Clinical study of risk factors and ultrasonographic correlation of endometrial hyperplasia according to the WHO classification 2014

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ABSTRACT

Background: Type 1 endometrial carcinoma is usually preceded by atypical hyperplasia. Nonatypical hyperplasia should be managed conservatively and atypical hyperplasia have to be managed aggressively. So, the diagnosis is crucial for its management.

Methods: The study population included women diagnosed with endometrial hyperplasia by histopathology as per WHO classification 2014 from the year January 2015 to February 2020. Women with endometrial polyp diagnosed by transvaginal ultrasonography and histopathology were excluded. Primary objective was to compare the endometrial thickness between the two types of hyperplasia. Secondary objective was to analyses the risk factors of the two types.

Results: In multivariate analysis of logistic regression, diabetic women have 1.57 times risk of developing atypia and obese women have 3.12 times risk of developing atypia. Polycystic ovarian disease is having borderline significance for causing atypia. There was significant difference in endometrial thickness between atypical and nonatypical hyperplasia (P=0.040). In premenopausal women, (P=0.069) the thickness difference in atypia is of only borderline significance. Heteroechoic pattern or cystic spaces in the endometrium also didn’t predict atypia.

Conclusions: Mean endometrial thickness is significantly different in atypical hyperplasia. Heteroechoic pattern of endometrium do not predict atypia. We need color doppler sonography to gain knowledge about atypia. Obesity and diabetes mellitus are significant risk factors of atypia.

Keywords: Endometrial hyperplasia, WHO classification, Risk factors, Endometrial thickness

INTRODUCTION

Endometrial hyperplasia is a premalignant condition, if untreated can lead to the adenocarcinoma of the endometrium which ranks first in the list of malignancies affecting women. The revised 2014 WHO classification of endometrial hyperplasia divides it into only two categories; Hyperplasia with and without atypia. Endometrial hyperplasia by all means, was considered as precursor to malignancy with variable risk of progression to malignancy.1 But the current knowledge gives more importance for atypia as a premalignant condition than hyperplasia without atypia. Type 1 endometrial carcinoma is usually preceded by atypical hyperplasia. Risk factors and predisposing conditions are different in both the categories. Existing literature has more evidence about hyperplasia of different categories of traditional histopathological classification which had variable degrees of diagnostic reproducibility. Based on present classification of hyperplasia, both the types have to be approached in a different manner. Nonatypical hyperplasia should be managed conservatively and
atypical hyperplasia have to be managed aggressively. So, the diagnosis is crucial for its management.

Transvaginal ultrasonography is routinely used to measure the endometrial thickness in evaluating the cause of endometrial pathology in women with abnormal uterine bleeding. Endometrial thickness in the premenopausal women varies from 4 mm to 16 mm in the various phases of menstrual cycle. In postmenopausal women, cut off for the normalcy of the endometrium is 4 mm. Various studies have validated the endometrial thickness to predict the atypia and malignancy in the postmenopausal women, but only limited literature is available in the perimenopausal women. In this study, we tried to analyse the risk factors and ultrasound characteristics of both the types of endometrial hyperplasia according to the WHO classification 2014 in premenopausal and postmenopausal women.

METHODS

We conducted this study in the tertiary medical center-Amrita Institute of medical sciences, Kochi, Kerala, India. The study population included women diagnosed with endometrial hyperplasia by histopathology as per WHO classification 2014 from the year January 2015 to February 2020. Women with endometrial polyp diagnosed by transvaginal ultrasonography and histopathology were excluded. Women with confirmed endometrial malignancy by hysterectomy were also excluded. This study is a retrospective study comparing the clinical and ultrasonographic features of nonatypical and atypical endometrial hyperplasia. Primary objective was to compare the endometrial thickness between the two types of hyperplasia. Secondary objective was to analyses the risk factors of the two types.

Women attending the gynaecology outpatient department with the complaints of abnormal uterine bleeding were screened by transvaginal ultrasonography after methodical clinical examination. For women with irregular cycles and prolonged bleeding (AUB) and postmenopausal bleeding (PMB), endometrial thickness (ET) was measured at the time of presentation. Others with heavy menstrual bleeding (HMB), intermenstrual bleeding (IMB), ET was measured in the secretory phase of the cycle. Endometrial thickness was measured between outer lining of anterior and posterior layers of endometrium in the midsagittal plane. Fluid in between the layers was not included in the thickness. Details of associated imaging findings were also recorded. According to the consultant’s discretion and the clinical condition of the patient, dilatation and curettage, pipe line sampling or hysteroscopy and biopsy were done to get the sample for histopathological diagnosis. All these data including the clinical details were taken from the electronic medical records of the patient which is prospectively maintained.

Estimation of sample size and statistical analysis

Group1- hyperplasia with atypia mean ET 12.47±3.47, group 2 hyperplasia without atypia 9.07±3.16. Based on the mean and standard deviation of endometrial thickness in both the groups, observed in a small pilot study conducted with 20 samples in women diagnosed with endometrial hyperplasia with and without atypia, with 80% power, 95% confidence, the minimum sample size comes to 15 per each group

Mean and standard deviation of continuous variables-age, endometrial thickness in women diagnosed with hyperplasia with 95% confidence was computed. To test the statistical significance of difference in mean of continuous variables between two groups, student’s t test was used. To test the statistical difference in the proportion of categorical variables-parity, symptoms, duration, all risk factors and endometrial hyperplasia with and without atypia, chi square test was used.

RESULTS

Total of 948 histopathology reports of endometrial hyperplasia were retrieved using lesion index from the prospective database.13 of malignancy, 31 of polyps and 16 of hyperplasia in the hysterectomy specimen were excluded. Others with repeated medical record numbers (entries) and reports based on old WHO classification were also excluded. The remaining 599 was our study population. They were divided into two groups of Hyperplasia with and without atypia. Basic demographic details and symptomatology are given in (Table 1). Risk factors distribution is depicted in (Table 2, 3). Ultrasonographic features of both groups are given in (Table 4). Women with nonatypical hyperplasia (n=376) and atypical hyperplasia (n=223) were analysed for their clinical and ultrasonographic presentation.

Mean age, parity and distribution of menopause and pre menopause were not different in both the groups. Nulliparity is not common in our groups and equally distributed in both women. Nonatypical hyperplasia group has more of higher parity women. As anovulation revolves around perimenopause, typical presentation of anovulatory cycle-amennorhoea followed by AUB is more common in nonatypical hyperplasia. HMB is the next frequent symptom in both the groups. IMB is very less in our population. 12.5% of the total study population was asymptomatic. Women without atypia were more among asymptomatic women. The presentation was significantly different in both groups. AUB and incidental finding were more common in women without atypia (p=0.021) Women without atypia had shorter duration of symptoms than women with atypia. Chronic symptomatology was equally prevalent.

Diabetes mellitus (type 2) and obesity (BMI>28) were considered to be significant risk factors for atypia. In multivariate analysis of logistic regression, Diabetic women have 1.57 times risk of developing atypia and obese women have 3.12 times risk of developing atypia.
Polycystic ovarian disease (PCOD) is having borderline significance for causing atypia. All these factors can cause chronic anovulation and hyperestrogenism. Hypertension, personal and family history of malignancy didn’t find significance as risk factor in our study.

Table 1: Basic demographic details and symptomatology.

| Variable          | Category               | Hyperplasia with atypia (n=223) | Hyperplasia without atypia (n=376) | P value |
|-------------------|------------------------|----------------------------------|------------------------------------|---------|
| Mean age          |                        | 46.62±7.25                       | 47.14±7.39                         | 0.410   |
| Premenopause mean age |                    | 45.14±6.13                       | 45.22±6.50                         | 0.896   |
| Menopause mean age |                        | 54.85±7.59                       | 54.70±5.69                         | 0.905   |
| Parity            | Uniparous              | 15 (42.9%)                       | 20 (57.1%)                         |         |
|                   | Nulliparous            | 33 (30.6%)                       | 75 (69.4%)                         | 0.091   |
|                   | 2 Parity               | 145 (41%)                        | 209 (59%)                          |         |
|                   | 3 Parity               | 19 (26.8%)                       | 52 (73.2%)                         |         |
|                   | ≥4 parity              | 11 (35.5%)                       | 20 (65.5%)                         |         |
| Symptoms          | AUB                    | 112 (38.1%)                      | 182 (61.9%)                        | 0.021   |
|                   | HMB                    | 61 (46.9%)                       | 69 (53.1%)                         |         |
|                   | IMB                    | 5 (33.3%)                        | 10 (66.7%)                         |         |
|                   | PMB                    | 26 (30.6%)                       | 59 (69.4%)                         |         |
|                   | Incidental             | 19 (25.3%)                       | 56 (74.7%)                         |         |
| Duration of symptoms | ≤6 months          | 125 (34.1%)                      | 242 (65.9%)                        | 0.079   |
|                    | 6 months-1 year        | 43 (47.8%)                       | 47 (52.2%)                         |         |
|                    | 1-2 years              | 26 (42.6%)                       | 35 (57.4%)                         |         |
|                    | 2-11 years             | 20 (40.8%)                       | 29 (59.2%)                         |         |
| Menopause         | Premenopause           | 189 (38.7%)                      | 300 (61.3%)                        | 0.129   |
|                   | Menopause              | 34 (30.9%)                       | 76 (69.1%)                         |         |

Table 2: Comorbid conditions associated with endometrial hyperplasia.

| Variable                      | Hyperplasia with atypia (n=223) | Hyperplasia without atypia (n=376) | P value |
|-------------------------------|----------------------------------|------------------------------------|---------|
| Family h/o malignancy        | Yes                             | 32 (41.6%)                        | 45 (58.4%)| 0.400   |
|                               | No                              | 191 (36.6%)                       | 331 (63.4%)|         |
| Diabetes mellitus            | Yes                             | 44 (47.3%)                        | 49 (52.7%)| 0.029   |
|                               | No                              | 179 (35.4%)                       | 327 (64.6%)|         |
| Hypertension                  | Yes                             | 48 (40.3%)                        | 71 (59.7%)| 0.433   |
|                               | No                              | 175 (36.5%)                       | 305 (63.5%)|         |
| Hypothyroidism               | Yes                             | 43 (40.6%)                        | 63 (59.4%)| 0.433   |
|                               | No                              | 180 (36.5%)                       | 313 (63.5%)|         |
| Dyslipidemia                  | Yes                             | 19 (38%)                         | 31 (62%)    | 0.906   |
|                               | No                              | 204 (37.2%)                      | 345 (62.8%)|         |
| Obesity                      | Yes                             | 15 (65.2%)                       | 8 (34.8%)    | 0.005   |
|                               | No                              | 208 (36.1%)                      | 368 (63.9%)|         |
| PCOD                          | Yes                             | 11 (55%)                         | 9 (45%)     | 0.094   |
|                               | No                              | 212 (36.6%)                      | 367 (63.4%)|         |
| Personal h/o malignancy      | Yes                             | 4 (36.4%)                        | 7 (63.6%)    | 0.952   |
|                               | No                              | 219 (37.2%)                      | 369 (62.9%)|         |

Table 3: Results of logistic regression analysis of risk factors of endometrial hyperplasia with atypia.

| Variable | B     | SE  | Wald | P value | Odds ratio | Lower | Upper |
|----------|-------|-----|------|---------|------------|-------|-------|
| Obese    | 1.139 | .449| 6.43 | 0.011   | 3.12       | 1.29  | 7.53  |
| Diabetics| .452  | .230| 3.86 | 0.049   | 2          | 1.00  | 2.46  |
There was significant difference in endometrial thickness between atypical and nonatypical hyperplasia (p=0.040). Though there is significant difference, diagnostic cut off to predict atypia could not be achieved. If ET cut off of 11.95 was taken to predict atypia, area under curve in ROC analysis was only 54% which cannot accurately predict atypia. The difference is not noted among menopausal women. In premenopausal women, (p=0.069) the thickness difference in atypia is of only borderline significance. Heteroechoic pattern or cystic spaces in the endometrium also didn’t predict atypia.

### Table 4: USG associations of endometrial hyperplasia.

| Variable               | Hyperplasia with atypia (n=223) | Hyperplasia without atypia (n=376) | p value |
|------------------------|---------------------------------|-----------------------------------|---------|
| Mean ET                | 13.45±13.59                     | 11.87±4.78                        | 0.040   |
| Premenopause-Mean ET   | 14.06±14.55                     | 12.42±4.59                        | 0.069   |
| Menopause-Mean ET      | 10.05±4.65                      | 9.70±4.89                         | 0.730   |
| Cystic spaces in Endometrium |                                 |                                   |         |
| Present                | 79 (40.1%)                      | 118 (59.9%)                       | 0.309   |
| Absent                 | 144 (35.8%)                     | 258 (64.2%)                       |         |
| Fibroid                | 73 (38.4%)                      | 117 (61.6%)                       | 0.681   |
| Adenomyosis            | 81 (37.5%)                      | 135 (62.5%)                       | 0.918   |
| Ovarian cyst           | 4 (50%)                         | 4 (50%)                           | 0.452   |
| Diagnostic methods     |                                 |                                   |         |
| D and C                | 172 (38.7%)                     | 273 (61.3%)                       | 0.146   |
| Hysteroscopy+D and C   | 18 (42.9%)                      | 24 (57.1%)                        |         |
| Pipelle                | 33 (29.5%)                      | 79 (70.5%)                        |         |

**DISCUSSION**

The standard screening method to investigate abnormal uterine bleeding in any age group of women is trans vaginal sonography. Architectural complexity in glands size and shape, cystic dilatation of glands are markers to diagnose hyperplasia without atypia according to the WHO classification 2014. More layers of glands also can point towards nonatypical hyperplasia. Cellular atypia is the hallmark feature of hyperplasia with atypia. As the diagnostic criteria has become simplified and specific and with increase in the age of menopause, we encounter endometrial hyperplasia more frequently. As the diagnosis of this condition is essentially by histopathology, this study is done to know whether transvaginal sonography can be used to distinguish atypia from nonatypia. In our study, there was significant difference in the endometrial thickness between hyperplasia with and without atypia. (P value=0.040) in premenopausal group of women, endometrial thickness shows only borderline difference between two types of hyperplasia. To diagnose premalignant and malignant lesions of the endometrium in women with abnormal uterine bleeding, ET cut off of 10 mm/11 mm is found in premenopausal women. But no study has reported the ET cut off for atypical lesion alone in premenopausal women. In women with PCO, ET of 7mm as cut off had been observed by Cheng et al but in obese PCO women ET of 9.35 mm has been observed to diagnose hyperplasia. In the present study mean ET for nonatypia is 12.42±4.5mm and with atypia is 14.06±4.5mm. There is overlap of both types of hyperplasia in lower values. Endometrial stripe abnormality, defined as cystic or heterogenous pattern can predict better than thickness alone as observed by Kim et al. But in our study, mixed echogenicity or hyperechoic nature of endometrium with cystic spaces is not a pointer towards atypia. Ill-defined end myometrial junction, turbid intrauterine fluid collection, associated complex adnexal masses, cystic areas in the endometrium can predict malignant lesion along with endometrial thickness abnormality in premenopausal and perimenopausal women.

In the current study, there is no significant difference in thickness between nonatypia and atypia groups in postmenopausal women. There are many studies showing the cut off of endometrial thickness in asymptomatic postmenopausal women to predict premalignant and malignant lesion-the cut off being 10-11mm. Asymptomatic postmenopausal women with ET>12mm and positive doppler flow signals are best predictor of malignancy. Postmenopausal women with recurrent bleeding, who are diabetic have higher risk of endometrial malignancy with ET>11mm. In a study by Ulu et al ET of 15 mm and above, risk of malignancy is 3.043 times higher and symptomatic women have higher risk than asymptomatic women. To predict premalignant and malignant endometrial lesion among the women with abnormal uterine bleeding, cut off can be deducted with ease as the difference is huge. Among the premalignant lesion, cut off to predict atypia is difficult to get as there is significant overlap of measurements. But as the
thickness increases, atypia risk also increases. Instead of
thickness alone, morphometric analysis of endometrium
according to international endometrial tumour analysis
group can provide more insight into the nature of the
lesion. Here Saline infusion sonography and colour
doppler examination are also used along with routine
sonography. Large study by Van den bosch et al
described the findings for endometrial pathologies
according to IETA terminologies. In nonatypical
hyperplasia, interquartile range of ET was 9-17 mm,
Endometrium hyperechoic, undefined midline, regular
endometrial-myometrial junction, lesser colour score,
multivessel vascular pattern were present. In atypia,
interquartile range of ET was 8-18 mm, nonuniform
heterogenous endometrium, undefined midline, regular
junction and colour score of 2-3 with multivessel of
multifocal origin were present. No specific finding can
characterize atypia except vascular pattern.

Obesity and diabetes are two major risk factors for atypia
in our study. As atypia closely follows malignancy of
endometrium, these risk factors should be taken into
consideration during management and counselling should
be offered to modify the risk. In premenopausal women,
obesity is the leading risk factor for complex hyperplasia
and malignancy and as BMI increases above 40, there is
19.79 times risk of getting malignancy. Even in younger
women, 10-25 years old, BMI above 30 has significant
risk of developing carcinoma endometrium. Diabetes and
hormone replacement therapy has increased risk for
hyperplasia.¹⁵,¹⁶

**CONCLUSION**

Mean endometrial thickness is significantly different in
atypical hyperplasia. Heteroechoic pattern of
endometrium do not predict atypia. Colour doppler
sonography can be used to gain knowledge about atypia.
Obesity and diabetes mellitus is significant risk factors
of atypia. More research is needed to predict risk of
progression in atypia in terms of molecular indicators.

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**Institutional Ethics Committee**

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