International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Kanthi JM et al. Int J Reprod Contracept Obstet Gynecol. 2020 Dec;9(12):4989-4994
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20205235

Original Research Article

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

Janu Mangala Kanthi[1]*, Sudha Sumathy[1], Anu Vasudevan[2], Gokulkumar Kamalanathandurai[1]

[1]Department of Obstetrics and Gynecology, [2]Department of Biostatistics, Amrita School of Medicine, Amrita Viswavidyapeetham, Kochi, Kerala, India

Received: 16 September 2020
Revised: 30 October 2020
Accepted: 04 November 2020

***Correspondence:**
Dr. Janu Mangala Kanthi,
E-mail: janu_durai@yahoo.com

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, pipelle 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.[15] 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-amenorrhoea 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%)	0.091
	Nulliparous	33 (30.6%)	75 (69.4%)	
	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 transvaginal 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.[2,3] 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.[4,5] In the present study mean ET for nonatypia is 12.42±4.5mm and with atypia is 14.06±14.5 mm. 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.[6] 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.[7]

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.[8-10] Asymptomatic postmenopausal women with ET>12mm and positive doppler flow signals are best predictor of malignancy.[11] 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.[12] 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. Inatypia, 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.[13] Even in younger women, 10-25 years old, BMI above 30 has significant risk of developing carcinoma endometrium.[14] 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 are significant risk factors of atypia. More research is needed to predict risk of progression in atypia in terms of molecular indicators.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. New classification system of endometrial hyperplasia WHO 2014 and its clinical implications. Available at: https://europepmc.org/article/pmc/pmc5834925#free-full-text. Accessed on 30 October 2020.
2. Giannella L, Cerami LB, Setti T, Bergamini E, Boselli F. Prediction of Endometrial Hyperplasia and Cancer among Premenopausal Women with Abnormal Uterine Bleeding. Bio Med Res Int. 2019;2019:8598152.
3. Malpani A, Singer J, Wolverson MK, Merenda G. Endometrial hyperplasia: value of endometrial thickness in ultrasonographic diagnosis and clinical significance. J Clin Ultrasound. 1990;18(3):173-7.
4. Cheung AP. Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome. Obstet Gynecol. 2001;98(2):325-31.
5. McCormick BA, Wilburn RD, Thomas MA, Williams DB, Maxwell R, Aubuchon M. Endometrial thickness predicts endometrial hyperplasia in patients with polycystic ovary syndrome. Fertil Steril. 2011;95(8):2625-7.
6. Kim M-J, Kim J-J, Kim SM. Endometrial evaluation with transvaginal ultrasonography for the screening of endometrial hyperplasia or cancer in premenopausal and perimenopausal women. Obstet Gynecol Sci. 2016;59(3):192-200.
7. El Agwany AS. Sonographic Criteria for Uterine Curettage: Suspecting Endometrial Neoplasia. Ind J Surg Oncol. 2019;10(4):679-84.
8. Alcázar JL, Bonilla L, Marucco J, Padilla AI, Chacón E, Manzour N, et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness≥11 mm: A systematic review and meta-analysis. J Clin Ultrasound. 2018;46(9):565-70.
9. Ghoubara A, Emovon E, Sundar S, Ewies A. Thickened endometrium in asymptomatic postmenopausal women - determining an optimum threshold for prediction of atypical hyperplasia and cancer. J Obstet Gynaecol J Inst Obstet Gynaecol. 2018;38(8):1146-9.
10. Ozelci R, Dilbaz B, Akpınar F, Kınay T, Baser E, Aldemir O, et al. The significance of sonographically thickened endometrium in asymptomatic postmenopausal women. Obstet Gynecol Sci. 2019;62(4):273-9.
11. Li Z, Li L. Risk of malignancies among asymptomatic postmenopausal women with thickened endometrium: A cohort study. Medicine. 2019;98(6):e14464.
12. Van den Bosch T, Verbakel JY, Valentin L, Wynants L, De Cock B, Pascual MA, et al. Typical ultrasound features of various endometrial pathology described using the International Endometrial Tumor Analysis (IETA) terminology in women with abnormal uterine bleeding. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2020;2.
13. Wise MR, Jordan V, Lagas A, Showell M, Wong N, Lensen S, et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: A systematic review. Am J Obstet Gynecol. 2016;214(6):689e1-17.
14. Rosen MW, Tasset J, Kobernik EK, Smith YR, Johnston C, Quint EH. Risk Factors for Endometrial Cancer or Hyperplasia in Adolescents and Women 25 Years Old or Younger. J Pediatr Adolesc Gynecol. 2019;32(5):546-9.
15. Ricci E, Moroni S, Parazzini F, Surace M, Benzi G, Salerio B, et al. Risk factors for endometrial

hyperplasia: results from a case-control study. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2002;12(3):257-60.

16. 16. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol. 2014;135(1):163-71.

Cite this article as: Kanthi JM, Sumathy S, Vasudevan A, Kamalanathandurai G. Clinical study of risk factors and ultrasonographic correlation of endometrial hyperplasia according to the WHO classification 2014. Int J Reprod Contracept Obstet Gynecol 2020;9:4989-94.