no significant difference was reported between both groups regard pattern of bleeding, number of used vulval pads in the last month and hemoglobin concentration at presentation [Table 2].

According to FIGO classification, the most common pathology was secretory endometrium [24.52%], followed by simple hyperplasia without atypia [23.58], then disordered proliferative endometrium [16.98%]. Other pathologies were complex hyperplasia without atypia [10.37%], endometritis [7.54%], complex hyperplasia with atypia [5.66%] and endometrial carcinoma [1.88%] [Table 3].

In the current work, endometrial thickness was significantly increased in group A [15.54±4.16] and group B [14.15±4.37], when compared to control group [6.26±1.74]. However, the difference between groups A and B was statistically non-significant. In addition, both PI and RI were significantly lower in groups A and B when compared to control group. Furthermore, PI and RI were significantly lower in group B when compared to group A [Table 4]. For the detection of pathological AUB, RI was more sensitive than PI [area under the curve was 0.998 and 0.834 respectively]. PI yielded sensitivity of 70.8%, specificity of 92% at a cut-off value of 1.82; while RI yielded sensitivity of 96.2% and specificity of 100.0% at a cutoff value of 0.575 [Table 5 and figures 4,5]

Table [1]: Patient characteristics of the studied populations

Variable	Control group [n=50]	Group A [n=52]	Group B [n=54]	P value
Age [years]	46.32±2.77	45.67±2.39	45.33±2.18	0.18
Parity	**3.24±1.3**	**3.96±1.66**	**3.63±1.41**	*0.043*
BMI [Kg/m²]	27.68±2.62	26.54±2.14	27.61±2.45	0.26

Table [2]: Features of abnormal uterine bleeding among the studied populations

Variable		Group A [n=52]	Group B [n=54]	P value
The duration of AUB in months		**4.66±2.3**	**6.45±2.1**	**<0.001***
Pattern of bleeding	Heavy menstrual bleeding	28[53.8%]	30[55.56%]	0.85
	Intermenstrual bleeding	18 [34.6]	20 [37]	0.79
	Both Patterns	6 [11.5]	4 [7.5]	0.47
Number of bleeding days in the last month		**12.6±2.4**	**14.0±2.1**	**0.018***
Number of the used vulval pads in the last month		18.6±3.7	20.0±3.8	0.057
Hemoglobin at presentation		10.1±2.2	9.8±2.0	0.46

Table [3]: Pathological spectrum according to the International Federation of Gynecology and Obstetrics [FIGO] classification in patients with AUB groups

Endometrial pathology [n=106]	n [%]
Secretory endometrium	26 [24.52]
Simple hyperplasia without atypia	25 [23.58%]
Disordered proliferative endometrium	18 [16.98%]
Complex hyperplasia without atypia	11 [10.37%]
Endometritis	8 [7.54%]
Complex hyperplasia with atypia	6 [5.66%]
Endometrial carcinoma	2 [1.88%]

Table [4]: Comparison between groups regarding ultrasound findings

Variable	Control group [n=50]	Group A [n=52]	Group B [n=54]	P value
Endometrial thickness [mm]	6.26±1.74	15.54±4.16	14.15±4.37	**P1<0.001*; P2 < 0.001*; P3 = 0.148**
Uterine artery PI	2.15±0.30	1.97±0.25	1.08±0.15	**P1<0.001*; P2 < 0.001*; P3 < 0.001***
Uterine artery RI	0.625±0.029	0.596±0.019	0.524±0.024	**P1<0.001*; P2 < 0.001*; P3 < 0.001***

P1: P-value between Control and Group A; P2: P-value between Control and Group B; P3:P-value between group A and Group B; * indicate significant difference

Table [5]: Test Reliability measures of uterine artery PI and RI in detection of pathological ABU

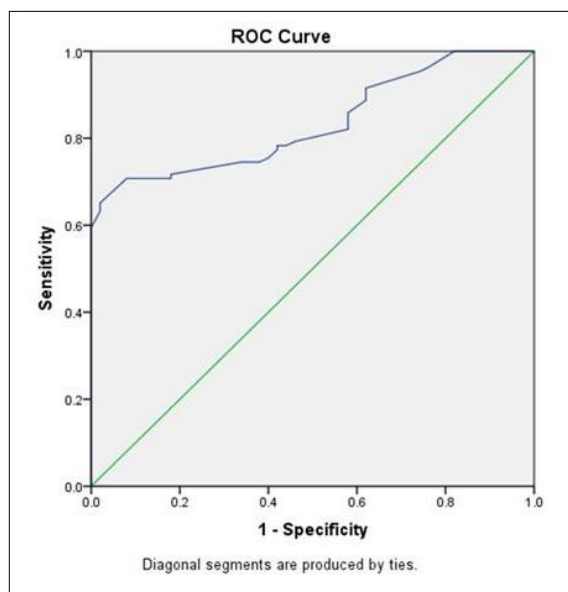|	Cut-off value	AUC	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]	Accuracy [95% CI]
UA-PI	1.82	0.834	70.8% [0.61-0.79]	92% [0.8-0.97]	94.9% [0.87-0.98]	69.9% [0.48-0.71]	78% [0.70-0.84]
UA-RI	0.575	0.998	96.2% [0.90-0.99]	100% [0.91-1]	100% [0.95-1]	92.6% [0.81-0.98]	97% [0.93-99

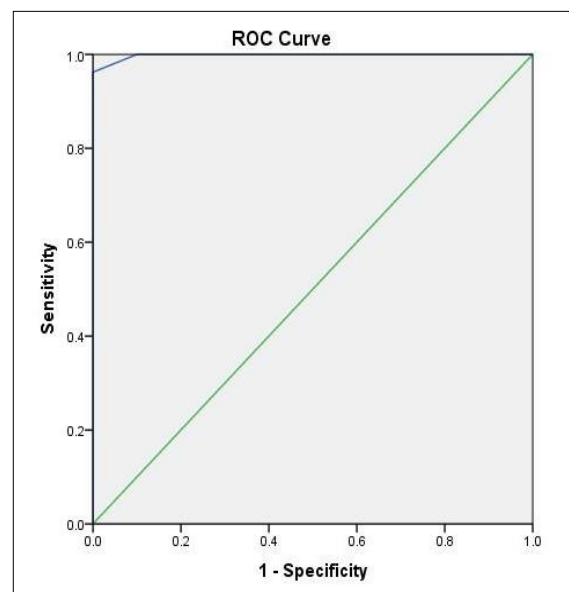Figure [4]: ROC curve for PI in detection of pathological AUB

Figure [5]: ROC curve of RI in detection of pathological AUB

DISCUSSION

In the current study, we included 106 peri-menopausal women suffered from AUB. Both females with dysfunctional and pathological AUB were comparable regarding patient age [around 45 years], BMI, pattern of bleeding, number of used vulval pads, and hemoglobin concentration. On the other side, pathological ABU was significantly associated with high parity, long duration of bleeding, increased number of bleeding days/last month, and significantly lower values of uterine artery PI and RI. Endometrial thickness was significantly increased in ABU when compared to control group. Finally, RI was sensitive than PI in diagnosis of pathological AUB.

These results are comparable to those reported by Chapagain and Dangal [11] who reported that, the most common age group of females with AUB was 40 to 44 years. The majority of women were multiparous [parity 3 or more]. Proliferative endometrium was more common than secretory endometrium.

Endometrial sampling was used in the perimenopausal period to diagnose the AUB. However, it is challenged due to rarity of endometrial carcinoma in females around their mid-forties [12-13]. However, Mingels *et al*. [14] demonstrated that, endometrial pathology may exist frequently in asymptomatic females as recognized in hysterectomy specimens in uterovaginal prolapse. They reported a simple hyperplasia in 15%; complex hyperplasia in 2%; atypical hyperplasia in 3%; complex atypical hyperplasia in 3% and a small focus of intramucosal endometrioid endometrial carcinoma in 3%.

In addition, other researchers have recommended endometrial sampling in obese patients with a BMI > $30.0 kg/m^2$, due to increased probability of endometrial pathology. For example, Guraslan *et al*. [15] reported that, females with a BMI ≥30 kg/m^2 were four-times more likely to develop complex hyperplasia or cancer.

In addition, comparable results were reported by Wise *et al*. [16] in perimenopausal females with ABU. Gawron *et al*. [12] also reported that, high BMI raises the chance of atypical hyperplasia in endometrial biopsy [OR 1.16]. We could not document the effect of obesity on probability of increased endometrial histopathological abnormalities, as the studied groups were comparable as regards to BMI.

By histopathological examination, endometrial hyperplasia was the most common organic cause of AUB in our study affecting 42/106 [39.62%] [25 simple hyperplasia without atypia, 11 complex hyperplasia without atypia and 6 complex hyperplasia with atypia] followed by secretory endometrium [24.25%], disordered proliferative endometrium [16.98%], endometritis [7.54%] and finally endometrial adeno-carcinoma [1.88%]. The incidence and distribution of pathologies in previous studies is greatly variable. For example, incidence of endometrial hyperplasia as low as 5-10% in the study of Abdullah and Bondagji [17] and as high as 60-62% in others [18].

Nonspecific chronic endometritis as a cause of AUB in perimenopausal women has also been reported by Khadim *et al*. [19] and Michail *et al*. [20] to be affecting 6.4% and 20.7% of their study groups, respectively. Gawron *et al*. [12] reported endometrial carcinoma in 2/213 cases [0.9%].

Pennant *et al*. [13] estimated the risk of endometrial cancer to be 0.33% and risk of atypical hyperplasia was 1.31% in premenopausal women. Another Turkish study, included 350 women with AUB and revealed that, proliferative endometrium in 36%, secretory endometrium in 24.6%, decasualization in 10.9%, endometrial polyp in 8.3%, endometritis in 6.8%, endometrial hyperplasia in 4.6%, irregular shedding in 3.7%, atrophic endometrium in 3.1%, endometrial cancer in 1.1% and placental retention in 0.9% [21].

Results of the current work [regarding thick myometrium in females with AUB] are in line with El Agwany [22] who reported that, the characteristic ultrasound features associated with endometrial pathology are thick irregular endometrium, ill-defined endometrial myometrial junction, and myometrial invasion by endometrial cells. However, Kim *et al*. [23] reported that, endometrial thickness as a simple measure had a limited role in the diagnosis of endometrial cancer or hyperplasia [the high number and heterogeneity of patients included in their study could explain such difference]. They instead recommended endometrial stripe abnormality as a

significant factor to diagnose endometrial hyperplasia in perimenopausal women with and without AUB. They remain in line with the current study regarding the overall role of ultrasound in the diagnosis of endometrial pathology.

Regarding results of uterine artery Doppler indices, both RI and PI were good diagnostic indicators of pathological AUB; RI was better than PI with sensitivity above 95% and specificity of 100.0%. These results are in line with the conclusion of Bayram *et al*. [24] who reported that, transvaginal color Doppler ultrasound may be of value in the identification of the etiology of AUB in premenopausal females. In addition, results of our study come in agreement with Dragojević *et al*. [25] reported that, endometrial thickness significantly different between studied groups and endometrial carcinoma was not found in the endometrium < 8 mm thick. In addition, significantly lower PI values were obtained in patients with pathological endometrium, when compared to other groups. They concluded that, transvaginal Doppler has a crucial role in the assessment of AUB in peri- and post-menopausal females. It could help in the differentiation of normal from malignant [abnormal] endometrial changes. Kumari *et al*. [26] reported that, the histopathology of endometrium revealed 34.48% of patients had simple hyperplasia without atypia, 20.68% hyperplasia with atypia and secretory endometrium, and 10.34% endometrial carcinoma. The rate of cancer in their study is higher when compared to the current work. They attributed this higher rate to the state of their center as a regional center.

Stachowiak *et al*. [27] concluded that, the most important factors in the diagnosis of AUB are endometrial thickness, uterine vascularity indices, which allow differentiation between normal and pathological, and between benign and malignant changes in the endometrium. These results are supported by the current work. Veena *et al*. [5] valued the role of power Doppler in addition, to grey scale transvaginal ultrasound as it improved the specificity and negative predictive value when compared to hysteroscopy for assessment of AUB. Finally, Ozer *et al*. [21] concluded that, transvaginal ultrasound is efficient in the preliminary diagnosis of pathologies associated with AUB, especially in the absence of hysteroscopy or hysteroscopy-guided endometrial biopsy. Weiner *et al*. [28] studied the correlation between uterine artery RI and ultrasonographic evaluation of endometrial thickness to histo-pathological picture of the endometrium in 85 women with AUB. They found that the mean uterine artery RI in cases with non-pathological changes in the endometrium is significantly higher than in cases of endometrial hyperplasia or carcinoma [0.85 ± 0.08 and 0.77 ± 0.03 respectively]. They concluded that uterine artery RI has 100% sensitivity and 62% specificity in the detection of endometrial pathology. Similarly, Emoto *et al*. [29] found that RI<0.9 was strongly correlated with abnormal endometrial pathology. Another study used the univariate analysis found that PI < 2 and RI < 0.9 were correlated with abnormal endometrium [30].

The controversial results between our and previous studies [regarding percentages of detected pathologies] can be interpreted in the light of differences in populations and study design. In addition, different menopausal status, the use of hormonal replacement therapy and rate of endometrial cancer.

The inclusion of a control group represented a strength point of this study, especially to compare ultrasound findings. However, Inability to extend the period of follow up to record the clinical outcome of patients with significant causes of AUB as well as the small number of patients with malignant lesions, constitute unintended limitations of the current study.

In conclusion, transvaginal Doppler sonography is a noninvasive, sensitive, and specific technique for the diagnosis of endometrial abnormalities in females with perimenopausal AUB. Doppler sonography can help in differentiating dysfunctional from pathological endometrial changes. We suggest cut off values for both PI and RI [1.82 and 0.575] to discriminate between dysfunctional and pathological causes of perimenopausal bleeding. Thus, we can suggest to limit endometrial biopsy only to cases with RI less than 0.575.

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None

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