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Original Research Paper

Pathology

HISTOPATHOLOGICAL STUDY OF ENDOMETRIUM IN ABNORMAL UTERINE BLEEDING AND SIGNIFICANCE OF IMMUNOHISTOCHEMICAL STUDY OF ESTROGEN AND PROGESTERONE RECEPTOR EXPRESSION IN CASES OF ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CARCINOMA.

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ABSTRACT

Introduction: Abnormal uterine bleeding (AUB) is defined as bleeding from uterus that is longer than usual (>7days), more than normal volume (>80ml/cycle) and varying in frequency. AUB is commonly seen in reproductive women and affects the quality of life. **Aim:** To assess Histo-morphological pattern of endometrium in women with AUB and To evaluate IHC analysis of Estrogen and Progesterone receptors in Endometrial hyperplasia & Carcinomas. **Materials And Methods:** The present study was an observational study with samples ofDilatation&Curettage, endometrial biopsies and hysterectomy specimens; conducted at NRI Institute of Medical Sciences, Sangivalasa,Visakhapatnam, in the Department of Pathology over a period of 20 months from December 2020 to July 2022 with a sample size of 100 patients. **Results:** Out of 100 cases, the predominant age group was reproductive comprising of 44cases(44%), followed by perimenopausal 38cases(38%) and postmenopausal 18 cases(18%). The common specimens were hysterectomies 56cases(56%),D&C 37cases(37%) and Endometrial biopsies 7cases(7%). The most common bleeding pattern was menorrhagia in reproductive women. Thecommonest endometrial pattern was proliferative endometrium 30cases(30%), followed by secretory endometrium 27cases(27%), disordered proliferative endometrium 8cases(8%), atrophic endometrium& polypconstituting 7 cases (7%) each, endometrial carcinoma 3 cases (3%). Immunohistochemical analysis of ER&PR expression was done on 17 cases out of which 11 werehyperplasiaswith 7/11 were positive for ER and 9/11were positive for PR; among 3 malignant cases, 2/3 cases were positiveand 1 case was negative for both ER&PR; and 3 taken as controls. **Conclusion:** AUB was common in reproductive women and menorrhagia was the chief complaint.IHC revealedreduced expression of ER&PR from non malignant to malignant cases, While low grade endometrioid carcinoma revealed better expression of ER&PR indicatingbetter prognosis than type 2 serous carcinoma.

KEYWORDS : Abnormal uterine bleeding,Endometrial biopsy, Immunohistochemistry, Dysfunctional uterine bleeding.

INTRODUCTION:

Abnormal Uterine Bleeding (AUB) is defined as an excessive cyclical bleeding of amount more than 80ml per cycle or for duration of more than 7days which occurs at normal interval periods. AUB is commonly seen in women of reproductive age group and it significantly affects the quality of life.[1,2] The most common presenting complaints are menorrhagia, metrorrhagia and polymenorrhea.[3,4,5] International Federation of Gynaecology and Obstetrics (FIGO) introduced PALM – COEIN system of classification in 2011 to define the causes of AUB which include-

Structural causes: Polyp, adenomyosis, leiomyoma, malignancy and hyperplasia.**Non structural causes**: Coagulopathy, ovulatory dysfunction, endometrial cause, iatrogenic, not yet classified.[1]

Dysfunctional Uterine Bleeding (DUB) is a subtype of AUB, defined as bleeding not associated with organ pathology in women of child bearing age. DUB can be due to oestrogen or progesterone breakthrough bleeding, and oestrogen withdrawal bleeding.Estrogen and progesterone receptors are nuclear receptorslocated in the endometrial stroma and glands.[6]In this study Immunohistochemical analysis of Estrogen and Progesterone receptors in combination with histopathological study was evaluated in patients of AUB .[6]

MATERIALS AND METHODS:

The present study was an observational study with samples of Dilatation& Curettage, endometrial biopsies and hysterectomy specimens; conducted at NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam, in the Department of Pathology over a period of 20 months from December 2020 toJuly 2022 with a sample size of 100 patients. Relevant clinical data were obtained from medical records.The samples received in 10% buffered formalin were processed by routine tissue processing,4-6μ were cut and stained with Haematoxylin and Eosin.

Out of 100 cases, in 17 cases Immunohistochemical studies for ER and PR were done on Proliferative Endometrium, Secretory Endometrium, Endometrial Hyperplasia and Endometrial Carcinoma. To perform IHC procedure charged slides were used and microwave was used for antigen retrieval using Tris EDTA buffer. The slides were examined under light microscope for the histopathological patterns and ER , PR expression. The data was prepared in Microsoft Excel and managed using SPSS software version16. Analysis was done in the form of percentages and proportions represented in the form of tables and graphs.

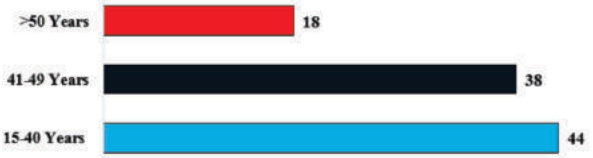
RESULTS:

A total of 100 cases were taken into this study and histopathological evaluation was done and correlated with IHC for ER & PR expression.

Out of 100 cases,(table-1,graph-1) predominant age group was reproductive comprising of 44 cases(44%), followed by perimenopausal 38 cases(38%) and postmenopausal 18 cases(18%).

Table 1. Age wise distribution of patients with AUB (N:100)

AGE GROUP		TOTAL	PERCENTAGE(%)
18-40 Years	Reproductive	44	44%
41-49 Years	Peri Menopausal	38	38%
>50 Years	Post Menopausal	18	18%
TOTAL		100	100%



Graph-1. Age wise distribution of patients with AUB (N:100)

Out of 100cases,(table-2) the commonest type of specimen were hysterectomy specimens comprising 56cases (56%), followed by D&C – 37cases(37%) and Endometrial biopsy (pipelle biopsy) 7cases (7%).

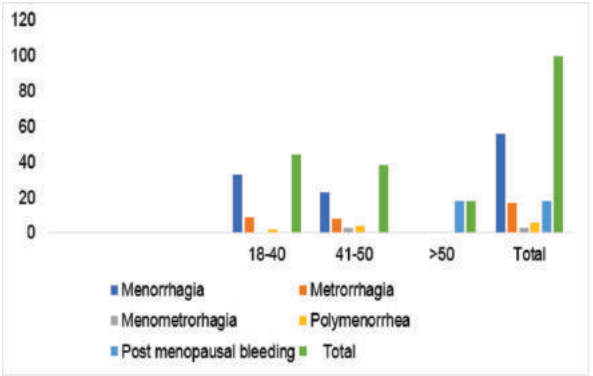
Table 2: Type of specimen in the cases of AUB (N:100)

Type of specimen	No of cases
Hysterectomy	56
Dilatation and Curettage	37
Endometrial biopsy	7
TOTAL	100

According to the age wise distribution,(table-3,graph-2) the most common bleeding pattern was menorrhagia in both reproductive and perimenopausal women comprising of 30 cases (30%) and 26 cases(26%) respectively. Post menopausal bleeding was seen in 18 cases(18%).

Table 3. Correlation of bleeding pattern with age in patients with AUB (N:100)

S. NO.	PATTERN OF BLEEDING	18-40 Years	41-50 Years	>50 Years	Total	%
1	Menorrhagia	33	23	-	56	56%
2	Metrorrhagia	9	8	-	17	17%
3	Menometrorrhagia	-	3	-	3	3%
4	Polymenorrhea	2	4	-	6	6%
5	Post menopausal bleeding	-	-	18	18	18%
Total		44	38	18	100	100%



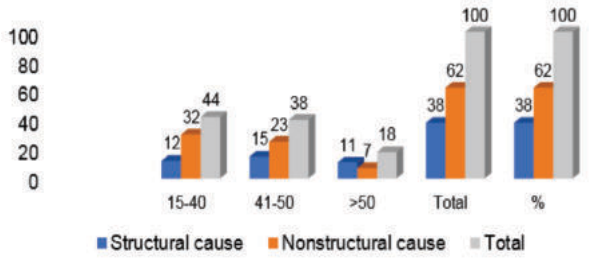
Graph-2.Correlation of bleeding pattern with age in patients with AUB (N:100)

In the present study non structural causes (table 4,graph 3) were high comprising of 62 cases(62%) and common in reproductive women followed by perimenopausal women. The structural causes constitute 38 cases (38%) and common in perimenopausal women comprising 15 cases(15%) and common structural causes were fibroids 19 cases (19%), and Adenomyosis 6 cases (6%).

Table-4. Correlation of structural and non structural causes with age group in cases of AUB (N:100)

CAUSE OF AUB	18-40 Years	41-50 Years	>50 Years	Total	%
Structural cause	12	15	11	38	38
Non-structural cause	32	23	7	62	62
Total	44	38	18	100	100

Structural causes: Polyp,Adenomyosis,Leiomyoma, Malignancy & Hyperplasia Non structural causes: Ovulatory dysfunction, Endometritis, etc.



Graph-3. Correlation of structural and non structural causes with age group in cases of AUB (N:100)

(Table-5)In **reproductive** women, commonest pattern was late proliferative endometrium (Fig 1A, 1B- IHC for ER &PR)constituting 16% followed by early secretory endometrium 16%, disordered proliferative endometrium 4%, polyp 2% and endometrial hyperplasia 2%. In **perimenopausal** women, the commonest pattern was late proliferative endometrium 11%, followed by early secretory endometrium 8%, endometrial hyperplasia 7%,atrophic endometrium 4% and polyp 4%, disordered proliferative endometrium 3%, endometrial carcinoma 1%. In **postmenopausal** women, late proliferative & early secretory endometrium, endometrial hyperplasia and atrophic endometrium constitute 3% each, followed by endometrial carcinoma 2%, others such as polyp, chronic endometritis, disordered proliferative endometrium and irregular ripening constitute 1% each.

Table-5. Histological patterns of endometrium according to age (N:100)

S NO.	HISTOPATHOLOGICAL DIAGNOSIS	18-40 YEARS	41-50 YEARS	>50 YEARS	TOTAL	%
1	Late Proliferative endometrium	16	11	3	30	30
2	Early Secretary endometrium	16	8	3	27	27
3	Endometrial hyperplasia without atypia	2	6	3	11	11
4	Atrophic endometrium	-	4	3	7	7
5	Disordered proliferative endometrium	4	3	1	8	8
6	Polyp	2	4	1	7	7
7	Endometrial carcinoma	-	1	2	3	3

8	Chronic endometritis	1	-	1	2	2
9	Irregular ripening	-	1	1	2	2
10	Inadequate luteal phase	1	-	-	1	1
11	Pill induced endometrium	1	-	-	1	1
12	Endometrial breakdown	1	-	-	1	1
	TOTAL	44	38	18	100	100

IHC analysis of ER& PRwere done in 17 cases out of 100 cases, among them 11 were endometrial hyperplasias(EH), 3 were malignant(M) and 3 taken as controls. Among these 14 cases (11EH+ 3M) endometrial hyperplasias were positive for ER in 6/14 cases (42.85%) and 8/14cases(57.15%)were positiveforPR. From these 3 malignant cases, 2/14cases (14.28%) were positive for both ER&PR.In control group,1 case of late proliferative and 2 cases of early secretory endometrium were taken as controls which showed all 3 cases positive for both ER&PR expression. Among the 3 malignant cases, 1/14 case(7.14%) was Endometrioid Carcinoma with strong ER&PR expression, 1/14 case(7.14)%) was Moderately Differentiated Carcinoma with moderate ER&PR expression and 1/14(7.14%) case was Serous carcinoma with negative ER&PR status.

The correlation of IHC markers ER&PR(table-6) with histopathological diagnosis showed **ER positive** in 9/14cases **(64.28%)** and **PR positive** in 11/14cases (78.57%). Among the cases of endometrial hyperplasia without atypia (Fig 2A,2B-H&E;2C,2D) ER &PR positive were 7/11 cases(63.63%) and 9/11 cases(81.8%) respectively. Among the cases of endometrial carcinoma ER&PR were positive in 2/3 cases 66.66% each and in **control group 3 cases** were taken out of which 1 case was late proliferative endometrium with ER&PR 100% positive, 2 cases of early secretory endometrium with ER&PR constituting 50% and 100% respectively.

Endometrial hyperplasia and endometrial carcinoma were not included in the calculation of P value as the sample size is small. The statistical analysis revealed the proliferative endometrium, secretory endometrium and endometrial hyperplasia were showed the P value < 0.05 which is significant in the study.

Table-6. Correlation of IHC markers ER and PR with Histopathological diagnosis (N:100)

Histopathological finding	ER		PR		P-value
	N(positive)	%	N (positive)	%	
Endometrial hyperplasia without atypia	07/11	63.63%	09/11	81.81%	<0.05
Endometrial carcinoma	02/3	66.66%	02/03	66.66%	
Total	9/14	64.28%	11/14	78.57%	

Control group – 3cases : 1 case of Late proliferative phase, 2 cases of Early secretory phase.

In the present study, Allred intensity and proportion score were calculated for ER, PR expression.Among these three malignant cases,one case was Low Grade Endometrioid Carcinoma (Fig 4A,4B-H&E; 4C,4D-IHC for ER&PR)showed strong intensity and proportion score of 4 with allred score 7 indicating the better prognosis with therapy.

The second case diagnosed as Moderately differentiated adenocarcinoma showed weak intensity and proportion score 2 indicating bad prognosis. The third case, Serous Carcinoma (Fig 5A,5B-H&E; 5C,5D) was negative for ER&PR expression indicated worst outcome.

Photomicrographs

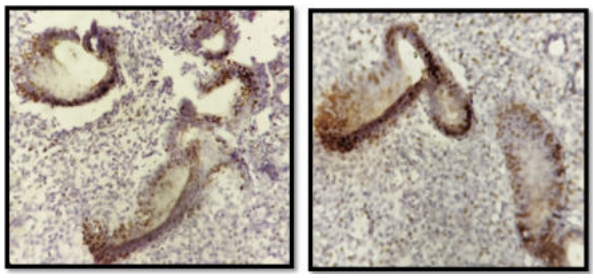


Fig 1A&1BLate proliferative phase – IHC ER&PR(40X) Photomicrographs show strong positivity.

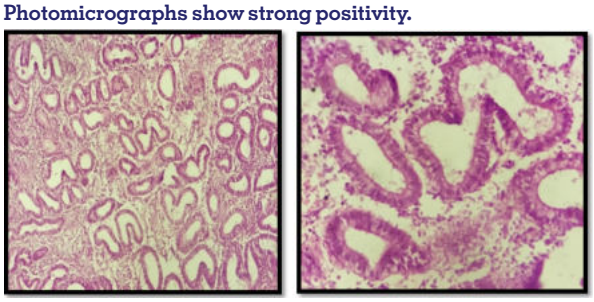


Fig2a&2b: Endometrial Hyperplasia Without Atypia (H&E,10x,40X): Photomicrographs show Back to back arrangement of crowded tubular glands in a relatively scant stroma.

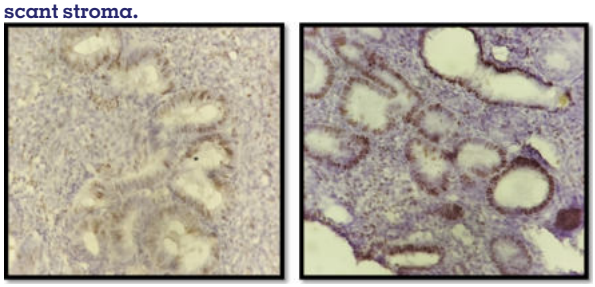


FIG 3A&3B: Photomicrographs show Endometrial Hyperplasia Without Atypia (IHC,10X - ER moderate positivity); (IHC,10X - PR moderate positivity)

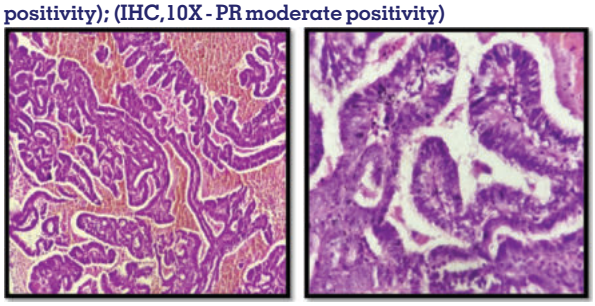


FIG 4A&4B: Photomicrograph shows Endometrioid Carcinoma – Villoglandular Pattern(10X)H&E; (40X)-Photomicrograph shows neoplastic cells with moderate eosinophilic cytoplasm and moderate nuclear atypia with inconspicuous nucleoli).

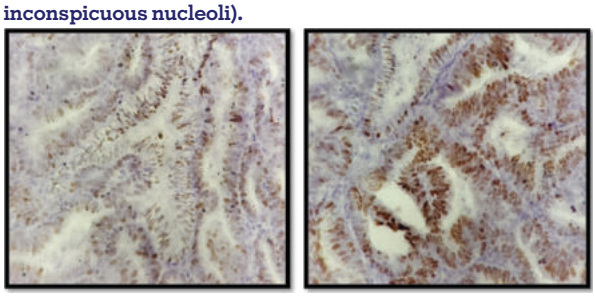


FIG 4C&4D: Photomicrographs show Endometrioid

Carcinoma – Villoglandular Pattern (ihc;40x Er – Moderate Positivity, Ihc;40x Pr – STRONG POSITIVITY)

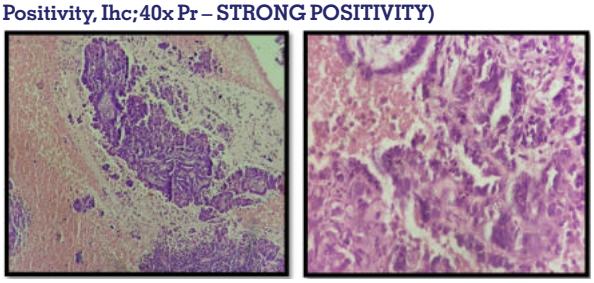


FIG 5A&5B: Photomicrographs shows Serous Carcinoma – H&E;10X&40X– Complex papillary pattern and focal solid pattern.

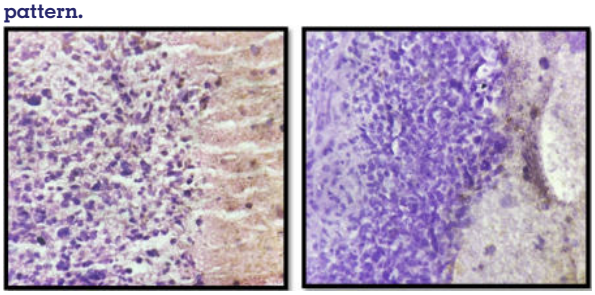


FIG 5C&D: Photomicrographs show Serous Carcinoma (H&E;40X, IHC 40X respectively) Negative expression of ER.

DISCUSSION

Abnormal uterine bleeding is termed as any vaginal bleeding not fulfilling the criteria of normal menstrual bleeding. The International Federation of Gynaecology and Obstetrics (FIGO) has given a classification of causes of AUB categorizing into structural and non structural causes. Histopathological examination of the endometrial tissue by pipelle biopsy or hysterectomy specimen is the diagnostic tool. An adjunct to this is IHC markers ER, PR, HER2/NEU and Ki 67 can be important for planning the treatment stragery.[7]

The highest incidence of AUB in the present study was noted in reproductive women(43%), with the second highest incidence in perimenopausal women (38%) where as in the other studies done by Themthingla[8], Manjani[9] et al etc perimenopausal women constituting 74.3%,49% respectively. Thestudy done by Neha[10] et al showed premenopausal age group as common(53%) followed by perimenopausal age group 30%.

The most common presenting complaint was menorrhagia In this study (63%) similar to the studies done by Junudevi[11] et al(68.8%), Neha[12]et al(53%), Niddiet al[13](49%) where as in Anupamasuresh et alpost menopausal bleeding was the commonest complaint 43.6%.

Among the causes of AUB,(table-9) non structural causes were common in the present study(62%) similar to the studies Junudevi et al[11](70.4%), Manjani et al[9](53%),Doraiswami et al[14](51.3%). Whereas the study done by Nadia et al[15] showed structural causes as most common (61.80%). In the studies done by Junudevi et al and Nadia et al showed 34cases(6.8%), 7cases (4.6%) as inadequate biopsy and diagnosis respectively.

Table-9: Comparison study on structural and non structural causes of AUB

Serial no.	Name of the study	Structural cause(%)	Non structuralcause(%)	Inadequate sample
1	Present study	38%	62%	-
2	Junu devi et al11	22.80%	70.40%	6.8%
3	Manjani et al9	47%	53%	-
4	Nadia et al15	61.80%	33.50%	4.7%
5	Doraiswami et al14	48.66	51.34%	-

Structuralcauses: Polyp, Adenomyosis,Leiomyoma, Malignancy & Hyperplasia Non structural causes: Ovulatory dysfunction, Endometritis, etc.

The common histopathological diagnosis are proliferative endometrium 30 cases (30%), followed by secretory endometrium 27 cases(27%) in the present study similar to the studies done by Themthingla et al[8] (PE :17cases, 24.3%; SE:4cases 5.7%), Neha et al[10] (PE:154 cases 42%,SE:43 cases12%) and Vani et al[16](PE:30%,SE:26%). While hyperplasia was commonest diagnosis in Manjani et al[9] (34%) followed by Proliferative endometrium (20.6%). Atrophic endometrium comprises of 7% in this study, whereas in the study Junu et al[11] it has shown the maximum incidence of 36.2% and in other studies like Themthingla et al[8](7%), Neha et al[10](7%),Vani et al[16](5.6%), Anupamasuresh et al[13](5.6%) and Doraiswami et al[14](2.4%) in pre and post menopausal age group.

Endometrial polyps include 7% in the present study which is similar to Themthingla et al[8], Neha et al[10], Vani et al[16], Manjani et al[9],Doraiswami et al[14], Junudevi et al[11]and Anupamasuresh et al[13] constituting 21.4%, 4%, 2.6%,4% ,11.2%, 2.2% and 8.6% respectively.

Endometrial Hyperplasias constitute 11% in this study and all are hyperplasias without atypia. In the studies of Junu et al[11] endometrial hyperplasia without atypia is common comprising of 16% similar to the other studies like Themthingla et al[8] (12.8%) and Manjani.S et al[9] 21.3% among hyperplasias.

Endometrial carcinoma is the most common invasive gynaecologic malignancy in developing countries.[17]It commonly affects post menopausal women with presenting complaint of abnormal vaginal bleeding. As Black women are diagnosed in advanced stage they have 90% of 5 year mortality than in white women.[18]Endometrial carcinomas in the present study were 3 cases (3%) out of them one case is Endometrioid carcinoma (type 1 endometrial carcinoma – villoglandular type), one case is Moderately differentiated endometrial adenocarcinoma and the other case is Serous endometrial carcinoma which is aggressive and has poor prognosis (type 2 endometrial carcinoma). The other comparative studies include similar incidence of endometrial carcinoma constituting Themthingla et al[8] 4.28%, Neha et al[10] 1%, Vani et al[16] 0.86%, Niddi et al[12] 2%,Archana.T et al[19] 5%, Manjani.S[9] 4.9% and Doraiswami.S et al[14] 4.4%. whereas the study done by Anupamasuresh et al[13] has the high incidence of 23 case (6.4%) out of 359 cases. Endometrial carcinomas are common in peri and post menopausal women in this study similar to all these studies.

Molecular analysis of endometrial carcinoma is done by Immunohistochemical markers ER and PR (pharmDx kit of Dako). These are used to analyse the expression of EstrogenProgesterone receptors which are usually present in the endometrial glands and endometrial stroma.

The intensity of staining is estimated by **Allred score** which is **a sum of proportion score and intensity score** in the present study.[20]

The positivity of ER or PR has been associated with the prognosis of endometrial carcinoma. In the present study ER&PR markers were done in 17/100 cases out of which 1 case was proliferative endometrium showed 100% nuclear positivity, 2 were secretory endometrium which showed 80% nuclear positivity; 11 were hyperplasias showed 63.6% ER

positive, 81.8% PR nuclear positive. Endometrioid carcinoma had shown high ER(50%)& PR(55%) nuclear positivity indicating better prognosis and better survival. High grade endometrioid carcinoma and serous carcinoma show low ER,PR expression; they are found less responsive to chemotherapy and have poor prognosis.[21]

The comparative study Themthingla et al[8] showed ER&PR positivity of 100% in hyperplasias and 2cases (66.7%) positive of endometrial carcinoma. The other study Fangshen et al[22] showed ER(92.1%), PR(91%)case positivity in type 1 cancers and ER (71.9%), PR(64.8%) case positivity in type 2 cancers.The study done by Samina waqar et al[23] showed PR expression in 66.1% followed by ER(44.6%) Her2/neu(7.1%) and expressed significant association with high grade and serous carcinomas.

CONCLUSION:

In the present study structural causes constitute 38% and non structural causes constitute 62%.Immunohistochemical studies for ER&PR expression were done on allhyperplasias (14) and endometrial carcinomas(3) reported in these 100cases and 3 cases were taken as control out of which 1 case was late proliferative and 2 were of early secretory endometrium. IHC studies revealed 100% expression of ER&PR in late proliferative, early secretory endometrium. Hyperplasias showed 42.85% and 57.15% positivity with ER &PR. Out of 3 endometrial carcinomas in the present study 2 were positive for ER&PR comprising of 14.28% each and 1 was negative for ER and PR comprising 7.14% each.

IHC of these 14 cases showed reduced expression of ER & PR from non malignant to malignant cases, While low grade endometrioid carcinoma revealed better expression than type 2 serous carcinoma indicating better prognosis in endometrioid cancer.

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