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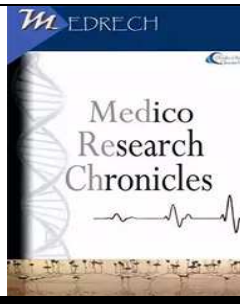

ROLE OF SERUM LACTATE DEHYDROGENASE (LDH) AND ENDOMETRIAL THICKNESS IN THE DETECTION OF ENDOMETRIAL CARCINOMA IN PERIMENOPAUSAL BLEEDING

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Introduction: Postmenopausal bleeding (PMB) refers to any uterine bleeding in a menopausal patient (other than the expected cyclic bleeding that occurs in patients taking combined (ie, estrogen-progestin), cyclic, postmenopausal hormone therapy. Perimenopausal bleeding (PMB) occurs in approximately 3% of women and it is the usual presenting symptom of endometrial carcinoma in approximately 93% of cases. **Objective**: To assess the role of serum lactate dehydrogenase (LDH) and endometrial thickness in the detection of endometrial carcinoma in perimenopausal bleeding. **Methods**: This prospective cross-sectional study was carried out at Obstetrics and Gynecology Department, Rajshahi medical College Hospital, Rajshahi, Bangladesh from January 2020 to June 2022. This study included 102 women with perimenopausal bleeding admitted to Obstetrics & Gynecology Department at RMCH. All cases were subjected to full history, full clinical examination, transvaginal sonography, serum LDH and Diagnostic endometrial biopsy was taken for histopathological examination. **Result:** In this study, endometrial thickness at 11.5mm cut off value showed 80.6% sensitivity, 53.7% specificity, PPV 53.7%, NPV 80.5%and diagnostic accuracy 64.4%. 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 80.6%, specificity

57.4%, PPV 55.7% and NPV 81.5% with a diagnostic accuracy of 66.7%. Thus, total serum LDH can be used as a good negative test using the cut-off level (430 U/L). Combination of evaluation of endometrial thickness by TVS (with specificity of 53.7% and accuracy of 64.4%) and serum LDH (with specificity of 57.4% and accuracy of 66.7%) increase the specificity to 72.2%. also increase the accuracy to 67.7%. **Conclusion:** 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.

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INTRODUCTION

Postmenopausal bleeding (PMB) refers to any uterine bleeding in a menopausal patient (other than the expected cyclic bleeding that occurs in patients taking combined (ie, estrogen-progestin), cyclic, postmenopausal hormone therapy**.** Perimenopausal bleeding (PMB) occurs in approximately 3% of women and it is the usual presenting symptom of endometrial carcinoma in approximately 93% of cases. About 5–15% of perimenopausal women with abnormal bleeding may have endometrial cancer. In regions such as North America and parts of Europe, the incidence of endometrial cancer is disproportionately higher than in other developed countries, which may be attributed to higher rates of obesity, as well as other important risk factors such as aging, early menarche, late menopause, null parity, and postmenopausal estrogen therapy use [1]. Most endometrial cancers are diagnosed at a localized stage and are often curable with surgery, with a 5-year survival of approximately 95%. In contrast, 5-year survival for late-stage (stage IV) endometrial cancer ranges from 16% to 45% [2, 3]. However, studies evaluating early detection strategies for endometrial cancer are lacking, and at present no recommendation for population-based screening exists. Transvaginal ultrasonography (TVS) has become a common method to monitor endometrial thickness with sensitivity 80–100% if a level of 5 mm is used as a cut-off [2]. However, specificity of the TVS is low, partly because of other reasons for thick endometrium like hormone replacement therapy, and partly because the endometrium might not be clearly identified due to myometrial echoes. In patients with thick endometrium or inconclusive findings, there is a need for further confirmation of hyperplasia, chronic endometritis, or tumors usually by histology [4]. In women with postmenopausal bleeding, numerous studies have established TVS-ET as an initial screening procedure to ascertain whether a cut off limit for endometrial thickness can be proposed to rule out endometrial pathology [5]. Endometrial stripe cut off values widely ranging from 3 to 14 mm have been suggested in various studies to detect endometrial pathology in premenopausal women also [6]. There are, however, scarce studies undertaken to determine the cut off limit of ET in perimenopausal women for choosing patients to offer an invasive endometrial sampling. Along with TVS, the role of Doppler is debated with studies depicting conflicting results [7]. Moreover, high levels of tumor markers may represent tumor invasiveness and metastasis to lymph nodes and/or other organs and may indicate a poor prognosis for the patient. Strictly speaking, tumor markers are not tumor-specific but tumor-associated substances [8]. Lactate dehydrogenase (LDH) is a cytosolic enzyme present in all tissues,

exhibiting origin- and tissue-specific isoenzymatic pattern [9]. LDH is one of the major glycolytic enzymes that catalyzes the last step of glycolysis, (conversion of pyruvate to lactate). Routine serum measurement of this enzyme is of clinical use in the diagnosis and monitoring of certain diseases including cancer especially endometrial cancer [10]. 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. 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 [11]. Cancer cells use anaerobic pathways for energy acquisition even in the presence of oxygen, a phenomenon described as "anaerobic glycolysis". Noninvasive methods are needed for screening and early detection of endometrial cancer. Measurement of serum LDH is considered another simple method. Combined with TVS it can improve diagnosis of endometrial cancer [12]. The lactate released by this anaerobic metabolism passes outside the cancer cells leading to the acidification of the extracellular matrix. This is responsible for the development of aggressive malignant phenotype as low pH enhances cancer cell invasive and metastatic ability.

MATERIALS AND METHODS

This prospective cross-sectional study was carried out at Obstetrics and Gynecology Department, Rajshahi medical College Hospital, Rajshahi, Bangladesh from January 2020 to June 2022. This study included 102 women with perimenopausal bleeding admitted to Obstetrics & Gynecology Department at RMCH. All cases were subjected to full history, full clinical examination, transvaginal sonography, serum LDH and Diagnostic endometrial biopsy was taken for histopathological examination.

Inclusion criteria:

- Cases of perimenopausal bleeding.

Exclusion criteria:

- Women known to have other malignancies such as breast cancer.
- Hepatic, renal, cardiac patients or patient with other diseases that may elevate LDH level.
- Cases with blood disorders,
- Medications that may result in vaginal bleeding.

An informed consent was obtained from each patient after explanation of the study aim and procedure. History taken with special refer 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. Laboratory investigations as CBC and full metabolic panel, Detection of systemic causes of bleeding, Serum LDH level is measured, 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. Parameters to be recorded as thickness, texture, abnormal focal lesions. Diagnostic curettage or Hysteroscopic guided biopsy was done for histopathological examination. All data statistical analyzed windows SPSS version 19.0.

RESULT

Out of 102 patients included in our study. Patients mean age (60 ±17.6) and BMI (Kg/m²) (28±4). 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 this study, endometrial thickness at 11.5 mm cut off showed 80.6% sensitivity, 53.7% specificity, PPV 53.7%, NPV 80.5% and diagnostic accuracy 64.4%. An LDH level cutoff value of 430 could differentiate malignant from benign lesions with a sensitivity of 80.6%, specificity 57.4%, PPV 55.7% and NPV 81.5% with a diagnostic accuracy of 66.7% (p <0.0001). 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 72.2% also increase the accuracy to 67.7%.

Table-1: Demographic data of studied cases (N=102)

Variable	Median (mean ± SD)	Range
Age (years)	(60 ± 17.6)	45-78
Parity	(5.1 ± 1.8)	3-7
BMI (Kg/m²)	(28 ± 4)	24-32

Table-2: Comparison between different types of histopathological findings and TVS measurement of endometrium thickness and LDH (N=102)

	Histopathology						p-value
	Atrophic endometrium	Polyp	Simple hyperplasia	atypia	carcinoma	sarcoma	
Endometrial thickness (mm)	2.0±0.0	10.6±3.7	12.8±4.3	13.4±4.6	20.8±9.0	39.5±6.6	0.00**
LDH (U/L)	213.5±14.8	486.4±178.3	433.4±121.2	478.8±187.2	593.4±159.4	656.1±172.06	0.02*

Table 3: Association between cutoff values for endometrial thickness and serum LDH level with lesion pathology (N=102)

		Lesion pathology		Total	p-value
		Benign	Malignant		
Endometrium thickness	<11.5	29 (48.3%)	7 (16.7%)	36 (35.29%)	0.001**
	>11.5	25 (41.7%)	29 (28.4%)	54 (52.9%)	
LDH	<430	31 (51.7%)	7 (6.9%)	38 (37.25%)	0.00**

	>430	23 (38.3%)	29 (28.4%)	52 (50.98%)	
Endometrium thickness and LDH	-VE	39 (65.0%)	14 (13.7%)	53 (51.96%)	0.002*
	+VE	15 (25.0%)	22 (21.7%)	37 (36.3%)	
Total		60 (100%)	42 (100%)	102 (100%)	

Table-4: Agreement between cutoff serum LDH and endometrial thickness (N=102)

		Endometrium thickness		**Total**	**p-value**
		<11.5	>11.5		
LDH	<430	21 (50.0%)	27 (45.0%)	60 (58.8%)	0.012*
	>430	21 (50.0%)	33 (55.0%)	42 (41.2%)	
Total		42 (100%)	60 (100%)	102 (100%)	

Table-5: Validity of new cut-off.

	Cutoff	**Sensitivity**	**Specificity**	**+VE Predictive**	**-VE Predictive**	**Accuracy**
Endometrium thickness	>11.5	80.6%	53.7%	53.7%	80.5%	64.4%
LDH	>430	80.6%	57.4%	55.7%	81.5%	66.7%
Endo & LDH		61.1%	72.2%	59.4%	73.5%	67.7%

DISCUSSION

This study was done to show the role of serum lactate dehydrogenase and transvaginal sonography in the diagnosis of endometrial carcinoma in cases of perimenopausal bleeding. Out of 102 patients included in our study. Patients mean age (60 ±17.6) and BMI (Kg/m²) (28 ±4). Bender et al [13] studied with abnormal uterine bleeding (age range 45-86 years). 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 80.6% sensitivity, 53.7% specificity, PPV 53.7%, 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 [14] who studied 155 normal postmenopausal women using 4mm endometrial thickness cut-off limit by vaginal ultrasound and reported a sensitivity of 81%. Endometrial echogenicity and morphology were subjected to individuals and were variable and had no sharp definition. Also, the study of other ultrasound parameters as echogenicity, borders and its homogeneity are very important. 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 [15] 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. 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 [16]. Leiomyomata could also be diagnosed by vaginal ultrasonography. They have a variety of sonographic textures ranging from hypoechoic to echogenic with a calcified border. Alternatively, degeneration and necrosis may result in decreased echogenicity. This is to be expected since these tumors have a varying amount of smooth muscle and connective tissue. However, they are most commonly identified by a deformation of the contour and size of the uterus. One can utilize TVS as a mean of monitoring the size of leiomyomas and is particularly helpful in identifying intra-ligamentous fibroids and pedunculated subserous fibroids, as well as differentiating these from intramural masses [17]. Moreover, in a study conducted by Grandberg et al., [18] to determine the value of endo-vaginal ultrasonography in women presenting with perimenopausal bleeding by comparing it to classical diagnostic curettage, 205 patients were considered. Then, curettage was performed by an experienced gynecologist. No endometrial abnormality was found if the endometrium was less than 5mm thickness [19]. Guner et al. [18] suggested taking a 4mm cut-off point for excluding endometrial abnormality in postmenopausal women, and a cut-off point of 8mm in premenopausal women. Malinova and Pehlivanov et al. [20] studied that woman with postmenopausal bleeding by transvaginal sonography. They compared these results together with results of 30 control women in relation to the histopathological results of endometrial biopsy. They found no cases of endometrial cancer when the endometrial thickness is<6mm. They conducted that a cut-off value of 6mm has a sensitivity of 100% and that there is no need to perform curettage if the endometrium <6mm [20]. They found the mean endometrial thickness for benign, hyperplastic and malignant endometrium to be 3.38mm, 6.09mm and 8.96mm; respectively [13]. It has been shown that 70% of curettages performed for postmenopausal bleeding could have been avoided if an endometrium less than 5mm had been demonstrated vaginosonographically [21]. Regarding total serum LDH, Cases with atrophic endometritis showed significantly lower mean LDH when compared to patients with simple hyperplasia, hyperplasia with atypia, endometrial carcinoma, and endometrial polyp p< 0.0001. An LDH level cutoff value of 430 could differentiate malignant from benign lesions with a sensitivity of 80.6%, specificity 57.4%, PPV 55.7% and NPV 81.5% with a diagnostic accuracy of 66.7%. 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 [22]. In a previous study in lung cancer, serum LDH dropped sharply after surgery showing that serum LDH is indeed a tumor effect [23]. 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 [24]. To our knowledge, this systematic review and meta-analysis is the first to evaluate the prevalence of PMB in endometrial cancer and the risk of endometrial cancer in women with PMB, important variables for evaluating the role of PMB in early detection of endometrial cancer. Our findings can support risk-informed decision making in clinical management of women with PMB. Finally, our results suggested a lower prevalence of endometrial cancer in retrospective and prospective cohort studies compared with cross-sectional studies. Cross-sectional studies may have been more likely to include women with recurrent bleeding; however, few studies distinguished between incident vs recurrent PMB.

CONCLUSION

TVS allows the detection of an endometrial pathology in many patients with perimenopausal bleeding. 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.

Conflict of Interest: None.

REFERENCES:

1. Mansour GM, El-Lamie IK, El-Kady MA, El-Mekkawi SF, Laban M, Abou-Gabal AI. et al. Endometrial volume as predictor of malignancy in women with postmenopausal bleeding. Int J Gynaecol Obstet. 2007; 99:206-10.
2. Timmermans MB, Gerritse BC, Opmeer FW, Jansen BW Mol, Veersema S. "Diagnostic accuracy of endometrial thickness to exclude polyps in women with postmenopausal bleeding," Journal of Clinical Ultrasound. 2008; 36(5):286-290.
3. Baser E, Gungor T, Togrul C, Turkoglu O, Celen S. Preoperative prediction of poor prognostic parameters and adjuvant treatment in women with pure endometrioid type endometrial cancer: what is the significance of tumor markers? Eur J Gynaecol Oncol. 2014; 35(5):513-8
4. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri: FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet*. 2006;95(suppl 1): S105-S143. doi:10.1016/S0020-7292(06)60031-3
5. UK CR. Uterine cancer statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer. Updated July 3, 2017. Accessed January 18, 2018.
6. Kitson SJ, Evans DG, Crosbie EJ. Identifying high-risk women for endometrial cancer prevention strategies: proposal of an endometrial cancer risk prediction model. *Cancer Prev Res (Phila)*. 2017;10(1):1-13. doi:10.1158/1940-6207.CAPR-16-0224.
7. Castle PE, Katki HA. Screening: a risk-based framework to decide who benefits from screening. *Nat Rev Clin Oncol*.

2016;13(9):531-532. doi:10.1038/nrclinonc.2016.101
8. Girschik J, Miller LJ, Addiscott T, et al. Precision in setting cancer prevention priorities: synthesis of data, literature, and expert opinion. *Front Public Health*. 2017; 5:125. doi:10.3389/fpubh.2017.00125
9. Kotdawala P., Kotdawala S., Nagar N. Evaluation of endometrium in peri-menopausal abnormal uterine bleeding. *Journal of Mid-Life Health.* 2013;**4**(1):16–21. doi: 10.4103/0976-7800.109628.
10. Takreem A., Danish N., Razaq S. Incidence of endometrial hyperplasia in 100 cases presenting with polymenorrhagia/menorrhagia in perimenupausal women. *Journal of Ayub Medical College: JAMC.* 2009;**21**(2):60–63.
11. Nazim F., Hayat Z., Hannan A., Ikram U., Nazim K. Role of transvaginal ultrasound in identifying endometrial hyperplasia. *Journal of Ayub Medical College: JAMC.* 2013;**25**(1-2):100–102.
12. Ryszard B., Rzepka-Górska I. [Transvaginal ultrasonography in the diagnosis of endometrial and uterine cavity changes in perimenopausal women] *Ginekologia Polska.* 2002;**73**(11):985–990.
13. Bender HG. Unexpected cancer diagnosed at gynecologic surgery. Clin Obstet Gynecol. 2002; 45(2):439 -48.
14. Osmers R, Volksen M, Schauer A . Vaginosonography for early detection of endometrial carcinoma? Lancet. 1990; 335:669 -71.
15. Momtaz M, Khalil A, Al Balkini N, El Shennofi O , Mosaad M . Transvaginal sonographic characterization of endometrial hyperplasia. The journal of Egyptian society of obstetrics and gynecology. 1993; XIX(1):43.
16. Kelly P, Dobbs SP, McCluggage WG. Endometrial hyperplasia involving endometrial polyps: report of a series and discussion of the significance in an endometrial biopsy specimen. BJOG. 2007 ; 114(8):944 -50. Epub 2007 Jun 12.
17. Opmeer BC, van Doorn HC, Heintz AP. Improving the existing diagnostic strategy by accounting for characteristics of the women in the diagnostic work up for postmenopausal bleeding. BJOG. 2007 ; 114(1):51 -8.
18. Guner H, Tiras MB, Karabacak O, Sarikaya H, Erdema M , Ylidirim M. et al. Endometrial assessment by vaginal ultrasonography might reduce endometrial sampling in patients with postmenopausal bleeding: a prospective study, Aus N.Z.J. Obstet Gynecol. 1996; 36:175 -8.
19. Granberg S, Wikland M, Karlsson B, Norstrom A , Friberg L (1991): Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. Am. J. Obstet. Gynecol. 1990; 164:47 -52.
20. Malinova M , Pehlivanov B . Transvaginal sonography and progesterone challenge for identifying endometrial pathology in postmenopausal women. Intern J obstet Gynecol. 1996; 52:49 -53.
21. Dueholm M, Marinovskij E, Hansen ES, Møller C, Ørtoft G. enopause. 2015; 22(6):616 -26 .
22. Krishnamoorthy N, Fatima Shanthini N. Int J Reprod Contracept Obstet Gynecol. Role of transvaginal sonography and hysteroscopy in abnormal uterine bleeding: does the diagnostic yield increase by combining transvaginal sonography, hysteroscopy and biopsy. 2014 ; 3(4):919 -92 3 .

23. Ramanathan R, Mancini RA, Suman SP, Beach CM. "Covalent Binding of 4 - Hydroxy - 2 -nonenal to Lactate Dehydrogenase Decreases NADH Formation and Metmyoglobin Reducing Activity." J Agric Food Chem. 2014; 62(9):2112 – 7

24. Xu HN, Kadlececk S, Profka H, Glickson JD, Rizi R, Li LZ. et al. "Is Higher Lactate an Indicator of Tumor Metastatic Risk? A Pilot MRS Study Using Hyperpolarized (13)C - Pyruvate.". Acad Radiol. 2014; 21(2):223 -31 .