



## Evaluation of diagnostic role of combined endometrial thickness and serum LDH for detection of endometrial carcinoma in Perimenopausal bleeding: A prospective cross-sectional study

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### Abstract

**Introduction** Per menopausal 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 per menopausal women with abnormal bleeding may have endometrial cancer. A reliable and minimally invasive method is needed to identify or exclude those cases. The tumor environment is highly hypoxic so that cancer cells have an intensified anaerobic metabolism. Cancer cells use anaerobic pathways for energy acquisition even in the presence of oxygen, a phenomenon described as "anaerobic glycolysis". 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.

**Aim of the work:** This study was done to show the role of serum lactate dehydrogenase and endometrial thickness in the detection of endometrial carcinoma.

**Material and methods:** This study was carried out at Tanta University hospital, Obstetrics and Gynecology Department, in the period from April 2017 to December 2018. This study included 90 women with perimenopausal bleeding admitted to Obstetrics & Gynecology Department at Zagazig University Hospital.

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.

**Keywords:** combined, endometrial, thickness, carcinoma, Perimenopausal

### Introduction

Per menopausal 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 per menopausal women with abnormal bleeding may have endometrial cancer. A reliable and minimally invasive method is needed to identify or exclude those cases <sup>[1]</sup>

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 <sup>[2]</sup>. 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 <sup>[3]</sup>.

Tumor markers may be useful for monitoring the clinical course of therapy and early detection of recurrence for which cytologic examination cannot be done. 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 <sup>[4]</sup>.

Lactate dehydrogenase (LDH) is a cytosolic enzyme present in all tissues, exhibiting origin- and tissue-specific isoenzymatic pattern <sup>[5]</sup>. LDH is one of the major glycolytic enzymes that catalyzes the last step of glycolysis, (conversion of pyruvate to lactate). It is a titrimetric protein composed of two

immunologically distinct subunits, “M” (muscle) and “H” (heart) type, which combine to form five isoenzymes [6].

Routine serum measurement of this enzyme is of clinical use in the diagnosis and monitoring of certain diseases including cancer especially endometrial cancer [7].

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].

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 [9].

### **Aim of the Work**

To evaluate the diagnostic role of combined endometrial thickness and serum LDH for Detection of endometrial carcinoma in cases of per menopausal bleeding.

### **Patients and Methods**

This is a prospective cross-sectional study was carried out at oncology unit, Tanta University hospital, Obstetrics and Gynecology Department, in the period from April 2017 to December 2018, to evaluate the diagnostic reliability of combined serum LDH and endometrial thickness in diagnosis of endometrial carcinoma in cases of perimenopausal bleeding. This study included 90 women with perimenopausal bleeding admitted to Obstetrics & Gynecology Department at Tanta University hospital.

- **Inclusion criteria:** Cases of perimenopausal bleeding.
- **Exclusion criteria:**
  - a. Women known to have other malignancies as breast cancer.
  - b. Hepatic, renal, cardiac patients or patient with other diseases that may elevate LDH level.
  - c. 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.

### **All patients were assured that**

1. No harmful maneuvers were to be used.
2. All data were to be secret (for research purpose only).
3. All samples were to be used in this research only.
4. The procedure will be for their benefit.
5. They could withdraw from the study at any time without giving any reasons.

### **All patients were subjected to**

- History taking 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. Measurement of endometrium was obtained in exact midsagittal plane excluding sub endometrial sonolucent 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.

### **Result**

This is a prospective cross-sectional study was carried out at oncology unit Tanta University hospital, Obstetrics and Gynecology Department, in the period from April 2017 to December 2018. This study included 90 women with perimenopausal bleeding admitted to Obstetrics & Gynecology Department at Tanta University hospital.

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 11.5mm 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 57.4%, PPV 55.7% and NPV 81.5% with a diagnostic accuracy of 66.7%. 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

Variable	Median (mean ± SD)	Range
Age (years)	(60 ± 17.6)	45-78
Parity	(5.1 ± 1.8)	3-7
BMI (Kg/m <sup>2</sup> )	(28 ± 4)	24-32

**Table 2:** Comparison between different types of histopathological findings and TVS measurement of endometrium thickness and LDH

	Histopathology						P
	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

		Lesion pathology		Total	X <sup>2</sup>	P
		Benign	Malignant			
Endometrium thickness	<11.5	29 (53.7%)	7 (19.4%)	36 (40.0%)	10.5	0.001**
	>11.5					
LDH	<430	31 (57.4%)	7 (19.4%)	38 (42.2%)	12.76	0.00**
	>430	23 (42.6%)	29 (80.6%)	52 (57.8%)		
Endometrium thickness and LDH	-VE	39 (72.2%)	14 (38.9%)	53 (58.9%)	9.91	0.002*
	+VE	15 (27.8%)	22 (61.1%)	37 (41.1%)		
Total		54 (100%)	36 (100%)	90 (100%)		

**Table 4:** Agreement between cutoff serum LDH and endometrial thickness

		Endometrium thickness		Total	X <sup>2</sup>	P	Kappa agreement	P
		<11.5	>11.5					
LDH	<430	21 (58.3%)	17 (31.5%)	38 (42.2%)	6.38	0.012*	0.266	0.012*
	>430	15 (41.7%)	37 (68.5%)	52 (57.8%)				
Total		36 (100%)	54 (100%)	90 (100%)				

**Table 5:** Validity of new cutoffs

	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. 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.* (1993) [10] 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 [10]. 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. 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 [12]. 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.* (1990) [13] who studied 155 normal postmenopausal women using 4mm endometrial thickness cut-off limit by vaginal ultrasound and reported a sensitivity of 81% [13].

Moreover, in a study conducted by Grandberg *et al.* (1991) 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. Patients were scanned endovaginally the day before operation by a transducer of 7MHz frequency. Then, curettage was performed by an experienced gynecologist. No endometrial abnormality was found if the endometrium was less than 5mm thickness [14].

Guner *et al.* (1996) [15] suggested taking a 4mm cut-off point for excluding endometrial abnormality in postmenopausal women, and a cut-off point of 8mm in premenopausal women [15].

Malinova and Pehlivanov (1996) [16] studied that women 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 [16].

Bender (2002) [17] studied 242 patients with abnormal uterine bleeding (age range 45-86 years). They found the mean endometrial thickness for benign, hyperplastic and malignant endometrium to be 3.38mm, 6.09mm and 8.96mm; respectively [17].

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 vaginasonographically [18].

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  $P < 0.05$ .

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 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). Uterine

leiomyomas patients showed intermediate LDH levels, while patients with breast fibroadenomas and ovarian cystadenomas had LDH serum levels close to carcinomas [19].

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 cutoff 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 [20].

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 [9].

## Conclusion

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

Further studies are needed using LDH isoenzymes profile and TVS endometrial morphology.

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