International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2020; 4(1): 243-247
Received: 22-11-2019
Accepted: 25-12-2019

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Assessment of endometrial thickness by ultrasonography and its histological correlation in postmenopausal women

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DOI: https://doi.org/10.33545/gynae.2020.v4.i1d.471

Abstract
Background: Endometrial cancer is currently the most common gynaecological malignancy in developed countries. The incidence of endometrial cancer is 3.7% to 17.9% in women with abnormal uterine bleeding. Most patients who have endometrial cancer present with postmenopausal uterine bleeding early in the development of the disease. Application of an appropriate and accurate diagnostic test in this situation usually results in early diagnosis, timely treatment, and a high cure rate
Methods: A total of 60 postmenopausal women attending the outpatient and inpatient cases in Department of Obstetrics and Gynaecology of PESIMSR, Kuppam, AP from May 2017 to April 2019 were included for this study. All women were subjected to transvaginal ultrasonography to look for endometrial thickness and endometrial morphological characteristics and the same was compared to histopathology findings obtained by Pippel biopsy of endometrium.
Results: The Mean endometrial thickness in atrophic endometrium was 3.86mm.The Mean endometrium in carcinoma endometrium was 21.29mm. Taking 4mm as cut off to define abnormal endometrium; this had a sensitivity of 85.71%, specificity of 62.50%, PPV of 66.66%, NPV of 83.33%.
Conclusions: The reduction to three criteria in the diagnostic formula (with the simple rule: benign if-endometrial thickness is<4 mm, endometrial structure is homogeneous, and endometrial-myometrial border is regular; otherwise pathological) resulted in a useful sonmorphological differentiation of the endometrial findings and averts unnecessary invasive intervention like endometrial biopsy in women with benign cause of postmenopausal bleeding

Keywords: Postmenopausal bleeding, endometrial pathology, endometrial thickness, ultrasonography

Introduction
The menopause is defined by the WHO as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity [1]. It 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.
The average age at menopause ranges from 45 yrs in the Indian woman to 51 years in the Western population depending on the hereditary, life style and nutritional factors [2]. Thus a woman spends more than two to three decades of life in her menopause.
Endometrial cancer is currently the most common gynaecological malignancy in developed countries. Endometrial cancer is the fourth most common cancer, ranking behind breast, lung, bowel cancer, and eighth leading cause of death from malignancy in women [3, 4]. The incidence of endometrial cancer is 3.7% to 17.9% in women with abnormal uterine bleeding [5, 6]. The incidence of endometrial cancer in asymptomatic women was 0.13% and atypia was seen in 0.63% [7].
Endometrial carcinoma when detected early can be cured with less morbidity and mortality. It has much higher cure rates if diagnosed early. Routine screening for endometrial cancer are currently not undertaken because of the lack of an appropriate, cost-effective, and acceptable test that reduces mortality [8].
Fortunately, most patients who have endometrial cancer present with postmenopausal uterine bleeding early in the development of the disease, when the tumour is still confined to the uterus. Of women diagnosed to have endometrial carcinoma, more than 90% present with irregular postmenopausal bleeding [9]. Application of an appropriate and accurate diagnostic test in this situation usually results in early diagnosis, timely treatment, and a high cure rate.

Localized disease (stage I and II) has a 5 year survival of 87% and 76% respectively, but it is much poorer for stage III with 5 year survival rate of <60% [10].

In post-menopausal women the mean endometrial thickness is considerably less than in premenopausal women. Thickening of the endometrium may indicate the presence of significant pathology. Endometrial thickness is directly related to endometrial pathology [11].

Traditionally for years, dilatation and curettage was considered "gold standard" for diagnosis of endometrial pathology. But because of the associated surgical risk, expense, postoperative pain other substitute were evaluated. Of the suitable substitute for D&C, office technique using Pipelle was found to be advantageous.

Hence a non-invasive examination like ultrasound is preferred to identify women in need of endometrial biopsy and should be the first choice in postmenopausal women with bleeding. Transabdominal sonography can be used to detect endometrial pathology including cancer but Transvaginal sonography (TVS) yields even more detailed images of the uterus [12], hence TVS is preferred. TVS is a simple, inexpensive, well-tolerated office procedure to triage patients [13]. Transvaginal sonography facilitates the measurement of endometrial thickness and morphology with good patient acceptance. Transvaginal sonography measurement of endometrial thickness and morphology has been demonstrated to have high accuracy in excluding endometrial polyps, hyperplasia and cancer in women with post-menopausal bleeding [14]. It is minimally invasive, cost effective and has high cancer detection rates [15]

Hence, this study aims at utilizing transvaginal sonography as the initial test in evaluation of post-menopausal bleeding, with biopsy as gold standard.

Methods

A total of 60 postmenopausal women attending the outpatient and inpatient cases in Department of Obstetrics and Gynecology of PESIMSR, Kuppam, AP from May 2017 to April 2019 were included for this study.

The women were selected based on the inclusion and exclusion criteria.

Inclusion Criteria

- Last menstrual cycle 12 months back (Menopausal women).
- All patients with complaints of post-menopausal bleeding.
- Age 40 years and above.

Exclusion Criteria

- Women having clinical evidence of lesion in vulva, vagina, ectocervix
- Blood dyscrasis.
- Hormonal replacement treatment.
- Patient taking tamoxifen.

Method of collection of Data

A predesigned proforma was used for all case. Detailed history including obstetric, medical, pharmacological therapy was documented and clinical examination was performed. Necessary investigation including transvaginal sonography, endometrial sampling by Pippele biopsy was done following written consent. Treatment plan was formulated depending upon the Histopathological report.

Transvaginal sonography

The subject is informed about the procedure and Transvaginal Sonography is done in dorsal position.

- The endometrium was imaged in the longitudinal and cross sectional plane through the body and fundus of the uterus.
- The thickest point of the endometrium was measured from the anterior to posterior myometrial-endometrial junction.
- Both layers of the endometrium were measured, that is the anterior and the posterior layers.
- If there was fluid in the cavity each layer was measured separately and summed up.
- Morphological changes like appearance of the endometrial strip (homogenous /heterogeneous), endometrial thickness (diffuse/focal), margin (regular/irregular) were also noted.

Endometrial Biopsy

After TVS patients were subjected to Pippele endometrial biopsy within 24 hours. All the tissue were fixed in 10% formalin and sent for Histopathological examination. The histopathology of the endometrium was considered gold standard.

Results

All 60 cases were subjected to TVS followed by Histopathological examination of endometrial biopsy and results analysed in comparison.

Following *criteria* were assessed by TVS

Endometrial thickness, characteristics of endometrial thickening (focal/diffuse), endometrial structure and endometrial-myometrial border.

Endometrial thickness was considered diffuse when whole of the endometrial cavity was thickened and focal, if limited to a part of endometrial cavity. The structure was defined as homogeneous if the entire endometrium was characterized by uniform echogenicity. A heterogeneous endometrium was associated with varying echogenicity and an amorphous structure. The endometrial-myometrial border was assessed as being regular (with a smooth course) or irregular (with an uneven course).

Age distribution ranged between 42 to 72 yrs. Most of the women belonged to 46-50 yrs of age (30%), 76% of women were below 60 yrs of age. Women of all parity were represented in the study. 28% had 3 pregnancies. 61.66% sought medical care for post-menopausal bleeding within 3 months of onset of symptoms. Most of the women presented with postmenopausal bleeding within 5 years (48.33%) of menopause. Range of distribution was between 1 to 18 years after menopause

All 60 cases were subjected to Pippele endometrial biopsy. Histopathological diagnosis was obtained in 54 cases. In 6 cases histological diagnosis was not possible either due to insufficient sample or no sample at all, these cases were presumed to be due to atrophic endometrium

Table 1: distribution of finding in histopathology of endometrium

S. N.	Histopathology Report	No of Cases	% Of Total N
1.	Atrophic	16	26.7%
2.	Atrophic -Sample Insufficient For Diagnosis	6	10.0%
3.	Proliferative	8	13.3%
4.	Secretory	2	3.3%
5.	Leiomatous Polyp With Simple Hyperplasia	1	1.7%
6.	Adenomatous Polyp With Simple Hyperplasia	1	1.7%
7.	Simple Hyperplasia	9	15.0%
8.	Simple Hyperplasia With Atypia	2	3.3%
9.	Complex Hyperplasia	2	3.3%
10.	Complex Hyperplasia With Atypia	6	10.0%
11.	Adenocarcinoma	6	10.0%
12.	Squamous Cell Carcinoma	1	1.7%
Total		60	100.0%

Histological diagnosis of the endometrium obtained was considered "gold standard". Atrophic, Secretory and proliferative endometrium which constituted about 53.33% were considered normal. Polyp, hyperplasia and carcinoma which constituted 46.66% were considered to be pathological and labelled as abnormal.

Table 2: comparison of histopathology with endometrial thickness

S. N	Histopathology	No Of Cases	% Of Total	Et–Minimal (Mm)	Et-Maximum(Mm)	Et-Mean(Mm)
1.	Atrophic	16	26.7%	2.6	9.0	4.01
2.	Atrophic -Sample Insufficient For Diagnosis	6	10.0%	1.8	4.0	2.73
3.	Proliferative	8	13.3%	3.6	14	8.63
4.	Secretory	2	3.3%	6.0	18	12.00
5.	Leiomatous Polyp With Simple Hyperplasia	1	1.7%	32	32	32.00
6.	Adenomatous Polyp With Simple Hyperplasia	1	1.7%	15	15	15.00
7.	Simple Hyperplasia	9	15.0%	3.2	15.2	7.84
8.	Simple Hyperplasia With Atypia	2	3.3%	8.0	20	14.00
9.	Complex Hyperplasia	2	3.3%	12.0	16.0	14.00
10.	Complex Hyperplasia With Atypia	6	10.0%	9.0	30.00	16.83
11.	Adenocarcinoma	6	10.0%	12.0	40.0	21.83
12.	Squamous Cell Carcinoma	1	1.7%	18	18	18.00
Total		60	100.0%			

Mean endometrial thickness in atrophic endometrium was 3.86mm.Mean endometrium in carcinoma endometrium was 21.29mm

Table 3: Accuracy of diagnosis by endometrial thickness with e.t >4mm to define abnormality.

Histopathology E.t >4mm	Abnormal	Normal	Total
YES	24	12	36
NO	4	20	24
TOTAL	28	32	60

Sensitivity:-85.71%, Specificity:-62.50%, PPV:-66.66%, NPV:-83.33%

Table 4: comparison of TVS findings with histopathology

Histopathology Tvs	Atrophic	Proliferative Secretory	Polyp	Hyperplasia	Carcinoma	Total
Atrophic	19	1	-	4	-	24
Hyperplasia	1	9	-	12	2	24
Polyp	1	-	1	1	-	3
Carcinoma	1	-	1	2	5	9
Total	22	10	2	19	7	60

Table 5: Accuracy of diagnosis by TVS findings

Histopathology TVS	Abnormal	Normal	Total
Positive TVS	24	12	36
Negative TVS	4	20	24
Total	28	32	60

Sensitivity:-85.71% Specificity:-62.50% PPV:-66.66% NPV:-83.33

All cases were subjected to TVS and diagnosis was arrived depending on the thickness, morphology, endometrial margins and echogenicity of endometrium.

Atrophic appearing endometrium constituted to 40% of cases and was considered normal.

Hyperplasia, polyp, carcinomatous appearing endometrium was considered pathological finding and constituted to 60% of cases

Over all comparing, TVS diagnosed 5 cases of endometrial carcinoma correctly and over diagnosed 4 cases which turned out to be hyperplasia in 2 cases, polyp and atrophic endometrium in 1 case each. 2 cases of endometrial carcinoma were missed and were diagnosed as hyperplasic endometrium hyperplasia. 12 cases of endometrial hyperplasia were diagnosed correctly, over diagnosing 12 cases out of which 10 cases turned out to be proliferative endometrium on HPE. TVS missed 7 cases of hyperplasia which were diagnosed as atrophic in 4 cases, polyp in 1 case, and carcinoma in 2 cases. Out of 22 cases

of atrophic endometrium diagnosed by histopathology, 19 cases of atrophic endometrium were diagnosed correctly by sonography; three cases were missed.

Discussion

The Present study was a prospective descriptive study. Factors like age at presentation, parity, duration of complaints, years after menopause at presentation, various characteristics of TVS findings and histopathology of endometrium were compared and analysed.

Most of the women belonged to 46-50 yrs of age (30%) with the range of age distribution between 42 to 72 yrs.

In the study group the mean age of occurrence of carcinoma was at 56 yrs with 85% of cases above the age of 50.Various studies have shown that the Endometrial carcinoma most often occurs in women in the sixth and seventh decades of life, at an average age of 60 years with 75% of cases occurring in women older than 50 years of age.

In our study there was no significant association between endometrial thickness and age. Women of all parity were represented in the study.

Table 6: Histopathological findings of the endometrium in postmenopausal bleeding women as compared to other studies.

Histopathology	Meta-Analysis [16] (N=4592)	Present Study (N=60)
Normal Endometrium	57.0%	53.3%
• Atrophic/Insufficient Sample	44.7%	36.7%
• Proliferative	08.8%	13.3%
• Secretory	01.0%	03.3%
Polyps	13.1%	3.4%
Hyperplasia	10.3%	31.6%
• Simple	08.6%	18.3%
• Complex	01.9%	13.3%
Carcinoma	11.0%	11.7%
Other Pathology	08.4%	-

The above table represents the summary of different endometrial pattern compared to a meta-analysis.

Following were the significant observation.

- Benign conditions (atrophic, proliferative & secretory) were the most common cause of post-menopausal bleeding contributing to 53% of cases.
- Polyps were noted only in 2 cases contributing to 3.4% of cases whereas other studies showed a varied incidence from (Weiderpass *et al.*) 9.4% to13.1%, 2 cases with polyp had associated hyperplastic endometrium.
- Incidence of hyperplasia in present study was 31.6% and the incidence of malignancy was 11.7% which correlates well with incidence in other studies.

So, half the case of post-menopausal bleeding will have benign pathology with chances of malignancy being 1 in 10.

Table 7: Endometrium thickness in postmenopausal bleeding women.

Biopsy results	Karlsson *et al.*		Present study	
	No of cases	Mean thickness in mm	No of cases	Mean thickness in mm
Atrophic	667	3.9	22	3.86
polyp	140	12.9	02	23.0
hyperplasia	112	12.0	19	11.93
Endometrial cancer	114	21.1	07	21.29

The above table compares the findings of mean endometrial thickness with histopathology as comparable with other similar studies [17].

In postmenopausal women, the maximum thickness of the endometrium is one of the main criteria used in the assessment of sonographic endometrial features. Through measurement of endometrial thickness, endometrial abnormalities are diagnosed with a high sensitivity but a low specificity. Most studies show that there is only a low incidence of an endometrial carcinoma when the endometrial thickness is < 4 or 5 mm

The Present study showed that the mean endometrial thickness was 3.86mm and there were no cases of cancer with thin endometrium. All patients with malignancy had an ET more than 12 mm with mean ET of 21mm. Hence 4 mm ET was taken as cut off to define endometrial pathology in our study. The Sensitivity, Specificity, Positive predictive value and Negative predictive value was calculated and compared with various other studies.

In this study, sonmorphological characteristics like structure (homogenous/heterogeneous) had sensitivity of 28.57%, specificity of 96.87%, PPV of 88.88% and NPV of 60.78%.Homogenous thickening of endometrium is caused by both benign and pathological condition yielding low sensitivity.

Comparison of the different studies with sonomorphological assessment is difficult because of the different sample sizes, patient characteristics (with and without postmenopausal bleeding), heterogeneous collectives (with and without hormone replacement therapy), different sonographic criteria, and different methods of statistical analysis. In addition, the analyses of sonographic assessments are aimed either at the detection of endometrial pathology in contrast to normal endometrium in some studies or at the detection of endometrial carcinomas in contrast to benign endometrial findings in other studies. A comparison of the discriminating criteria in these studies is difficult.

In present study analyses of sonographic assessments was aimed at the detection of endometrial pathology in contrast to normal endometrium.

Margin and character analysis yielded sensitivity of 85.71%, specificity of 62.50%, PPV of 66.66% and NPV of 83.33%. The accuracy of endometrial thickness as 4 mm cut off also yielded similar result inferring that, morphological characteristics and endometrial thickness has good correlation.

Hence, in present study sonmorphological analysis was unnecessary in cases with an endometrial thickness of < 4 mm. Value of morphological characteristics may add to accuracy in diagnosis of endometrial cancer from other condition when endometrial thickness >4mm.

Conclusion

Transvaginal sonography is safe, simple, non-invasive and cost effective tool in the diagnosis of endometrial disease.

It can be used as the first line investigation in women with postmenopausal bleeding.

Endometrial thickness ≤4mm is associated with benign lesion in women with postmenopausal bleeding.

The combination of morphological features with endometrial thickness on gray scale ultrasound increases the diagnostic accuracy when endometrial thickness >4mm.

The reduction to three criteria in the diagnostic formula (with the simple rule: benign if- endometrial thickness is<4 mm, endometrial structure is homogeneous, and endometrial-myometrial border is regular; otherwise pathological) resulted in a useful sonomorphological differentiation of the endometrial

findings.

A lesion if considered abnormal or suspicious can be further investigated and the mode of investigation can be decided based on findings.

Use of saline infusion sonohysterography can increase the accuracy of findings especially in diagnosing endometrial polyps.

Transvaginal sonography will certainly not replace the histological examination. Endometrial biopsy combined with hysteroscopy remains the gold standard for endometrial assessment. However, the combined assessment of sonographic endometrial morphology and measurement using the diagnostic guidelines may improve the diagnostic accuracy of TVS and averts unnecessary invasive intervention like endometrial biopsy in women with benign cause of postmenopausal bleeding

Declarations

Conflict of interest: None

Ethical approval: Obtained from institutional ethical committee

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