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Study of expression of cyclin D1 in endometrial lesions

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***Abstract*---**Background: Cyclin D1, a member of the cyclin protein family is instrumental in the cell cycle due to its influence on the progression from G1 to the S phase. Its overexpression causes reduced doubling time and is also associated with clonogenic growth. Aim of the study: The purpose of the present study was to assess cyclin D1 expression in patients with endometrial lesions. Methods: Prospective study in the department of pathology at A.C.S Medical College and Hospital on 210 patients with cyclin D1 marker was done. Results: Majority of the cases were endometrial hyperplasia without atypia constituting 21.4%, followed by Disordered proliferative endometrium occupying 20.4% , Secretory endometrium 17.7%, Atypical endometrial hyperplasia and Proliferative endometrium constituted 16.6% each, Endometrial carcinomas 7.1%. Among 15 cases of endometrial carcinomas, majority of carcinomas were of endometrioid type 66% (10/15) followed by adenosqamous 13.3% (2/15), serous papillary type of carcinomas 20% (3/15). Conclusion: Cyclin D1 expression is significantly higher in patients with endometrioid endometrial carcinoma. The extent of cyclin D1 expression is strongly correlated with nuclear and histological grade, myometrial invasion, lymphovascular invasion and lymph node invasion in patients with endometrioid endometrial carcinoma. These findings contribute in several ways to our understanding of cyclin D1 expression and provide a basis for future research on this topic.

***Keywords*---**cyclin D1, endometrioid endometrial carcinoma.

Introduction

Endometrial diseases are ranked amongst the most common gynaecological disorders, affecting women worldwide. [1] These constitute around 70% of all gynaecologic consultations in the peri-menopausal and postmenopausal age group. A large number of females with endometrial diseases present with abnormal uterine bleeding (AUB), hence it warrants an urgent diagnosis. Abnormal uterine bleeding affects nearly 9-14% of women between menarche and menopause, significantly impacting their quality of life and imposing a financial burden. [2]

Endometrial hyperplasia is of clinical significance because it is often a precursor lesion to adenocarcinoma of the endometrium [3,4]. The precursor lesion of type I endometrioid adenocarcinoma is endometrial intraepithelial neoplasia. Estrogenic stimulation of the endometrium, unopposed by progestins causes proliferative glandular epithelial changes. This finding is due to prolonged hormonal exposure which is biologically distinct from true precancerous lesions and true neoplasia.

Endometrial cancers can be broadly divided into two groups based on differences in their clinical presentation and behavior.[5,6] Endometrioid adenocarcinoma which accounts for most endometrial carcinomas typically occurs in association with endometrial hyperplasia and clinical findings consistent with unopposed estrogenic stimulation. In contrast, uterine serous carcinomas develop in atrophic endometrium in older women who lack the typical endometrial cancer risk factors associated with hyperestrogenism (unpublished data). In an accompanying report, we suggest that a recently described lesion termed "endometrial intraepithelial carcinoma" (EIC) [7] may represent a precursor of serous carcinoma.

Endometrioid carcinoma is often preceded by characteristic histopathologic lesions designated as endometrial hyperplasia,[8,9,10,11] and currently it is accepted that there is a continuum of changes that evolve to endometrioid carcinoma. Hyperplasia is usually associated with exogenous estrogen stimulation, and thus, estrogen is considered as an endometrial carcinogen. Other mechanisms of endometrial carcinogenesis include mutations in p53 and PTEN tumor suppressor genes and overexpression of cyclin D1. Specifically, mutations of p53 have been detected in serous endometrial carcinoma[12] and mutations or abnormal expression of PTEN have been reported in about 80% of endometrioid carcinoma and in 55% of endometrial precancer. Overexpression of cyclin D1 has been observed in endometrial carcinoma.[12]

Nikaido et al [13] and Shih et al[14] observed a significant association of cyclin D1 expression in endometrial carcinoma with histological grade, clinical stage and p53 expression**.** In this study, we investigated the expression of Cyclin D1 in 5 different pathological types of endometrial diseases including proliferative endometrium, secretory endometrium, endometrial hyperplasia with atypia, endometrial hyperplasia without atypia and endometrioid carcinoma. We also followed-up the patients and executed survival analysis to explore the possibility of Cyclin D1 as a diagnostic and prognostic marker for endometrial diseases.

Aims and Objectives

- To study the role of Cyclin D1 in Endometrial lesions.

Materials and Methods

Ethical institutional permission was taken. This is a Prospective study carried out at A.C.S Medical College And Hospital.All specimens received in the department of Histopathology over a period of 2 years. i.e.,from May 2020 to May 2022.

Inclusion criteria

- Endometrial curettage & hysterectomy specimens of females of all age groups were included.
- Only samples with adequate tissue material and definite histopathological diagnosis were included .
- Representative areas in the biopsies were only included.
- All endometrial lesions were considered.

Exclusion criteria

- All cases of stromal lesions were excluded.
- All inflammatory lesions were excluded.
- All hemorrhagic and necrotic samples were excluded.

Specimen Handling

All curettage & hysterectomy specimens were fixed in 10% neutral buffered formalin .After adequate fixation, examination of the specimen for gross details was done. Then representative tissue bits were taken and subjected for routine processing and paraffin embedding. 3-4 microns thick sections were taken from paraffin embedded blocks. These sections were routinely stained with hematoxylin and eosin (H/E) and were examined. Histopathological features were noted and the tumors were typed according to WHO classification system. The paraffin blocks of the samples which had met the inclusion criteria were collected. The details of each case such as biopsy number, age, histopathological diagnosis were noted..

Procedure for IHC for cyclin D1 using FLEx monoclonal rabbit human cyclin clone EP 12 (DAKO) (RTU,cat.no.ISo8430-2). From selected blocks 3-4 micrometer thick sections were taken on polylysine coated slides. Deparaffinization with xylene and hydration in alcohols and tap water was performed .Heat induced epitope retrieval using Tris /EDTA Ph 9.0 buffer was done using microwave method for 20 minutes. Endogenous peroxidase inactivation using 1drop of 3% aqueous hydrogen peroxide was done for 5 minutes. Incubation with primary antibody anti human cyclin D1 clone EP12 was done for 20 minutes at room temperature in a moist chamber. Incubation with secondary antibody horseradish peroxidase was done for 20 minutes. Incubation with freshly prepared diaminobenzediene (DAB) chromogen was done for 5 minutes. Counter staining was performed using

hematoxylin. The slides were then subjected to dehydration , clearing, and mounting.

Results

Table 1 : Age distribution

Age distribution	No. of cases	Percentage
20-29 years	37	17.6%
30-39 years	30	14.2%
40-49 years	55	26.1%
50-59 years	68	32.3%
>60 years	20	9.5%
Total	210	99.7%

Most of the endometrial hyperplasias without atypia fell in the age group of 40-49 years, while most of the endometrial hyperplasias with atypia and carcinomas were above the age of 40 years. The mean age of the above cases was 50.2 years (range 20 to more than 60 years).

Table 2: Distribution of clinical features

Clinical features	No. of cases	Percentage
Vaginal bleeding	140	66.6%
Vaginal bleeding with pain abdomen	50	23.8%
Uterovaginal prolapse	20	9.5%
Total	210	99.9%

The most common presenting feature were vaginal bleeding which was found in 66.6% (140/210) and vaginal bleeding with pain abdomen in 23.8% (50/210) cases and 9.5% (20/210) cases in uterovaginal prolapse.

Table 3 : Distribution of total cases on Histopathology

Histopathology	No. of cases	Percentage
Proliferative endometrium	35	16.6%
Secretory endometrium	37	17.6%
Disordered proliferative endometrium	43	20.4%
Endometrial hyperplasia without atypia	45	21.4%
Atypical endometrial hyperplasia	35	16.6%
Endometrial carcinoma	15	7. 1%
Total	210	99.7%

Majority of the cases were endometrial hyperplasia without atypia constituting 21.4% , followed by disordered proliferative endometrium occupying 20.4%, secretory endometrium 17.7%, atypical endometrial hyperplasia and proliferative endometrium constituted 16.6% each and endometrial carcinomas 7.1%.

Among 15 cases of endometrial carcinomas, majority of carcinomas were of endometrioid type 66% (10/15) followed by adenosqamous 13.3% (2/15), serous papillary type of carcinomas 20% (3/15).

Table 4: Distribution of total cases with cyclin D1 immunostaining

Histopathology	Positive	Negative	Total
Proliferative endometrium	15 (7.1 %)	20(9.5%)	35(16.6 %)
Secretory endometrium	20(9.5 %)	17(8.09 %)	37(17.6 %)
Disordered proliferative endometrium	20(9.5%)	23 (10.9%)	43(20.4 %)
Endometrial hyperplasia without atypia	10(4.7%)	35(16.6 %)	45(21.4 %)
Atypical endometrial hyperplasia	7(3.3 %)	28(13.3 %)	35(16.6 %)
Endometrial carcinoma	8(3.8 %)	7(3.3 %)	15(7.1%)
Total	80(38%)	130(61.9%)	210(99.9 %)

In our study 80 cases out of 210 (38%) cases were positive for cyclin D1. The percentage of positive cases for cyclin D1 was 4.7% in those with hyperplasia without atypia, 3.3% hyperplasia with atypia and 3.8% in those with endometrial endometrioid carcinoma. P value was < 0.001 between the groups and was considered significant. Patients with endometrial endometrioid carcinoma showed higher mean cyclin D1 expression.

Table 5 : Extent of cyclin D1 immunoreactivity

Histopathology	0	1+	2+	3+	Total
Proliferative endometrium	20(9.5 %)	15(7.1 %)	-	-	35(16.6%)
Secretory endometrium	17(8.09 %)	20(9.5%)	-	-	37(17.6%)
Disordered proliferative endometrium	23 (10.9 %)	20(9.5 %)	-	-	43(20.4%)
Endometrial hyperplasia without atypia	35(16.6 %)	6(2.8%)	2(0.95 %)	2(0.95 %)	45(21.4 %)
Atypical endometrial hyperplasia	28(13.3%)	2(0.95%)	4(1.9 %)	1(0.47%)	35(16.6 %)
Endometrial carcinoma	7(3.3%)	4(1.9%)	1(0.47%)	3(1.4 %)	15(7.1 %)
Total	130(61.9%)	67(31.9 %)	7(3.3 %)	6(2.8 %)	210(99.9 %)

In our study the expression of cyclin D1 was expressed as 1+ in 15 cases of proliferative and 20 cases of secretory endometrium.
1+ in 6 cases, 2 + in 2 cases and 3+ in 2 cases of endometrial hyperplasia without atypia,
1+ in 2 cases, 2 + in 4 cases and 3+ in one cases of endometrial hyperplasia with atypia,
1+ in 4 cases, 2 + in 1 case and 3+ in 3 cases of endometrial carcinoma.

Diffuse positivity for cyclin D1 was observed in Grade 2 and Grade 3 endometrial carcinomas. Statistical analysis showed a significant difference in extent of cyclin D1 immunoreactivity between endometrial hyperplasia without atypia and

endometrial hyperplasia with atypia and carcinoma (p = 0.016 and p = 0.034, respectively). No significant difference was found between endometrial hyperplasia without atypia and endometrial hyperplasia with atypia. On comparing the intensity of Cyclin D1 expression, significant difference was seen between secretory endometrium and endometrial hyperplasia without atypia (p=0.017) and secretory endometrium and endometrial hyperplasia with atypia (p=0.0017).

Discussion

Comparative studies related to Age distribution

In the present study most of the endometrial hyperplasias without atypia fell in the age group of 40-49 years, while most of the endometrial hyperplasias with atypia and carcinomas were above the age of 40 years. The mean age of the above cases was 50.2 years (range 20 to more than 60 years). Hulya et al[15] study included 193 patients with a mean age of 54 ± 10 years. In Ch sherva et al[16] study the age of 38 patients of EC ranged from 35 to 79 years with a median age of 46 years. 63% patients were between 40 and 59 years with the peak incidence (17 cases, 44.7%) observed at the age group of 40-49 years. 26 cases of CH aged between 20 and 69 years and the median age was 45 years. The maximum number of patients (15 cases, 57.7%) was in the age group of 40-49 years. Seventy-eight patients of SH aged between 20 and 69 years with the median age of 43.5 years. In Karuna et al[17] study the age of the patients was in the range of 26 to 75 years. Out of 20 cases, 15(75%) with endometrial carcinoma were in the post-menopausal age group. In complex hyperplasia, four cases were of atypia while six cases were complex hyperplasia without atypia. In Parveen et al [18] study age from 27 years to 78 years with the maximum number of cases in the age group of 41-50 years. The mean age for simple hyperplasia was 43.9 years with maximum number of cases in the age group of 41-50 years. For complex hyperplasia, the mean age of 52.3 years was calculated while maximum number of cases fall in the age group of 41-50 years. In Shaffy et al [19] study, the age of the patients ranged from 27-73 years with a median age being 45.62 ± 11.07 years.

Comparative studies related to Clinical features

In our study the most common presenting feature was vaginal bleeding which was found in 66.6% (140/210) and Vaginal bleeding with pain abdomen in 23.8% (50/210) cases and 9.5% (20/210) uterovaginal prolapse. In Parveen et al[18] study the most common presenting feature was vaginal bleeding which was found in 23 cases of simple hyperplasia and 12 cases of complex hyperplasia. One case of simple hyperplasia presented with uterovaginal prolapse.

Comparative studies related to Histopathology distribution

In the present study majority of the cases were endometrial hyperplasia without atypia constituting 21.4%, followed by disordered proliferative endometrium occupying 20.4% , secretory endometrium 17.7%, atypical endometrial hyperplasia and proliferative endometrium constituted 16.6% each, endometrial carcinomas 7.1%. Among 15 cases of endometrial carcinomas, majority of

carcinomas were of endometrioid type 66% (10/15) followed by adenosquamous 13.3% (2/15), serous papillary type of carcinomas 20% (3/15). In Hulya et al[15] study 30 patients (16%) were diagnosed as hyperplasia without atypia, 40 (20%) had Endometrial intraepithelial neoplasia while the remaining 123 (64%) patients had endometrial endometrioid cancer. In Ch sherva et al [16] study 38 cases of endometrial carcinoma, 26 cases of complex hyperplasia (CH) and 78 cases of simple hyperplasia (SH) were diagnosed. In Karuna et al[17] study amongst endometrial carcinoma, 15 cases (60%) were of endometrioid type (two cases revealed villoglandular pattern while squamous morules were seen in three cases), 3 cases were reported to be clear cell type and two cases were papillary serous carcinoma. In Parveen et al [18] study 24 cases were of simple hyperplasia along with 12 cases of complex hyperplasia and 10 cases each of secretory and proliferative endometrium. Out of 12 cases of complex hyperplasia, 5 cases were complex hyperplasia without atypia and seven cases were complex hyperplasia with atypia. In Shaffy et al [19] study 10 cases each (20%) were there in proliferative and secretory phase 12 cases (24%) were found in the group simple hyperplasia without atypia. 7 cases (14%) were reported in the group complex hyperplasia without atypia and 4 cases (8%) were there in the complex hyperplasia with atypia group and 7 cases (14%) belonged to endometrial carcinoma group.

Comparative studies related to Cyclin D1 expression

In our study 80 cases out of 210 (38%) cases were positive for cyclin D1. The percentage of positive cases for cyclin D1 was 4.7% in those with hyperplasia without atypia, 3.3% hyperplasia with atypia and 3.8% in those with endometrial endometrioid carcinoma. P value was < 0.001 between the groups and was considered significant. Patients with endometrial endometrioid carcinoma showed higher mean cyclin D1 expression. In Hulya et al [15] study nearly 131 out of 193 (68%) cases were positive for cyclin D1 (Mean percentage 26.3 ± 19.4%). The percentage of positive cases for cyclin D1 was 30% in those with hyperplasia without atypia, 60% in those with EIN and 78% in those with endometrial endometrioid cancer. The difference between groups was significant (P < 0.001). Patients with endometrial endometrioid carcinoma displayed higher mean cyclin D1 expression. In Parveen et al study [18] Cyclin D1 immunostaining, out of total 56 cases, 32 cases (57.14%) showed Cyclin D1 positivity.

Extent of cyclin D1 immunoreactivity

The extent of cyclin D1 expression was in association with diagnosis, grade and stage of the endometrial pathology. In our study the expression of cyclin D1 was expressed as 1+ in 15 cases of proliferative and 20 cases of secretory endometrium.
1+ in 6 cases, 2 + in 2 cases and 3+ in 2 cases of endometrial hyperplasia without atypia ,
1+ in 2 cases, 2 + in 4 cases and 3+ in one case of endometrial hyperplasia with atypia,
1+ in 4cases, 2 + in 1 case and 3+ in 3 cases of endometrial carcinoma.

Diffuse positivity for cyclin D1 was observed in Grade 2 and Grade 3 endometrial carcinomas. Statistical analysis showed a significant difference in extent of cyclin

D1 immunoreactivity between endometrial hyperplasia without atypia and endometrial hyperplasia with atypia and carcinoma (p = 0.017 and p = 0.034). No significant difference was found between endometrial hyperplasia without atypia and endometrial hyperplasia with atypia. In Karuna et al[17] study 11 out of 15 (73.33%) endometrioid carcinoma were positive for cyclin D1. Statistical analysis showed a significant difference in extent as well as the intensity of cyclin D1 immunoreactivity between simple hyperplasia and carcinoma (p = 0.015 and p = 0.030, respectively). No significant difference was found between simple hyperplasia and complex hyperplasia. In T. Nikaido et al study [13]the expression of cyclin D1 was restricted to only a few cells of normal and hyperplastic endometrium, whereas it was preferentially expressed in 40% (30/74) of endometrial carcinomas. The cells that overexpressed cyclin D1 also overexpressed p53. Moreover, all 30 cases with varied distributions of cyclin D1-positive cells corresponded identically with the distribution of p53-positive cells. Diffuse positivity for cyclin D1 was specifically observed in clinically advanced stages of pathologic G2 and G3 tumors. In Parveen et al [18] study in proliferative phase endometrium, extent of staining was graded zero in 80% cases. Out of 24 cases of simple hyperplasia of endometrium, extent of staining was graded 2+ in ten cases (41.7%). In case of complex hyperplasia of endometrium, 50% cases showed an extent of 3+, followed by four cases (33.3%) of 2+ extent and one case (8.3%) of an extent of 1+. Only single case (8.3%) was found with zero extent. On comparing the extent of Cyclin D1 staining between non neoplastic and hyperplastic endometrium, significant difference was found between secretory endometrium and simple hyperplasia (p=0.049) and secretory endometrium and complex hyperplasia (p=0.0027). Also, significant difference was found between proliferative endometrium and simple hyperplasia (p=0.0129) and proliferative endometrium and complex hyperplasia (p=0.00066). However, no significant difference in extent was found between secretory endometrium and proliferative endometrium (p=0.606) and simple and complex hyperplasia (p=0.102).

Intensity of cyclin D1 immunopositivity

In our study the high intensity of cyclin D1 was noted in endometrial carcinoma. 1+ in 4 cases, 2+ in 1 case and 3+ in 3 cases of endometrial carcinomas. In endometrial hyperplasia with atypia, maximum cases showed 1+ and 2+ intensity of Cyclin D1 staining. On comparing the intensity of Cyclin D1 expression, significant difference was seen between secretory endometrium and endometrial hyperplasia without atypia (p=0.017) and secretory endometrium and endometrial hyperplasia with atypia (p=0.0017). In Parveen et al [18]study in case of simple hyperplasia, maximum cases showed 1+ intensity of Cyclin D1 staining. Majority of cases of complex hyperplasia had a 2+ intensity and one case showed 3+ intensity. On comparing the intensity of Cyclin D1 expression, significant difference was seen between secretory endometrium and simple hyperplasia (p=0.027) and secretory endometrium and complex hyperplasia (p=0.0027). Also, significant difference in intensity of Cyclin D1 expression was seen between proliferative endometrium and simple hyperplasia (p= 0.027) and proliferative endometrium and complex hyperplasia (p=0.0027). However, no significant difference in intensity of Cyclin D1 expression was found between secretory endometrium and proliferative endometrium (p=1) and simple hyperplasia and complex hyperplasia (p= 0.156).In Shaffy et al [19] In a total of 10 cases of

proliferative phase, three cases (30%) showed 1+ expression of Cyclin D1 expression whereas seven cases (70%) showed no staining for Cyclin D1. In a total of 10 cases of secretory phase two cases (20%) showed a 2+ expression of Cyclin D1 expression whereas two cases (20%) showed 1+ expression. Six cases (60%) showed no staining for Cyclin D1. In the 12 cases of simple hyperplasia, six cases (50%) showed a 1+ expression of Cyclin D1 expression whereas six cases (50%) were negative for Cyclin D1. In the 7 cases of complex hyperplasia without atypia, three cases (42.86%) showed a 1+ expression of Cyclin D1 expression whereas four cases (57.14%) were negative for Cyclin D1. In a total of 4 cases of complex hyperplasia with atypia one case (25%) showed a 3+ expression of Cyclin D1 expression whereas three cases (75%) showed 2+ expression of Cyclin D1 with an average expression of 63.63 in complex hyperplasia. In the 7 cases of endometrial carcinoma, one case (14.28%) showed a 3+ expression of Cyclin D1 whereas four cases (57.14%) showed 2+ expression with one case (14.28%) showing a 1+ immunostaining. One case was negative for Cyclin D1.

Conclusion

The present study demonstrates a significant difference in the level of cyclin D1 expression among patients with endometrial endometrioid carcinoma and hyperplasia with or without atypia; indicating that cyclin D1 expression might play a critical role in endometrial carcinogenesis. Our results also revealed a significant correlation between cyclin D1 expression and the stage and grade of the endometrial endometrioid carcinomas.

References

1. Bokhman JV: Two pathologic types of endomeu-ial carcinoma. Gynecol Oncol 15:10-17, 1983
2. Bur ME, Perlman C, Edelmann L, Fey E, Rose PG. p53 expression in neoplasm of the uterine corpus. Am J Clin Pathol. 1992;98:81–87.
3. CR Shevra, A Ghosh, and M KumarCyclin D1 and Ki-67 expression in normal, hyperplastic and neoplastic endometrium J Postgrad Med. 2015 Jan-Mar; 61(1): 15–20.
4. Deligdisch L, Holinka CF: Endometrial carcinoma: Two diseases? Cancer Detect Prev 10:237-246, 1987
5. Fattakhov, N., Normatova, S., Madaminov, S., Tilyakhodzhaeva, G., & Abdulkhakimov, A. (2021). Hirudotherapy as an effective method for treatment of migraine - a disease of unknown etiology. *International Journal of Health & Medical Sciences*, *4*(2), 232-237. https://doi.org/10.31295/ijhms.v4n2.1714
6. Hulya Tosun Yildirim, Dondu Nergiz, Canan Sadullahoglu, Zelal Akgunduz, Senay Yildirim, Selen Dogan1 , Cem Sezer
7. Jiko K, Sasano H, Ito K, Ozawa N, Sato S, Yajima A. Immunohistochemical and in situ hybridization analysis of p53 in human endometrial carcinoma of the uterus. Anticancer Res. 1993;13:305–310
8. Karuna Sangwan1 Monika Garg2 Nayana Pathak3 Lavleen Bharti Expression of Cyclin D1 in Hyperplasia and Carcinoma of Endometrium and Its Correlation with Histologic Grade, Tumor Type, and Clinicopathological

Features Journal of Laboratory Physicians Vol. 12 No. 3/2020 © 2020. The Indian Association of Laboratory Physicians
9. Kholer MF, Berchuck A, Davidoff AM, et al. Overexpression and mutation of p53 in endometrial carcinoma. Cancer Res. 1992;52:1622–1627.
10. Mary GS, Tarin AS and Patrice MW. Evaluation and management of abnormal uterine bleeding in premenopausal women.Am Fam Physician.2012; 85(1):35-43
11. Parveen R. Kundu, Anjali Sindhu*, Swaran Kaur, Amrita Kulhria, Ritika Hooda Expression of Cyclin D1 in normal and hyperplastic endometrium Kundu PR et al. Int J Reprod Contracept Obstet Gynecol. 2019 Nov;8(11):4474-4478
12. Risinger JI, Dent GA, Ignar-Trowbridge D, et al. p53 gene mutations in human endometrial carcinoma. Mol Carcinog. 1992;5:250–253.
13. Sarwar A, Haque A. Types and frequencies of pathologies in endometrial curretings of abnormal uterine bleeding. Int J Pathol 2005; 3:6570.
14. Shaffy Thukral1 , Shuaeb Bhat2*, Nusrat Bashir3 Original Research Article Study of expression of PTEN and Cyclin D1 in endometrium at a tertiary care centre International Journal of Advances in Medicine | March-April 2019 | Vol 6 | Issue 2 P
15. Sherman ME, Bitterman P, Rosenshein NB, et al: Uterine serous carcinoma: A morphologically distinctive neoplasm with unifying clinicopathologic features. Am J Surg Pathol 16:600-610, 1992
16. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Mod Pathol 2000;13:295–308. [PubMed]
17. Shih H-C, Shiozawa T, Kato K, Imai T, Miyamoto T, Uchikawa J, Nikaido T and Konishi I: Immunohistochemical expression of cyclins, cyclin-dependent kinases, tumor-suppressor gene products, Ki-67, and sex steroid receptors in endometrial carcinoma: positive staining for cyclin A as a poor prognostic indicator. Hum Pathol 34: 471-478, 2003.
18. Silverberg SG, Kurman RJ, Nogales F, Mutter GL, Kubik-Huch RA, Tavassoli FA. Epithelial tumours and related lesions. In: Tavassoli FA, Devilee P, editors. Pathology and genetics of tumours of the breast and female genital organs. World Health Organization classification of tumours. Lyon (France): IARC Press; 2003. p. 221–32. ⇦
19. Silverberg SG, Kurman RJ. Tumors of the Uterine Corpus and Gestational Trophoblastic Diseases. Washington, DC: Armed Forces Institute of Pathology; 1991:191–218. Atlas of Tumor Pathology; 3rd series, fascicle 3.
20. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Get vaccinated when it is your turn and follow the local guidelines. *International Journal of Health Sciences*, *5*(3), x-xv. https://doi.org/10.53730/ijhs.v5n3.2938
21. T Nikaido [1], S F Li, T Shiozawa, S FujiiCoabnormal expression of cyclin D1 and p53 protein in human uterine endometrial carcinomas Cancer. 1996 Sep 15;78(6):1248-53.
22. The extent of cyclin D1 expression in endometrial pathologies and relevance of cyclin D1 with the clinicopathological features of endometrioid endometrial carcinoma

Fig 1: Gross showing tumor in the endometrial cavity

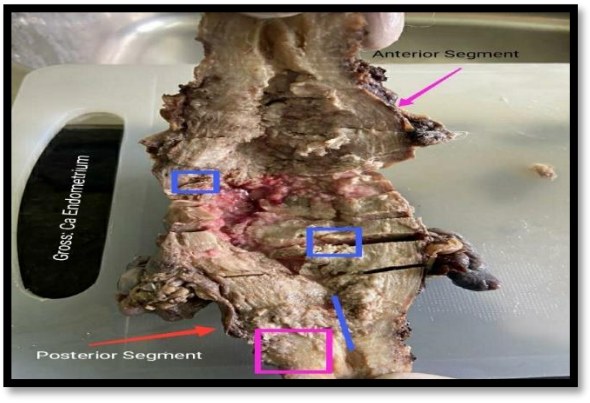

Fig 2:Cutsection showing tumor areas

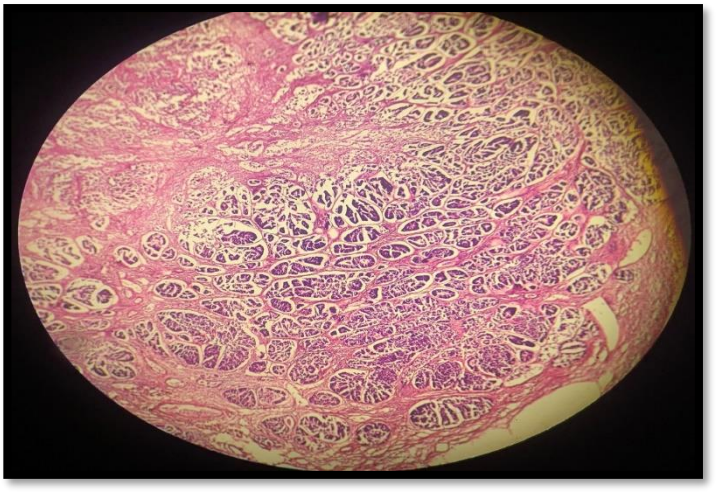

Fig 3:H & E 10 X showing atypical endometrial glands

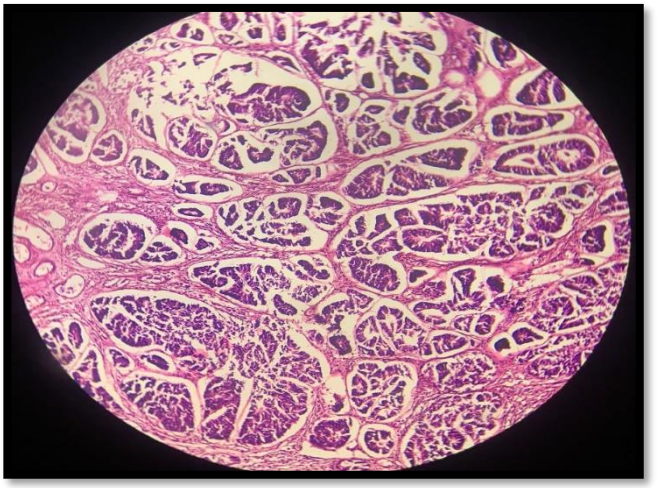

Fig 4:H & E 40 X showing atypical endometrial glands