



ORIGINAL RESEARCH PAPER

Pathology

ASSESSMENT OF ENDOMETRIUM USING TRANSVAGINAL SONOGRAPHIC ENDOMETRIAL THICKNESS AND ENDOMETRIAL BIOPSY IN PERIMENOPAUSAL ABNORMAL UTERINE BLEEDING

KEY WORDS: Abnormal uterine bleeding, Endometrial biopsy, Transvaginal sonography

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ABSTRACT

Background: Abnormal uterine bleeding (AUB) is a major gynecological problem in perimenopausal and postmenopausal age group. **Aim:** This study is intended to investigate the association between endometrial thickness in transvaginal sonography (TVS), the results of endometrial biopsy in perimenopausal women with AUB and to evaluate the combined use in diagnosis of endometrial lesions. **Materials And Method:** A retrospective study of 250 perimenopausal women with AUB were enrolled. Data was analyzed using SPSS V 22.0. **Results:** 160 samples were identified to be benign lesions, 85 were with Hyperplasia and 5 were Malignant. The mean endometrial thickness in subgroup benign were 6.57± 3.06 mm and Malignancy were 17.97±2.79mm. The sensitivity of endometrial biopsy to identify Hyperplasia with or without Atypia was 93.5% and carcinoma was 100%. **Conclusion:** The study infers that as the endometrial thickness rises the chances of getting abnormal endometrial histological finding increases. A cut-off point of 10.50mm for endometrial thickness using transvaginal ultrasound can predict the results of Pipelle endometrial sampling well.

INTRODUCTION

Normal menstruation is defined as the bleeding from secretory endometrium with an ovulatory cycle, not exceeding length of 5 days. Any bleeding not fulfilling the criteria is referred to as abnormal uterine bleeding (AUB). AUB includes a decrease or increase in blood loss during menses, a decrease or an increase in the length of menses and irregular bleeding episodes occur at frequent interval between menses. It may also occur as prolonged bleeding at irregular intervals.^{1,2}

AUB is a major gynecological problem in peri-menopausal and postmenopausal age group³, affects up to 50% of perimenopausal woman.⁵ AUB may be the most common presenting complaint in patients with pre-malignant or malignant endometrial lesion.⁴ One third of patients attending gynecology OPD present with complaints of AUB,⁵ pointing out the sheer magnitude of the disease .

The incidence of endometrial cancer is increasing steadily in countries around the world. Endometrial cancer is most commonly encountered in postmenopausal patients, although 25% cases occur prior to menopause, with 5% in patients younger than 40 years. As of a study in Korean 2010, 37.1% of cases occurred in women in their 50s, whereas 25.6% of cases occurred in women in their 40s (25.6%).⁷ For these reasons, it could be inferred that endometrial evaluation have clinical relevance in premenopausal women.

Simpler and less invasive technique may allow for the selection of subjects in whom an early diagnosis of endometrial cancer can be made. There are various methods of determining the endometrial pathology, even since time immemorial the invasive procedure of biopsy is considered to be the gold standard.^{8,9} There are a plethora of tools for performing an endometrial biopsy in outpatients. Pipelle is one of the most commonly used tools. Most studies on aspiration cytology have agreed upon the fact that endometrial aspiration smear are notoriously difficult to interpret owing to lack of adequacy defining criteria, distinct categorization of lesions and limited value for interpretation

of functional abnormality and require much expertise.⁸ However, they remain a convenient source for the identification of endometrial pathology; as it is an OPD procedure without demanding hospital admission ,gaining patients acceptance to the procedure.

Few studies have been carried out to determine the extent to which thinness of the endometrium can reject the probability of cancer. Transvaginal sonography (TVS) due to its simplicity, some doctors prefer it over endometrial biopsy. Due to the importance of early detection of malignancies in perimenopausal women and considering timely treatment for these patients, a positive step is taken through our study in diagnosing endometrial malignancies through assessing endometrial thickness using TVS.

AIM

The study aims to investigate the association between endometrial thickness in transvaginal ultrasound and the results of Pipelle endometrial sampling and its combined use in perimenopausal women with abnormal uterine bleeding. Also to correlate the findings with histopathology as a standard of final diagnosis, thus will help to pin point the underlying disease and in proper management of these patients. It will aid in obviating the need for more invasive diagnostic procedures

MATERIAL AND METHODS

The present study was a retrospective study conducted in Department of pathology K.V.G medical college and hospital, Sullia over a period of 2 years extending from January 2020-January 2022 in perimenopausal females patients with complains of abnormal uterine bleeding and who underwent a transvaginal ultrasonography. Later all of them had a Pipelle endometrial sampling performed by a gynecologist, followed by hysterectomy whenever indicated.

The patients were included in the study based on these criteria:

Inclusion Criteria

- Perimenopausal age group (40–55 years)

- Having abnormal uterine bleeding
- Undergone TVS with endometrial pipelle
- Hysterectomy whenever possible

Exclusion Criteria

- Postmenopausal bleeding
- Evident drug intake history or general cause that can lead to vaginal bleeding
- Hemorrhage due to systemic diseases such as coagulation and/or thyroid diseases, regular drug-induced bleeding, virgin women, bleeding caused by cervical and vaginal diseases, and fibroids.
- Pregnancy
- Genital tract infections and PID

Records available in department of pathology were analyzed based on inclusion and exclusion criteria. 250 women's reported with AUB were selected based on universal sampling technique. The data related to their age, parity, main complaints, duration of the problem, history of previous illnesses, history of menstrual-based problems, transvaginal ultrasound endometrial thickness, pipelle aspirate results and histopathological findings were recorded.

STATISTICAL ANALYSIS

Statistical analysis will be done by using descriptive and inferential statistics using Chi-square test, sensitivity, accuracy and software used in the analysis were Statistical Package for the Social Sciences (SPSS) 22.0 version and Fisher's Exact test the p value $p < 0.05$ is considered as the level of significance.

RESULTS

The present study comprises of evaluation of 250 clinically diagnosed cases of AUB which were received at the department of pathology, K.V.G medical college and hospital, Sullia.

Table 1: Demographic parameters of patients.

| Parameter | Most common findings | Percentage |
|----------------------|---------------------------------|------------|
| Age group | 41 – 50 YEARS (42.21 ± 4.94) | 64.8% |
| Parity | Multiparous (P2) | 34.8% |
| Bleeding pattern | Menorrhagia | 56.6% |
| Duration of symptoms | <6 Months | 64.8% |
| Previous cycles | Irregular | 52.2% |

Most common age group was 41 to 45 years, mean age being 42.18 ± 4.93 years. The incidence of AUB was found to be highest in multiparous and least in nulliparous women. Menorrhagia was the most common bleeding pattern seen in 56.6% of cases. 61.8% patients had symptoms for less than 6 months before seeking a medical opinion. 52.2% of patients had previous irregular menstrual cycle

Out of 250 patients, the most common pattern in pipelle biopsy was secretory endometrium, 88 cases (35.2%). This was closely followed by hyperplasia without atypia (32.8%) and proliferative endometrium (21.6%). Disordered proliferative endometrium was seen in 5.6%. Atypical Hyperplasia and chronic endometritis was seen in 1.2% of cases. Patient with endometrial adenocarcinoma was accounting for 2% of cases. One case of benign endometrial polyp was identified.

Table 2: Endometrial thickness (ET) on transvaginal sonography of and age correlation

| Pipelle finding | Age variation | ET by TVS | Number of patients |
|----------------------------|---------------|--------------|--------------------|
| Without disease/ benign | 41.11 ± 5.10 | 6.57 ± 3.06 | 160 (63.9%) |
| Hyperplasia without atypia | 44.06 ± 4.08 | 12.78 ± 4.79 | 82 (32.9%) |
| Atypical Hyperplasia | 40 ± 2.82 | 14 ± 5.65 | 3 (0.8%) |
| Malignancy | 45.60 ± 2.30 | 17.40 ± 2.79 | 5 (2%) |

According to the ultrasound results the mean endometrial thickness (ET) in subgroup without disease/ benign was 6.57 ± 3.06 , and endometrial carcinoma 17.97 ± 2.79 which was statistically significant ($p = 0.0001$). No abnormal histopathology finding was found below ET of <6mm. All cases with carcinoma had ET exceeding 5mm. When investigating the correlation between the patient's age and their ET, the results obtained from ultrasounds revealed that the age of patients was significantly and positively correlated with the ET. In other words, by growing older the thickness of the endometrium increases. There was a definite risk for endometrial carcinoma with advancing age

Table3: Comparison of pipelle biopsy with histopathology after hysterectomy

| PIPELLE | HISTOPATHOLOGICAL FINDINGS | | | | | | | | | |
|--------------------|----------------------------|----|----|----|------|------|---------|-----|-----|----|
| | PP | SP | CE | EP | HP-W | HP-A | HP-W+EP | ECA | DPE | NA |
| PP(54) | 31 | 0 | 1 | 7 | 0 | 0 | 0 | 0 | 0 | 15 |
| SP(88) | 0 | 50 | 3 | 8 | 0 | 0 | 0 | 0 | 0 | 27 |
| CE(3) | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| EP(1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| DPE(14) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 13 |
| HP-W(82) | 0 | 0 | 0 | 0 | 68 | 8 | 6 | 0 | 0 | 0 |
| HP-A(3) | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| ECA(5) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 |
| | 31 | 50 | 6 | 15 | 68 | 11 | 6 | 5 | 1 | 57 |
| Significance level | P < 0.0001 | | | | | | | | | |

(PP-proliferative phase, SP- secretory phase, CE- chronic endometritis, EP- endometrial polyp, DPE- disordered proliferative endometrium, HP-W- hyperplasia without atypia, HP-A-atypical hyperplasia, ECA- endometrial carcinoma)

Among 250 patients, 193 underwent subsequent hysterectomy for AUB. HPE pattern of the hysterectomy was analyzed and secretory phase was the most common one as in the Pipelle biopsy closely followed by hyperplasia without atypia. There were 5 cases of carcinoma endometrium. There were 54 cases of proliferative endometrium out of which 39 patients underwent hysterectomy. Among 39, 31 cases had similar findings, 7 patients had additional lesion of endometrial polyp and one had chronic endometritis. 88 cases of secretory endometrium out of which 61 underwent hysterectomy, 50 cases showed similar finding, 3 cases of chronic endometritis and 8 cases of endometrial polyp was noted. There were 82 cases of hyperplasia without atypia in Pipelle biopsy out of which all underwent hysterectomy. In subsequent report 8 had higher grade of lesion atypical hyperplasia and the remaining where in concordance with pipelle biopsy and 6 had additional lesion of endometrial polyp along with hyperplasia without atypia.

All 3 patients with atypical hyperplasia and 5 patients with endometrial carcinoma underwent hysterectomy and showed concordance in results. 3 cases of chronic endometritis and one case of endometrial polyp underwent medical management. 13 cases of disordered proliferative endometrium were managed medically and one underwent hysterectomy. The incidence of carcinoma endometrium among this study population was 2%.

Pipelle biopsy had 93.5% accuracy for atypical hyperplasia, and 100% for diagnosing carcinoma endometrium. In analyzing the validity of Pipelle biopsy for diagnosing endometrial hyperplasia and carcinoma by Fisher's Exact test the p value for both was $p < 0.0001$, and was statistically significant.

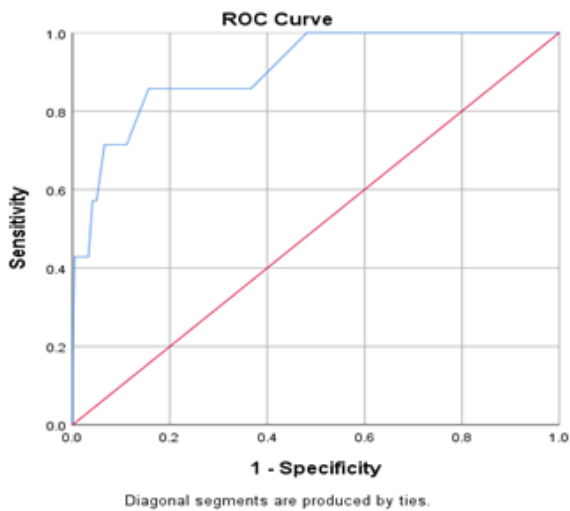


FIGURE 1: ROC curve showing the correlation between endometrial thickness and sensitivity diagnoses made based on Pipelle endometrial sampling

Based on the evaluation of the receiver operating characteristic curve (ROC) curve, the cut-off point for endometrial thickness was calculated to be 10.50, with a sensitivity of 61.84% and a specificity of 72.25 %.(Figure 1)

DISCUSSION

The primary objective of this study was to investigate the association between endometrial thickness in ultrasound and the results of Pipelle endometrial sampling.

The highest incidence of AUB was noted in the age group of 41-45years in the present study which is in concordance with the results of Mathew SM et al (2019)¹⁰, Gadge A et al(2018)¹¹, Gopalan U et al(2017)¹², Perween R et al(2016)¹³ and Mahapatra M et al (2015)¹⁴ whereas, Doraiswami Saraswathi (2011)¹⁵ reported maximum incidence in 41-50 years age group, Muzaffar et al (2005)¹⁶ reported maximum incidence in 31-40 years age group. Considering these discrepant observations, one may conclude that any age after menarche is not exempt from AUB.

In our study, AUB is most common in multipara i.e. para 2 (34.8%) patients than in nulliparous or primiparous. It is in concordance with the result of the study done by Bhosle et al. (2010)¹⁷ Jagadale et al. (2015)¹⁸. The importance of parity however lies primarily in relation to management, which is often determined by whether a women wants more children and whether hysterectomy is acceptable

The most common bleeding pattern in patients with AUB was Menorrhagia (56.6%). Muzaffer et al. (2005)¹⁶ and Bhosle et(2010)¹⁷ also found menorrhagia as being commonest type of bleeding pattern seen in 51.9%, 53.3% and 44% patients respectively.

In the present study secretory phase (35.2%) was found to be most common histological pattern followed by simple hyperplasia without atypia (32.8%). Among 250 cases, 82 cases were hyperplasia without atypia and 3 were hyperplasia with atypia. Hyperplasia without atypia was the commonest finding among the types of hyperplasia in AUB in present study which was similar to studies conducted by Allisan et al.¹⁹ and Vaidya et al.²⁰ Majority of the studies including the present study indicate that, the incidence of hyperplasia in AUB ranges from 19.4% to 31.25% whereas, a few other studies reported a higher incidence at 52 % to 62% range while the lowest incidence 7% was reported by Sanyal.²³

In 72 Of 82 cases operated for hyperplasia without atypia,

pipelle and post hysterectomy histology samples were in agreement, 8 had higher grade of lesion (atypical hyperplasia) in histopathology. Identification of endometrial hyperplasia is important because they are thought to be precursors of endometrial carcinoma. In the present study, the two important observations were made regarding endometrial hyperplasia in AUB and they are: Endometrial hyperplasia was highest in the age group of 41-50 years, it was highest in patients with history of heavy menstrual bleeding.

All the 3 case of atypical hyperplasia and 5 case of endometrial carcinoma were correctly identified in pipelle. The incidence of endometrial carcinoma varied between 1% and 6.4% in various studies on endometrial patterns in AUB. The present study reported an incidence of 2%. The mean age of patients with endometrial carcinoma was 45.60 ±2.30 years.

The accuracy of Pipelle endometrial biopsy was compared with studies by Mathew SM et al¹⁰, A S Alliratnam et al²¹, Sanam M et al ²². Pipelle was found to have an accuracy of 93% and 100% in detecting atypical hyperplasia and carcinoma endometrium respectively in our study.

Out of 21 cases of endometrial polyp only one case of polyp was picked up by the pipelle sampling. Failure of obtaining a sample was reported in 7% of the patients in pipelle sampling in A S Alliratnam et al²¹ study. This high rate of false-negative results is a problem for all blind endometrial sampling methods. Thus, if blind endometrial sampling fails to yield sufficient tissue for histological examination or if the histological report does not show evidence of endometrial disease, the clinician should consider the possibility of a missed lesion

However when pipelle histology was different from the corresponding post hysterectomy specimen, the actual endometrial pathology was due to benign condition.

By performing different analyses what is being addressed in the present study is the diagnostic accuracy of endometrial thickness in detecting malignancies from Pipelle endometrial sampling in the perimenopausal women. The mean ET in subgroup without disease was 6.57± 3.06 and endometrial carcinoma 17.97±2.79. In our series, all endometrial carcinomas were associated with an ET greater than 12 mm.

In this study we observed no abnormal histopathology finding was found below ET of 6mm. By carrying out an ultrasound and determining the thickness of the endometrium, a great deal of sampling can be reduced. We suggest an initial TVS to identify women at risk for endometrial disease. If a thin endometrial lining of 6 mm or less is visualized, patient can be safely followed up and no endometrial sampling is indicated.

One of the most important findings of this study was the calculation of the ET cut-off point. According to the result, the cut-off point obtained was 10.50 and this can be helpful in detecting malignancies in perimenopausal women. The cut-off point obtained in this study is similar to that mentioned in the parisa et al²³. In a study carried out by Getpook et al²⁴ The cut-off point for ET is 8mm, with a sensitivity and specificity of 80% and 53.8% respectively slightly lower value than in our study.

Another significant finding in this study was the effect of age's positive feedback on endometrial thickness. In other words, as women grow older, an increase in ET is not unexpected.

Based on the results of this study, the mean thickness of the endometrium was significantly higher in women with malignant diagnoses than in women with benign diagnoses.

Therefore, the results of this study indicated the association between endometrial thicknesses in TVS with malignant diagnoses made based on Pipelle endometrial sampling

However accurate ultrasonography may be, it must be emphasized that a sonographic picture cannot replace the histologic diagnosis of an endometrial lesion. Therefore, we propose the combined use of both TVS and endometrial sampling as an office-based approach to perimenopausal endometrial disease.

CONCLUSION

From this study, we inferred that as the endometrial thickness (ET) raises the chances of getting abnormal endometrial histological finding increases. Using the ET parameter in vaginal ultrasound can be effective in predicting benign or malignant endometrial sampling

Determining the cut-off point of 10.5mm for endometrial thickness using TVS in perimenopausal women is a suitable, noninvasive method, the results of which can predict the results of Pipelle endometrial sampling well.

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