Role of Ultrasonography And Endometrial Biopsy in Evaluation of Perimenopausal Abnormal Uterine Bleeding

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ABSTRACT

Background: Abnormal Uterine Bleeding is an important cause of health hazard in perimenopausal women. AUB in this age group may be the only clinical sign of endometrial cancer. Accurate diagnosis for the causative factor of AUB in this age group is important. Objective of the study was to study the various types of menstrual abnormalities prevalent in perimenopausal women and correlate the TVS findings with the histopathological examination of the endometrium.

Materials and methods: This prospective observational study was carried out on 197 women in the perimenopausal age group (40-55 years) for a period of one & half year. All these women underwent clinical examination, investigations and ultrasound examination followed by endometrial biopsy.

Results: Majority of the patients (55.8%) had menstrual disturbances in the age group of 40-45 years and 14.7% belonged to 51-55 years. Menorrhagia was the dominant presentation (44.7%) followed by metrorrhagia (22.3%) and menometrorrhagia (10.7%). Twenty eight patients (14.2%) presented with postmenopausal bleeding. Common uterine pathology were leiomyoma (n=49) and adenomyosis (n=36). Most common histopathology was found proliferative endometrium 73 (37%), followed by secretory endometrium 40 (20%). Disordered proliferative endometrium was observed in 11 cases (5.58%), 12 cases (6%) had endometrial hyperplasia with atypia and endometrial carcinoma was found in 2 women (1.02%). 113 patients had normal endometrial histopathology with ET of 5-12 mm, 14 cases had endometrial hyperplasia without atypia and 9 cases with atypia where ET was between 12-15 mm. Two cases had endometrial cancer when ET between 12-15 mm.

Conclusions: In perimenopausal women with AUB, TVS should be the first line investigation. Increased ET on TVS had association with abnormal endometrial tissue histopathology in women with AUB.

Keywords: Abnormal uterine bleeding, Histopathological examination, Transvaginal sonography, Endometrial thickness.

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INTRODUCTION

Abnormal uterine bleeding (AUB) is one of the common gynecological problems among perimenopausal women and its evaluation in this age group is important. Heavy (>80 ml) and or prolonged (>8 days) menstrual bleeding can exacerbate anemia and if remains untreated it can become life threatening eventually[1]. In 2011 International Federation of Gynecology and Obstetrics (FIGO) has introduced a new classification system for abnormal uterine bleeding pattern. This system is based on the acronym of PALM-COEIN. PALM stands for **P-** Polyps, **A-**Adenomyosis, **L-**Leiomyoma, **M-**

Malignancy. COEIN stands for **C-**Coagulopathy, **O-**Ovulatory disorder, **E-**Endometrial causes, **I-** Iatrogenic, and **N-** Not otherwise classified[2]. In around 10% of the premenopausal women with AUB, the histological findings were endometrial hyperplasia and 6% of the postmenopausal women with AUB had endometrial carcinoma[3]. Transvaginal ultrasonography (TVS) is a very simple and non-invasive diagnostic tool to measure endometrial thickness accurately and to diagnose the organic pelvic pathologies in AUB. The endometrial pattern can be accurately detected by the histopathological examination (HPE). An endometrial biopsy is also a very simple and cost-effective method with minimum complications. In the present study we used Transvaginal ultrasonography (TVS) and endometrial biopsy followed by histopathological examination (HPE) of endometrium as diagnostic methods. This study was conducted to assess the various clinical presentations of AUB in women of perimenopausal age group and to find out the role of ultrasonography and histopathological examination during their evaluation.

MATERIALS AND METHODS

The study was conducted in the Department of Obstetrics & Gynecology of Burdwan Medical College & Hospital, Burdwan for a period one & half years (January 2018-June 2019). This was a Prospective Observational study. Informed consent was taken from all the participants under study. Detailed history was taken regarding age, parity, menstrual symptoms including the amount, duration, regularity and frequency of vaginal bleeding, whether use of exogenous hormones or not and the presence of other gynecological problems if any. History of bleeding disorder, use of anticoagulants and endocrinological disorders like thyroid disorder and diabetes were also taken. To describe abnormal uterine bleeding pattern different terms were used, menorrhagia when menstrual blood loss was heavy (>80 ml) [4] and or flow was prolonged (>8 days) [4]; metrorrhagia in cases of irregular bleeding occurring in between cycles ; menometrorhhagia in cases of heavy/ prolonged bleeding along with irregularities of cycle; polymenorrhoea when there was frequent cycles <24 days of cycle [4] and postmenopausal bleeding when bleeding recurrred in a menopausal woman at least 1 year after cessation of cycles. All patients under study underwent general, systemic, per speculum and per vaginal examinations. Laboratory investigations including CBC, random blood sugar, coagulation profile, liver, kidney function tests and urine for pregnancy test were done. Perimenopausal women aged 40-55 years presenting with heavy/ prolonged or irregular menstruation in OPD and gynecological emergency of this Department and AUB not responding to medical treatment for 3 months were included in this study. Systemic disorders having hypothyroidism, diabetes, disease of liver and kidney, SLE, coagulopathy, thrombocytopenia, use of anticoagulants, history of intake of hormonal contraceptives, abnormal cervical pathology and PAP smear, iatrogenic causes of bleeding, suspected pregnancy complications were excluded from this study. All these patients were subjected to the transvaginal sonography prior to the dilatation and curettage. A 7.5 MH transvaginal probe was used in our study. All the patients were asked to evacuate her bladder before examination. TVS examination was done in supine position. The transducer was introduced in the vagina after covering it with a sterile condom containing the acoustic gel. The length, anteroposterior and transverse dimensions of the uterus were measured also to note presence of any pathology like leiomyoma, adenomyosis etc. The endometrium was examined for thickness, echogenicity and focal abnormality.

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Endometrial thickness (ET) was noted by the sum of measurements of both the anterior and posterior layers (double layer thickness) of the endometrium at the thickest segment on a midline longitudinal image. In premenopausal women endometrium was considered thickened or hyperplastic when ET ≥12 mm. In postmenopausal women endometrium was considered hyperplastic when ET ≥5mm. Endometrium was considered atrophic when ET less than 5mm. The Uterine cavity was examined to note the presence of submucous fibroid, endometrial polyps. Dilatation and curettage was done in all these patients as an inpatient procedure under anesthesia in OT after TVS examination. Specimens were immediately put in 10% formalin, appropriately labeled and sent for histopathological examination in Pathology Department. Informed written consent was obtained from each of the patients for the procedure. The findings of TVS were compared with histopathological findings. The sensitivity, specificity, PPV and NPV of the TVS were also calculated.

Statistical Analysis

Collected data were checked for completeness and consistency. Then the data were entered on Excel data sheets (Microsoft Excel, 2013). The principles of descriptive statistics were applied to organize and present the data in tables. Proportions in relation to different outcome variables were also calculated. Data were analyzed using Statistical Package for Social Sciences Statistical Package for the Social Sciences (SPSS) [IBM SPSS Statistics for Windows, Version 20.0. [(IBM Corp., Armonk, New York, USA)]. Chi-square test was applied as and when applicable basis considering p value <0.05 as statistically significant.

Ethical Clearance

The study proposals along with other relevant documents were submitted to the Institutional Ethics Committee of Burdwan Medical College for review and approval. The study was conducted only after approval.

RESULTS

The prospective observational analysis was performed for evaluation of clinical symptoms and etiology of AUB in the perimenopausal age group by TVS and histopathology. Total 197 women presented with AUB were evaluated.

Table 1: Age and parity distribution of study participants

Feature	Distribution	Total (n=197) (%)
Age	40-45	110 (55.8)
	46-50	58 (29.4)
	51-55	29 (14.7)
Parity	Nulliparous	11 (5.6)
	Parity 1	18 (9.1)
	Parity 2	76 (38.6)
	Parity 3	42 (21.3)
	Parity 4	28 (14.2)
	Parity 5 or more	22 (11.2)

Majority of the women (55.8%) were in the age group of 40-45 years, 29.4% were in age group of 46-50 years and 14.7% were in age group of 51-55 years. The mean (± SD) age of the study subjects was

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46.05(±3.597) years. Majority (38.6%) of women were of Parity 2 whereas Parity 4 or more contributed only 25.4% of these patients. Nulliparous women were lowest in number (5.6%).

Table 2: Showing Different menstrual symptoms

Menstrual Symptoms	Frequency	Percent
Menorrhagia (heavy and or prolonged bleeding)	88	44.7
Metrorrhagia (irregular bleeding, in between cycles)	44	22.3
Menometrorrhagia (heavy/prolonged along with irregularity)	21	10.7
Polymenorrhea (frequent bleeding <24 days cycles)	16	8.1
Postmenopausal Bleeding	28	14.2
Total	197	100.0

Most common presentation was menorrhagia (44.7%) followed by metrorrhagia (22.3%) and menometrorrhagia (10.7%). Twenty eight patients (14.2%) presented with postmenopausal bleeding.

Table 3: TVS Findings

Findings in TVS	Total (197) (%)
Endometrial Thickness (in mm)	
≤5	33 (16.75)
5-8	52 (26.4)
8-12	85 (43.15)
12-15	27 (13.71)
Examination of Uterus	
Normal	65 (32.99)
Leiomyoma	49 (24.87)
Adenomyosis	36 (18.27)
Endometrial polyp	12 (6.09)
Thickened / Hyperplastic Endometrium	35 (17.77)

Forty three percent of patients belonged to ET between 8-12 mm whereas 13.71% of patients belonged to ET>12 mm. Endometrial thickness of less than 5 mm was noted in 16.75 percent of cases.
Sixty five patients had no uterine abnormality. Common uterine pathologies were leiomyoma (n=49) and adenomyosis (n=36). Thickened endometrium was noted only in 35 cases.

Table 4: Histopathological Findings

Histopathology	Frequency	Percent
Proliferative Endometrium	73	37.06
Secretory Endometrium	40	20.3
Atrophic endometrium	16	8.12

Endometritis	12	6.09
Disordered Proliferative Phase	11	5.58
Endometrial Polyp	7	3.55
Endometrial hyperplasia without atypia	24	12.18
Endometrial hyperplasia with atypia	12	6.09
Endometrial Carcinoma	2	1.02
Total	**197**	**100.0**

Proliferative endometrium (37%) was most common histopathological finding followed by secretory endometrium (20%). Atrophic endometrium was found in 8.12% cases. The Endometrial hyperplasia without atypia observed in 12.18% cases and with atypia seen in 6.09% cases. We have reported endometrial carcinoma only in 2 cases in our study.

Table 5: **Relation of Endometrial thickness on TVS with histopathology**

Histo-pathological Findings	**ET (in mm)**				Total (%)	p Value
	Less than 5	Between 5-8	Between 8-12	Between 12-15		
Proliferative endometrium	14(42.42)	49(94.23)	10(11.76)	0(0)	73(37.06)	<0.001
Secretory endometrium	1(3.03)	1(1.92)	38(44.71)	0(0)	40(20.3)	
Atrophic endometrium	16(48.48)	0(0)	0(0)	0(0)	16(8.12)	
Endometritis	0(0)	0(0)	10(11.76)	2(7.41)	12(6.09)	
Disordered Proliferative phase	0(0)	0(0)	11(12.94)	0(0)	11(5.58)	
Endometrial Polyp	2(6.06)	0(0)	5(5.88)	0(0)	7(3.55)	
Endometrial hyperplasia without atypia	0(0)	2(3.85)	8(9.41)	14(51.85)	24(12.18)	
Endometrial hyperplasia with atypia	0(0)	0(0)	3(3.53)	9(33.33)	12(6.09)	
Endometrial Carcinoma	0(0)	0(0)	0(0)	2(7.41)	2(1.02)	
Total	33(100)	52(100)	85(100)	27(100)	197(100)	

The table shows that 113 patients had normal endometrium with the thickness of 5-12 mm, endometrial hyperplasia without atypia was found in 14 cases when ET between 12-15 mm and 9 cases had endometrial hyperplasia with atypia where ET was between 12-15 mm. Two cases had endometrial cancer when ET was between 12-15 mm.

Table 6: TP, TN, FP, FN, sensitivity, specificity, PPV, NPV of TVS

Diagnosis	**TP**	**TN**	**FP**	**FN**	**Sensitivity (%) (95%CI)**	**Specificity (%) (95%CI)**	**PPV (%) (95%CI)**	**NPV (%) (95%CI)**	**Diagnostic accuracy (%) (95%CI)**

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Proliferative endometrium	70	111	13	3	95.89 (95.50-96.28)	89.52 (88.92-90.12)	84.34 (83.62-85.05)	97.37 (97.05-97.68)	91.88 (91.34-92.41)
Secretory endometrium	38	147	10	2	95.00 (94.57-95.43)	93.63 (93.15-94.11)	79.17 (78.37-79.96)	98.66 (98.43-98.88)	93.91 (93.44-94.38)
Endometrial Hyperplasia	32	156	3	6	84.21 (83.50-84.93)	98.11 (97.85-98.38)	91.43 (90.88-91.98)	96.30 (95.93-96.67)	95.43 (95.02-95.84)
Endometrial Polyp	5	183	7	2	71.43 (70.54-72.31)	96.32 (95.95-96.69)	41.67 (40.70-42.63)	98.92 (98.72-99.12)	95.43 (95.02-95.84)

TP- True Positive, TN- True Negative, FP- False Positive, FN- False Negative, PPV- Positive Predictive Value, NPV- Negative Predictive Value.

The table shows transvaginal sonography with the good sensitivity, specificity and diagnostic accuracy of the normal (proliferative and secretory) and abnormal (endometrial hyperplasia and endometrial polyp) endometrium.

DISCUSSION

Total 197 women in the perimenopausal age group (40-55 years) presented with AUB who fulfilled the eligibility criteria were taken in our study. The history with full details was taken from all the cases and proper examination and necessary investigations were performed. TVS was performed and then endometrial biopsy was taken in all the cases. TVS findings of endometrial thickness were correlated with histopathological report. In our study majority (55.8%) of patients were in the age group of 40-45 years with mean age of participants was 46±3.60 (age range of 40-55 years) [Table 1]. In their study Varadarajan R et al[5] reported maximum number of patients (56.0 %) were in the age group 40 –43 yrs. Verma U et al[6] also reported majority of women belonged to the age group in 44 - 47 years. In the present study AUB was much more common in multiparous women, maximum patients (38.6%) belonged to parity 2 followed by parity 3 (21.3%) and parity 4 (14.2%). Nulliparous women were found only in 5.6% of cases [Table 1]. In their study Kumari A et al[7] showed AUB was more common in multiparous women. Menorrhagia was the most common presenting symptom (44.7%) in this study, followed by metrorrhagia (22.3%) and postmenopausal bleeding (14.2%) [Table 2]. Kumari et al aso reported menorrhagia (43.88%) was most common symptom followed by metrrorhagia (28.88%). In their study Babbar et al[8] also reported menorrhagia (62.1%) was the most common presenting symptom in this age group. Leiomyoma was the most common (24.87%) organic pathology of AUB in our study [Table 3]. Jaideep M et al[9] and Horn S D et al[10] also reported leiomyoma was most common organic cause of AUB and percentages were 21.33% and 25% respectively. Most common histopathological finding was proliferative endometrium observed in 73 cases (37%) [Table 4]. Singh S et al[11], Acharya et al[12] also reported similar findings. Secretory endometrium was found in 40 cases (20.3%) [Table 4]. But in their study Jetley et al[13] reported secretory endometrium was most common histopathological finding (32.4%), and then proliferative endometrium. Desai K et al[14] also reported secretory endometrium was associated with 23% of perimenopausal AUB. In our study endometritis was found in 12 cases (6.09%) [Table 4]. Gopalan et al[15] and Khan et al[16] both reported similar findings in their studies. In our study Disordered proliferative endometrium (DPP) was 5.6% [Table 4] which

corresponds well with study done by Gopalan et al. We found endometrial polyp in 3.55% of cases [Table 4]. Jetley S et al reported it was 2.7% of cases. We found endometrial hyperplasia with atypia in 6.09% cases and endometrial carcinoma in 1.02% of cases [Table 4]. Talat Mirza et al[17] and Babbar et al reported endometrial hyperplasia in 22% and 19.8% cases respectively. The findings of our study were comparable with other studies done by Kumari A et al**,** Pillai SS et al[18]. The incidence of endometrial cancer were less common in our study because important and established risk factors of endometrial carcinoma like PCOS, unopposed hormonal use, diabetes mellitus were excluded from the study. In our study majority (113 cases) had normal endometrial histopathology with endometrial thickness of 5-12mm, endometrial hyperplasia with atypia was seen in 9 cases when ET was between 12-15 mm, endometrial cancer was found in 2 cases when endometrial thickness between 12-15 mm [Table 5]. In our study endometrial hyperplasia with atypia was not observed at endometrial thickness less than 8 mm and malignancy was not noted when endometrial thickness less than 12mm [Table 5]. In their study Pillai SS et al did not observe any major endometrial pathology at ET<14.9 mm. In their study Machado et al[19] concluded that D&C was not needed at ET < 5 mm as any of the patients showed atypia or malignancy when ET<5 mm also the American Cancer Society in 2009[20]. Our study also showed almost similar finding. Present study showed high sensitivity, specificity, PPV and NPV of TVS [Table 6] which correlates well with the findings of Deshmukh et al[21] and Jain M et al[22].

Limitation of the Study

The Present study was done with small sample size and over shorter duration of time in a single centre. Functional causes of AUB like coagulopathy, iatrogenic causes, some endometrial causes were not included in the present study. TVS findings varies according to the operators experience, modernization of the instruments and timing. Hysteroscopy along with its guided biopsy for evaluation of AUB was not included in our study due to limitations of resources. Follow up was also not included in our study.

CONCLUSION

Evaluation of AUB in women of perimenopausal age group is utmost important particularly to exclude endometrial carcinoma and its precursor lesion endometrial hyperplasia with atypia. Both TVS and endometrial biopsy are essential investigations for assessment of perimenopausal women with AUB. TVS is very simple and non-invasive, helpful in diagnosis organic causes of AUB like leiomyoma, adenomyosis, and endometrial polyp. Measurement of endometrial thickness by TVS differentiates between normal and abnormal uterine endometrium. Histopathological diagnosis of endometrium is gold standard and can accurately diagnose the endometrial pathology. So both the sonography and histopathology are the cornerstones of diagnosis and management of perimenopausal AUB in modern practice.

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Conflicts of interest

There are no conflicts of interest.

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