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Research Article

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Histopathological profile of Endometrial Thickness and serum LDH in Women with Post-Menopausal Bleeding

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ABSTRACT

Introduction- Post menopause describes the period following the final menses. Despite a great increase in the life expectancy of women, the age at menopause remains remarkably constant. The life expectancy of women shows a steady rise in this era, hence women experience a longer postmenopausal phase [2]. A woman in the United States today will live approximately 30 years, or greater than a third of her life, beyond the menopause. The tumor environment is highly hypoxic so that cancer cells have an intensified anaerobic metabolism. **Objective**: To assess the histopathological profile of endometrial thickness and serum LDH in women with post-menopausal bleeding. **Methods**: This is a prospective cross-sectional study was carried out at Obstetrics and Gynecology, Sylhet MAG Osmani Medical College Hospital & Jalalabad Clinic, Modhushohid, Sylhet, Bangladesh from January to December 2021. Total 101 women were selected for the present study after applying inclusion and exclusion criteria. The diagnostic reliability of combined serum LDH and endometrial thickness in diagnosis of endometrial carcinoma in cases of perimenopausal bleeding. All cases were subjected to full history, full clinical examination, transvaginal sonography, serum LDH and Diagnostic endometrial biopsy was taken for histopathological examination. **Results**: Total 101 women were selected for the present study after applying inclusion and exclusion criteria. The age of menopause was between 40 and 45 years in 15.8% of the women, 39.5% of women were between 45 and 50 years and 44.5% were above 50 years of age. It was noted that the age group of patients with postmenopausal bleeding was between 45 and 50 years in 13.9% of women, 50 to 60 years in 56.4% of the women and above the age of 60 years in 29.7% of women. It was found that TVS evaluation of endometrial thickness is not sensitive enough to detect cancer of the endometrium and therefore, could not replace histological evaluation of the endometrial tissue in women with postmenopausal bleeding. LDH level cutoff value of 430 U/L could differentiate malignant from benign lesions with a sensitivity of 80.5%, specificity 58.3%, PPV 56.7% and NPV 82.9% with a diagnostic accuracy of 66.3%. Thus, total serum LDH can be used as a good negative test using the cut-off level (430 U/L).In this study, endometrial thickness at 11.5mm cut off value showed 80.5% sensitivity, 53.3% specificity, PPV 53.3%, NPV 80.5%and diagnostic accuracy 64.4%. Combination of evaluation of endometrial thickness by TVS (with specificity of 53.3% and accuracy of 64.4%) and serum LDH (with specificity of 58.3% and accuracy of 66.3%) increase the specificity to 73.3%. also increase the accuracy to 67.3%. **Conclusion**: In conclusion, the measurement of serum LDH is considered another simple method to be combined with TVS if endometrial cancer is suspected. However, further studies are needed using LDH isoenzymes profile and TVS endometrial morphology.

Key Words: *Combined, Endometrial, Thickness, Carcinoma, Perimenopausal.*

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INTRODUCTION

World Health Organization (WHO) defines menopause as cessation of menstruation permanently for a period of more than one year, which is resulted from loss of ovarian activity [1]. Menopause is the permanent cessation of menstruation due to loss of ovarian activity. It occurs at a mean age of 51 years. Menopause is defined retrospectively as the time of the final menstrual period followed by 12 months of amenorrhea. Post menopause describes the period following the final menses. Despite a great increase in the life expectancy of women, the age at menopause remains remarkably constant. The life expectancy of women shows a steady rise in this era, hence women experience a longer postmenopausal phase [2]. A woman in the United States today will live approximately 30 years, or greater than a third of her life, beyond the menopause. WHO has defined postmenopausal bleeding as bleeding from the genital tract occurring after menopause. The average age of menopause is 45–52 years [3,4]. Approximately 10% of the postmenopausal women develop postmenopausal bleeding and this alarming symptom in women makes them seek gynaecologist's opinion immediately and form a significant proportion of referrals due to suspicion of underlying malignancy [5]. Postmenopausal bleeding (PMB) is defined as bleeding from the genital tract, more than 12 months after

the last menstrual period in a woman not on hormone replacement (HRT) [6].80-90% of the women have benign conditions like endometrial or cervical polyps, endometrial atrophy, infection, simple endometrial hyperplasia, medical disorders (e.g., liver cirrhosis), decubitus ulcer in cases of uterovaginal prolapse, neglected pessary and forgotten intra uterine device [7]. Many women with postmenopausal bleeding and endometrial thickness ≥4mm do not have any endometrial abnormality, but will still undergo interventional diagnostic procedures such as endometrial biopsy by fractional curettage or hysteroscopic guided endometrial biopsy to exclude any endometrial abnormality [5]. Endometrial biopsy has been widely used over the past 30 years as the gold standard for diagnosis of endometrial pathology. In a meta-analysis of endometrial sampling studies (the best instrument) had a sensitivity of 99.6%, and the number of insufficient samples varied from 0% to 54% and often results in unnecessary diagnostic curettage. By being a blind procedure, it can miss focal lesions in the uterine cavity, such as polyp and sub mucous fibroid, and inadequate sampling may be obtained, particularly in postmenopausal women with thin endometrium. However, since the ability to obtain adequate endometrial sampling is mainly affected by the endometrial thickness [8]. Serious conditions like endometrial cancer must be ruled out first. Women with risk factors liken nulligravida, women with multiple sexual partner, obese, diabetic, taking exogenous estrogens/ tamoxifen, women who attain menopause late must be extensively investigated [9]. As the first line of investigation Transvaginal ultrasonography (TVS) is the recommended to assess the endometrial pathology, when the endometrial thickness is found to be more than 4 mm, it yields 98% sensitivity to detect endometrial cancer and Pap smear for cervical pathology [10]. In suspected cases Dilatation and curettage or hysteroscopic guided biopsy are found to be the best modality to diagnose the aetiology for the bleed.

Materials and Methods

This is a prospective cross-sectional study was carried out at Obstetrics and Gynecology, Sylhet MAG Osmani Medical College Hospital & Jalalabad Clinic, Modhushohid, Sylhet, Bangladesh from January to December 2021. Total 101 women were selected for the present study after applying inclusion and exclusion criteria. The diagnostic reliability of combined serum LDH and endometrial thickness in diagnosis of endometrial carcinoma in cases of perimenopausal bleeding.

Inclusion criteria:

1. Cases of perimenopausal bleeding.
2. Post-menopausal bleeding, defined as lack of menstruation for 1 year in women older than 45 years.

Exclusion criteria:

1. Patients who were taking hormone replacement therapy.
2. Vaginal atrophy is a frequent cause of abnormal bleeding. Evident drug intake that can lead to vaginal bleeding.
3. Vulval or cervical cause of bleeding. General causes that can cause vaginal bleeding.
4. Cases with blood disorders, general causes of vaginal bleeding and medications that may result in vaginal bleeding. An informed consent was obtained from each patient after explanation of the study aim and procedure

After a written informed consent all patients will be subjected to do the following: General examination. Abdominal and pelvic examination. Pv and local examination. Complete laboratory analysis. All women were examined trans-vaginally in the lithotomy position with empty bladder to measurement of endometrial thickness.

A thorough general physical examination was performed. Height and weight of the cases measured and body mass index (BMI) calculated. Blood pressure was recorded. Specific clinical examination including abdominal, speculum and bimanual pelvic examinations were performed to assess the cervix and to determine size, position and mobility of the uterus. Cervical smears were taken. Transabdominal scan was done to assess endometrial thickness. History taking with special refers for risk factors of endometrial cancer as age, obesity, diabetes, hypertension and family history and systemic causes of bleeding e.g. medical disorders. Time of onset of bleeding and associated discharge or pain. Previous medication for bleeding. General, abdominal and pelvic examination to assess general condition of the patient and possible detection of local asymptomatic cause of vaginal bleeding, to examine size of uterus, affection of adnexa and parametrium.

Ultrasound imaging:

TVS for evaluation of size and contour of uterus, morphology and echogenicity and endometrial thickness in mm as well as evaluation of endometrial myometrium junction to evaluate extent of any malignant tissue invasion, associated lesions in uterus, adnexa and pelvic organs. Measurement of endometrium was obtained in exact midsagittal plane excluding sub endometrial sonlucent area. Parameters to be recorded as thickness texture, abnormal focal lesions. Diagnostic curettage or Hysteroscopic guided biopsy was done for histopathological examination. All data will be subjected to statistical analysis.

Results

Total 101 women were selected for the present study after applying inclusion and exclusion criteria. The age of menopause was between 40 and 45 years in 15.8% of the women, 39.5% of women were between 45 and 50 years and

44.5% were above 50 years of age. It was noted that the age group of patients with postmenopausal bleeding was between 45 and 50 years in 13.9% of women, 50 to 60 years in 56.4% of the women and above the age of 60 years in 29.7% of women. Among the postmenopausal women with bleeding, 10.9% were nulliparous, 22.7% had two parity and 66.3% of women had parity more than 2. Hypertension (19.8%), diabetes mellitus (10.9%), overweight 50-100 kg (21.8%), obesity more than 100 kg (3%) and hypothyroidism (3%) were the common medical disorders associated with postmenopausal bleeding in the study. As regards studying endometrial thickness, the endometrial thickness for benign lesion is 7-17 mm and the endometrial thickness for malignant lesion is 13.93-30.35 mm, the mean thickness for atrophic, hyperplastic and malignant endometria were 2 mm, 12.8 mm and 20.8 mm respectively and there was statistical significant difference between endometrial thickness and different histopathological findings. In the present study, 69.3% of women had benign lesions (70) and 30.7% women had malignant lesions (31).In this study, endometrial thickness at 11.5mm cut off showed 80.6% sensitivity, 53.7% specificity, PPV 53.7%, NPV 80.5%and diagnostic accuracy 64 In this study, we constructed receiver operating characteristic curve and found the following results: area under the curve of 0.93 with confidence interval of 0.84- 1.00) $p < 0.0001$. An LDH level cutoff value of 430 could differentiate malignant from benign lesions with a sensitivity of 80.6%, specificity 58.3%, PPV 56.7% and NPV 82.9% with a diagnostic accuracy of 66.3%. Cancer patients had higher LDH levels compared to patients with benign diseases, but the difference did not reach significance (p=0.07). Patients with benign diseases had an intermediate LDH value (305+-83 U/L), that was of marginal significance compared to control group (p=0.06). Patients with endometrial cancer or leiomyomas had significantly higher serum LDH levels (349+-100U/L and 310+-68 U/L respectively) compared to control group (256+-68 U/L). (p=0.01 and p=0.05 respectively). Also, combination of evaluation of endometrial thickness by TVS and serum LDH increase the specificity to 73.3%. Also increase the accuracy to 67.3%.

Table-1: Demographic data of studied cases (N=101)

Age		
40-45	16	15.8
45-50	40	39.6
>50	45	44.5
Age (years)	(60 ± 17.6)	45-78
Age of postmenopausal bleeding (in years)		
45-50	14	13.9
50-60	57	56.4
>60	30	29.7
Parity		
Nullipara	11	10.9
Para 2	23	22.7
>2 Para	67	66.3
Parity	(5.1 ± 1.8)	3-7
Medical disease		
Hypertension	20	19.8
Diabetes mellitus	11	10.9
Overweight (50-100 kg)	22	21.8
Obesity (>100 kg)	3	3.0
Hypothyroidism	3	3.0

Table-2: Comparison between different types of histopathological findings and TVS measurement of endometrium thickness and LDH (N=101)

Histopathology	**Endometrial thickness (mm)**	**LDH (U/L)**	**p value**
Atrophic endometrium	2.0±0.0	213.5±14.8	0.00**
Polyp	10.6±3.7	486.4±178.3	
Simple hyperplasia	12.8±4.3	433.4±121.2	
atypia	13.4±4.6	478.8±187.2	
carcinoma	20.8±9.0	593.4±159.4	
sarcoma	39.5±6.6	656.1±172.06	

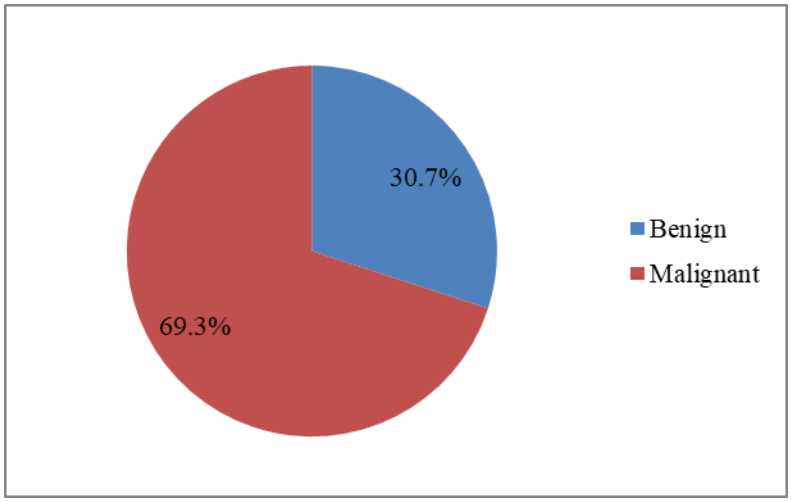

Figure 1: Histopathological findings.

Table-3: Association between cut-off values for endometrial thickness and serum LDH level with lesion pathology (N=101)

		Lesion pathology		Total	p value
		Benign	Malignant		
Endometrium thickness	<11.5	32(53.3%)	9 (21.9%)	41(40.6%)	0.001**
	>11.5	28(46.7%)	32(78.1%)	60(59.4%)	
LDH	<430	35(58.3%)	8(19.5%)	43(42.6%)	0.00**
	>430	25(41.7%)	33(80.5%)	58(57.4%)	
Endometrium thickness and LDH	-VE	44(73.3%)	15(36.6%)	59(58.4%)	0.002*
	+VE	16(26.7%)	26(63.4%)	42(41.6%)	
Total		60 (100%)	41 (100%)	101(100%)	

Table 4: Agreement between cut-off serum LDH and endometrial thickness (N=101)

		Endometrium thickness		Total	p value
		<11.5	>11.5		
LDH	<430	24(58.5%)	19(31.7%)	43(42.6%)	0.012*
	>430	17(41.5%)	41(68.3%)	58(57.4%)	
Total		41(100.0%)	60(100.0%)	101(100.0%)	

Table 5: Validity of new cut-offs.

	Cut-off	Sensitivity	Specificity	+VE Predictive	-VE Predictive	Accuracy
Endometrium thickness	>11.5	78.1%	53.3%	53.3%	80.5%	64.4%
LDH	>430	80.5%	58.3%	56.7%	82.9%	66.3%
Endo & LDH		63.4%	73.3%	58.3%	73.2%	67.3%

DISCUSSION

Postmenopausal bleeding is a sinister complaint of postmenopausal women. It is commonly observed 5 to 10 years after attainment of menopause and the common age of presentation is 50 to 60 years. Aetiology of postmenopausal bleeding includes benign causes like proliferative or atrophic endometrium, endometrial or cervical polyp, endometrial hyperplasia which may be simple or complex with or without atypia, senile endometritis and atrophic vaginitis. Malignant causes of postmenopausal bleeding include cervical cancer, endometrial carcinoma, uterine sarcoma, estrogen secreting ovarian tumours, vulval and vaginal carcinomas. Total 101 women were selected for the present study after applying inclusion and exclusion criteria. The age of menopause was between 40 and 45 years in 15.8% of the women, 39.5% of women were between 45 and 50 years and 44.5% were above 50 years of age. It was noted that the age group of patients with postmenopausal bleeding was between 45 and 50 years in 13.9% of women, 50 to 60 years in 56.4% of the women and above the age of 60 years in 29.7% of women. Among the postmenopausal women with bleeding, 10.9% were nulliparous, 22.7% had two parity and 66.3% of women had parity more than 2. Hypertension (19.8%), diabetes mellitus (10.9%), overweight 50-100 kg (21.8%), obesity more than 100 kg (3%) and hypothyroidism (3%) were the common medical disorders associated with postmenopausal bleeding in the study. Many studies have been developed

before to detect the ability of TVS to diagnose different types of endometrial hyperplasia by comparing different ultrasonographic pictures of the endometrium including its thickness, echogenicity, borders and its homogeneity. Momtaz et al [11] concluded that despite the high diagnostic accuracy of TVS in the diagnosis of endometrial hyperplasia, yet, it was not accurate in the evaluation of the subtypes of endometrial hyperplasia with poor sensitivity and high false positive and negative rates [11]. Endometrial sampling and biopsy done by conventional fractional curettage or office sampling using pipelles are mandatory procedures to be done on patients with postmenopausal bleeding. Hysteroscopic guided biopsy may be performed wherever available as it has more diagnostic value to the final diagnosis.8 Simultaneously, it enables therapeutic removal of polyps, small submucousmyomas in the same sitting in a single step. Endometrial polyps are identified with TVS by the presence of well-defined local thickening of the endometrium with increased reflectivity which is surrounded by a symmetrical area of low amplitude echoes [11]. Leiomyomata could also be diagnosed by vaginal ultrasonography. They have a variety of sonographic textures ranging from hypoechoic to echogenic with a calcified border. As regards studying endometrial thickness, the endometrial thickness for benign lesion is 7-17 mm and the endometrial thickness for malignant lesion is 13.93-30.35 mm, the mean thickness for atrophic, hyperplastic and malignant endometria were 2 mm, 12.8 mm and 20.8 mm respectively and there was statistical significant difference between endometrial thickness and different histopathological findings. The difference between thickness of atrophic endometrium as measured by vaginal ultrasound, and thickness of endometrium with carcinoma indicates that ultrasonography could be used as a very simple method to exclude endometrial abnormalities as the cause of perimenopausal bleeding. The range of endometrial thickness in patients with endometrial abnormalities has been studied by various authors together with the cut-off limit to diagnose endometrial pathology. In this study, endometrial thickness at 11.5mm cut off showed 78.1.6% sensitivity, 53.3% specificity, PPV 53.3%, NPV 80.5%and diagnostic accuracy 64.4%. Several studies however, have been done to detect the value of vaginal ultrasonography to evaluate endometrial thickness as a parameter for excluding endometrial abnormalities. One of the earliest was the study done by Osmer et al [12] who studied 155 normal postmenopausal women using 4mm endometrial thickness cut-off limit by vaginal ultrasound and reported a sensitivity of 81% [12]. Guner et al [13] suggested taking a 4mm cut-off point for excluding endometrial abnormality in postmenopausal women, and a cut-off point of 8mm in premenopausal women [13]. They found no cases of endometrial cancer when the endometrial thickness is < 0.0001. An LDH level cut-off value of 430 could differentiate malignant from benign lesions with a sensitivity of 80.5%, specificity 58.3%, PPV 56.7% and NPV 82.9% with a diagnostic accuracy of 66.3%. These partly agree with another study which found that the serum LDH levels were significantly higher in patients with endometrial adenocarcinoma and ovarian cystadenocarcinomas compared to healthy controls (p values 0.01 and 0.006, respectively). Uterineleiomyomas patients showed intermediate LDH levels, while patients with breast fibroadenomas and ovarian cystadenomas had LDH serum levels close to carcinomas [14]. Serum levels of LDH were significantly higher in patients with gynecological and breast cancer compared to healthy controls. The extent of tumor necrosis may affect the LDH release. It is difficult to adopt a proper cut-off point to avoid bias. In a previous study in lung cancer, serum LDH dropped sharply after surgery showing that serum LDH is indeed a tumor effect [15]. Cancer patients had higher LDH levels compared to patients with benign diseases, but the difference did not reach significance (p=0.07). Patients with benign diseases had an intermediate LDH value (305+-83 U/L), that was of marginal significance compared to control group (p=0.06). Patients with endometrial cancer or leiomyomas had significantly higher serum LDH levels (349+-100U/L and 310+-68 U/L respectively) compared to control group (256+-68 U/L). (p=0.01 and p=0.05 respectively). In other study measurement of total lactate dehydrogenase in matched normal and malignant uterine tissues corroborate that neoplastic transformation in human endometrium significantly increases the activity of this important glycolytic enzyme. Endometrial hyperplasia which is considered as a premalignant neoplasm shows a two or four-fold higher LDH levels than normal endometrium [16].

CONCLUSION

In conclusion, the total serum LDH can be used as a good negative test using the cut-off level (430 U/L). TVS allows the detection of an endometrial pathology in many patients with perimenopausal bleeding. Combination of evaluation of endometrial thickness by TVS and serum LDH increase the accuracy. So, measurement of serum LDH is considered another simple method to be combined with TVS if endometrial cancer is suspected.

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