e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(11); 1133-1140

Original Research Article

Histomorphological Patterns of Endometrial Biopsies and Their Association with ER / PR Receptors Expression in Abnormal Uterine Bleeding

Prashant Trivedi[1], Manoj Sharma[2], Sonia Agarwal[3]*, Purushottam Maderna[4], Manju Raghav[5]

[1,4] PG Student, Department of Pathology, MGMCH, Jaipur

[2] Associate Professor, Department of Onco-pathology, MGMCH, Jaipur

[3]Assistant Professor, Department of Pathology, MGMCH, Jaipur

[5]Professor &Head, Department of Pathology, MGMCH, Jaipur

Received: 14-09-2023 / Revised: 23-10-2023 / Accepted: 24-11-2023
Corresponding Author: Sonia Agarwal
Conflict of interest: Nil

Abstract:

Introduction: Abnormal uterine bleeding (AUB) is a broad term that describes irregularities in the menstrual cycle, up to one-third of women will experience abnormal uterine bleeding in their life.

Aim: To study histomorphological patterns of endometrial biopsies and their association with ER / PR receptors expression in abnormal uterine bleeding.

Methods: This prospective observational study was conducted in tertiary care hospital attached to medical college in northern India. All endometrial biopsies received during the period of January 2021 and June 2022 in the pathology department from both outdoor and inpatients with chief complaints of bleeding per vagina and of reproductive age and post menopausal age were included.

Results: 44 biopsies (40%) were in the age group of 30 to 40 years. 90.91% cases were non neoplastic, the most common histological pattern was 50% cases belong to proliferative phase endometrium, whereas in neoplastic, endometrioid carcinoma (7.27%). ER was positive in 60% and PR was positive in 27.27%. Both ER and PR negative EB has high chances of non malignant lesion (P=<0.001S).

Introduction

Abnormal uterine bleeding (AUB) is a broad term that describes irregularities in the menstrual cycle involving frequency, regularity, duration, and volume of flow outside of pregnancy. Up to one-third of women will experience abnormal uterine bleeding in their life, with irregularities most commonly occurring at menarche and perimenopause. [1] Fibroids, polyps, endometrial hyperplasia, endometrial carcinoma and complications of pregnancy are the common structural causes of AUB. An endometrial biopsy(EB) is considered the first-line test in women with AUB who are 45 years or older [2]. Endometrial sampling should also be performed in women younger than 45 with unopposed estrogen exposure, such as women with obesity and/or polycystic ovarian syndrome (PCOS), as well as a failure of treatment or persistent bleeding.

EB helps in deciding the management of patients. It is a safe, efficient and cost effective means of evaluating the uterine endometrium. It not only helps to rule out precursor lesion and malignancy but also serves to identify hormonal induced changes, inflammation and other pathology in patients with AUB [3].

The ER (Estrogen Receptor) and PR (Progesterone Receptor) expression can help localizing the intensity in glandular and stromal cells. Hence, its usage with supportive clinical feature and histopathology will be an essential diagnostic tool. The human endometrium ER and PR over expression is found in endometrial polyps indicating the hormone receptors contribute to endometrial polyp formation. ER and PR expression are generally decreased in endometrial carcinoma. Decrease in receptor activity is also found in atypical hyperplasia and are less sensitive to progesterone therapy. ER and PR expression assessment may be helpful in hormonal based treatment and necessary surgical intervention [4].

Moreover immuno histochemistry (IHC) examination is beneficial because of tissue localization and aids in assessing tissue distribution and intensity in glandular and stromal cells. IHC is a useful investigation which can be used along with pelvic ultrasound and histopathology of endometrial biopsies in management of AUB of endometrial cause in reproductive age group. [5]

Our hypothesis is with current advances in histopathology and adding new armor to diagnostic system, inclusion of IHC can help in differentiating pathology of AUB in different age group and can provide early diagnosis which significantly assist in choosing best treatment option thus will help favourable outcome in terms of morbidity or mortality.

Aims and Objective

This study was designed with primary objective of determining histomorphological spectrum of endometrial biopsies received in our department with chief complaints of AUB in 15 to 70 years age group. Secondary objective was to evaluate histopathology of endometrial biopsies with ER/PR expression and IHC examination for hormone receptor expression in distinguishing cause of AUB.

Methodology

This prospective observational study was conducted in tertiary care hospital attached to medical college in northern India. All endometrial biopsies received during the period of January 2021 and June 2022 in the pathology department from both outdoor and inpatients with chief complaints of bleeding per vagina and of reproductive age and post menopausal age were included. EB from patient with chief complain other than AUB, inadequate specimen and biopsies from less than 15 years of age were excluded. Informed consent were taken in a prescribed format.

Standard procedure for fixation of sample was followed, adequate processing of biopsy tissues were done. Histomorphological diagnosis was done after hematoxylin and eosin staining and which was further correlated with immunohistochemistry.

Statistical analyses were done using computer software (SPSS Trial version 23 and primer). The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analysed by using chi square test and the difference in means among the groups was analyzed using the student t test. Five percent probability level was considered as statistically significant i.e., $p<0.05$.

Results

Total 110 endometrial biopsies were considered to be acceptable after staining, these EB were evaluated as per study design and distribution data was prepared.

Distribution of the cases according to age:- In this study, EB were received from the patients ranged from 21 to 70 years of age (Mean± 2SD =54.67±13.05 years). Out of total 110 cases, 44 biopsies (40%) were in the age group of 30 to 40 years.

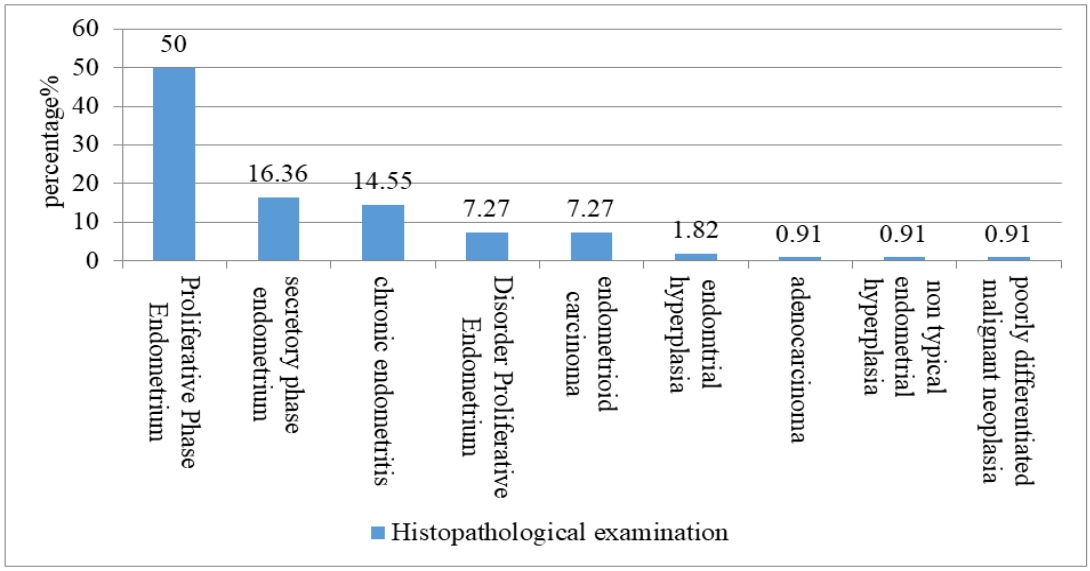
Pre menopausal bleeding cases were 83 (75.45%) and rest 27 (24.55%) suffered from postmenopausal bleeding. Menorrhagia (32.73%) is the most common clinical feature followed by polymenorrhagia (15.45%).

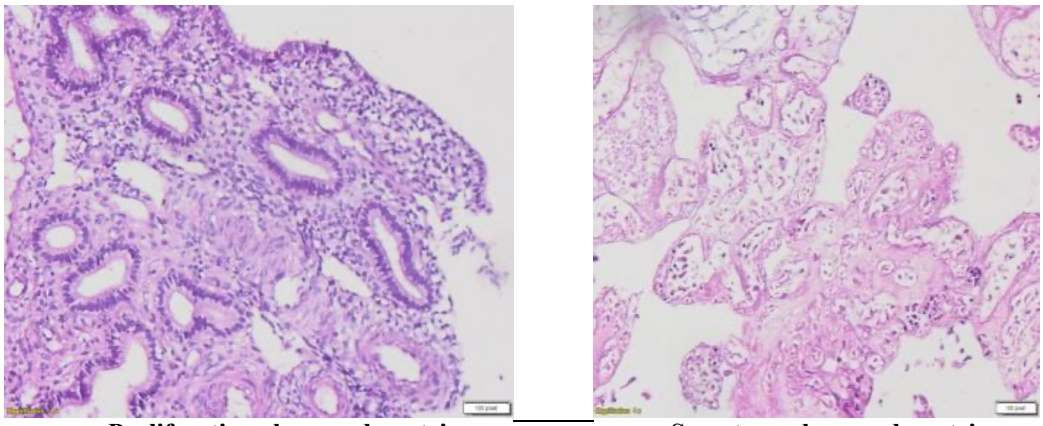
In the present study we have found that 90.91% cases were non neoplastic followed by 9.09% cases which were neoplastic.

Type of pathology	Number	Percentage(%)
Neoplastic	10	9.09
Non neoplastic	100	90.91
Total	110	100

Out of total 10 neoplastic cases diagnosed on HPE, 9 cases (90%) were in the age of >60years, and 1 case (10%) was in the age group of 51 to 60 year. Similar pattern was observed in non neoplastic cases, maximum number of the cases found 44% (44 cases) were in the age of 31 to 40 years, followed by 24% (24 cases) which were in the age of 21 to 30 years. This observation of distribution of age according to neoplastic and non neoplastic was statistically significant (P=0.001S) and reflect disease propensity towards higher age group of spectrum.

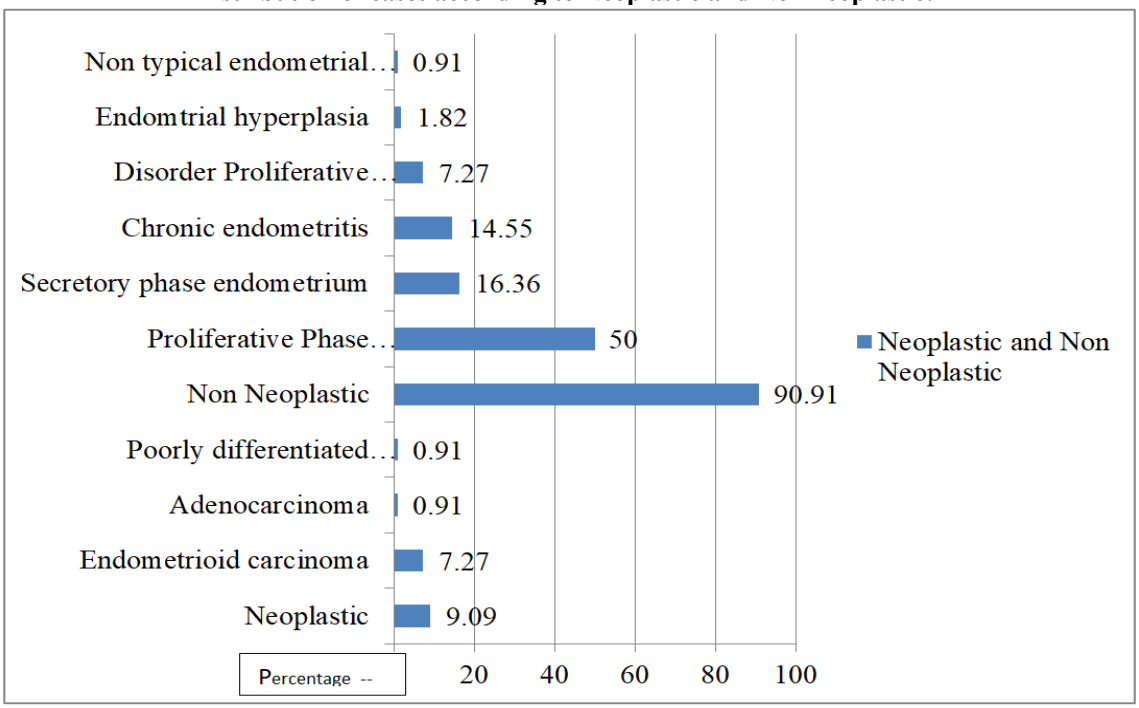
According to histopathological examination, 50% cases belong to proliferative phase endometrium followed by 16.36% cases were of secretory phase endometrium





Proliferative phase endometrium **Secretory phase endometrium**

Distribution of cases according to Neoplastic and Non neoplastic:-

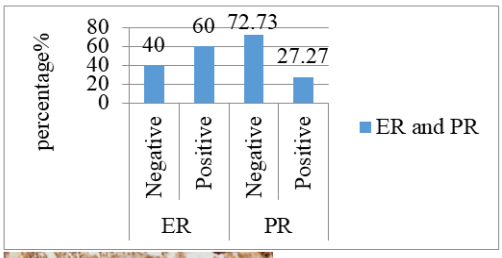


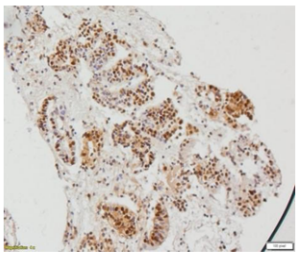
In **neoplastic**, we found endometrioid carcinoma in 7.27%, a single case of adenocarcinoma (0.91%) and poorly differentiated malignant neoplasia(0.91%) . In non **neoplastic**, the most common histological pattern in AUB was 50% cases belong to proliferative phase endometrium, followed by 16.36% cases belong to secretory phase endometrium.

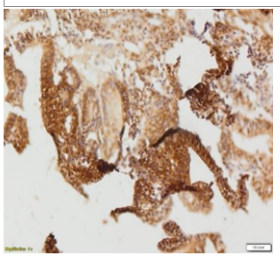
Comparison of cases according to histopathological examination with age:-

In Neoplastic cases**,** in endometrioid carcinoma mean ± SD of age was 65.5±6.78 yrs. In Non neoplastic, in proliferative phase endometrium cases (mean ± SD) was 36.09±9.28 yrs, secretory phase endometrium was (36.17±7.48) yrs, endometrial hyperplasia was (38±6.89) yrs. chronic endometritis was (40.25±7.24)yrs., disordered proliferative endometrium (44.13±8.17 yrs.), non typical endometrial hyperplasia (54±8.37 yrs) this difference of age were observed statistically significant and give distribution spectrum of disease.

Distribution of cases according to ER and PR:-



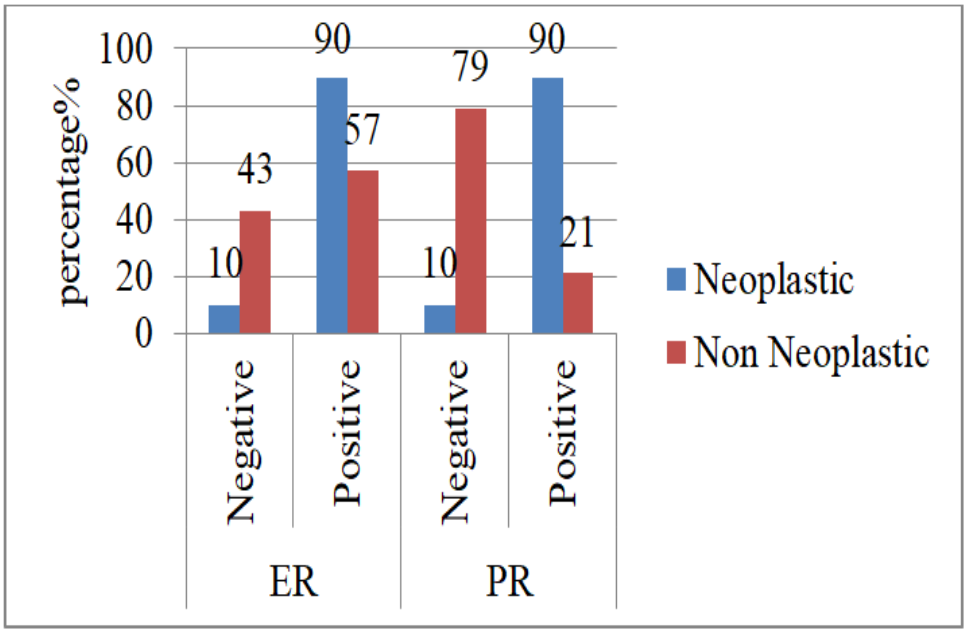




ER positive PR positive

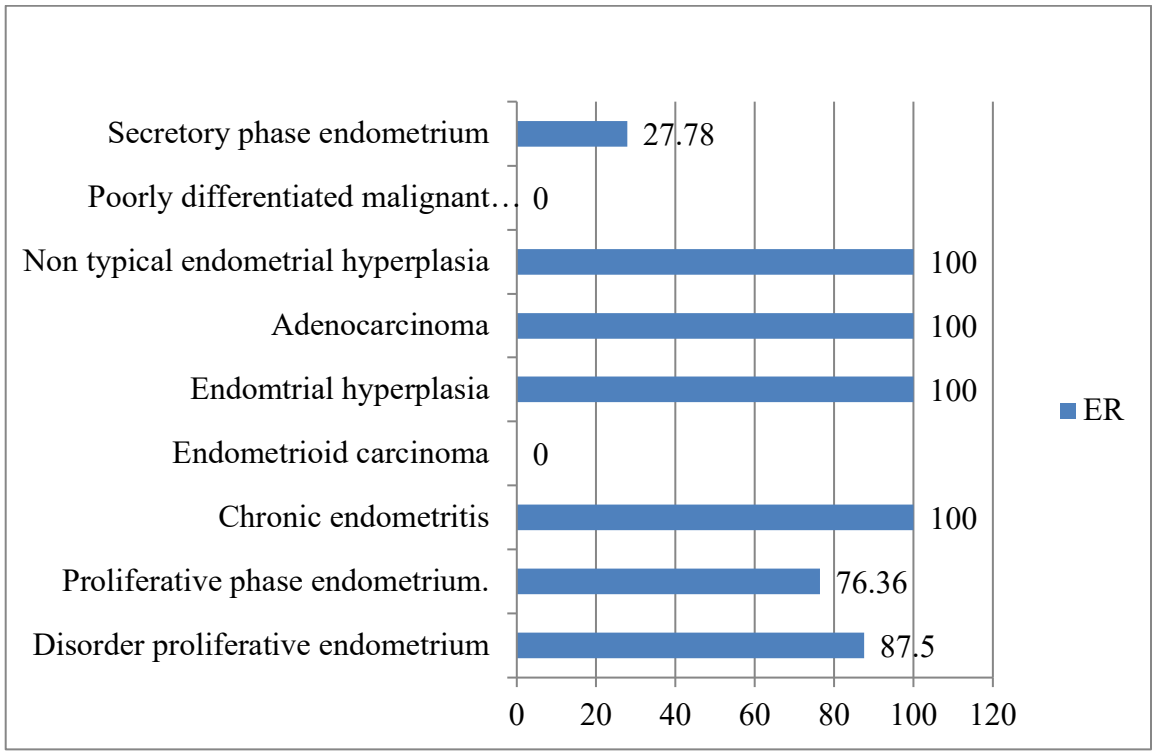
The above table depicts that ER was positive in 60% and PR was positive in 27.27%.

Association of ER /PR receptors with lesions:-



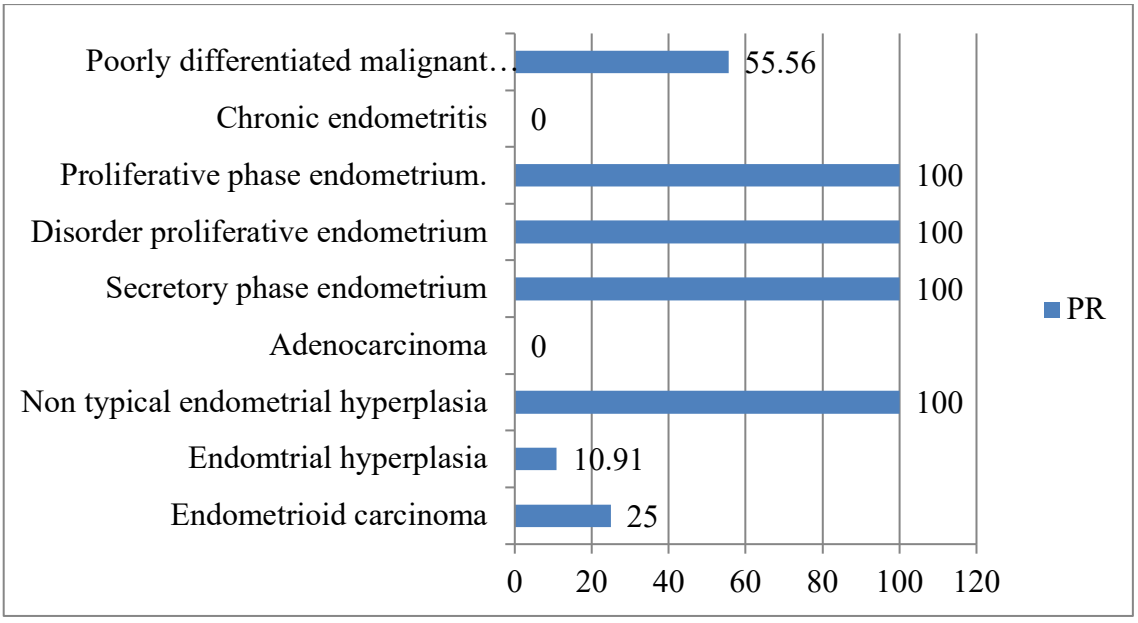
In neoplastic lesion, 90% cases were positive both for ER and PR whereas in non-neoplastic lesion, 57% wereonly ER positive while 21% were only PR positive. Thus both ER and PR negative EB has high chances of non malignant lesion. This observation was statistically significant. (P=<0.001S).

Association of ER receptors with lesions:-



In disordered proliferative endometrium (87.5%), proliferative phase endometrium (76.36%), endometrioid carcinoma (100%) [8/8], endometrial hyperplasia (100%) [2/2]and secretory phase endometrium(27.78%) [5/18] increased ER receptor expression was noted.

Association of PR receptors with lesions:-



Endometrioid carcinoma showed the expression of PR receptors 8/8 (100%), endometrial hyperplasia 2/2 (100%), non typical endometrial hyperplasia 1/1(100%), adenocarcinoma 1/1(100%), secretory phase endometrium 10/18(55.56%), disordered proliferative endometrium 2/8 (25%), proliferative phase endometrium 6/55(10.91%).

Discussion:

Distribution of cases according to Age

In this study we found that the mean age of women presenting with abnormal uterine bleeding was 54.67±13.05 yrs (Mean ± SD). While maximum EB were received from 31-40 years age group. This

finding is different from **Jairajpuri ZS et al [**6] **and Agrawal S et al (2014) [**7] **s**tudy. Their observation was that age group between 41-50 year constitute major bulk of AUB with diagnosis at mean age of 41 years. This difference in age group may be due to awareness of health education among this age group population, availability of diagnostic facility at community health centers. Early diagnosis treatment and better survival of uterine carcinoma cases causes shifting of age spectrum in last decade.

In the present study, distribution of **AUB** cases, premenopausal bleeding cases were more 75.45%. This study is comparable with observation of **Agrawal S et al (2014) [7]** that **AUB** predominantly affects women of perimenopausal (41-50 years) age group. A similar conclusion were made by **Damle RP et al (2013)** [**8]**, in their 2 year study where maximum number (73.94%) of cases were from peri-menopausal age group. The most common presenting complaint was menorrhagia (48.86%) followed by post-menopausal bleeding (26.05%).

Many studies have revealed that occurrence of menstrual disorders of excessive type increased with age. A gradual increase in patients with respect to age was noted in the present study also. An increased number of cases in this age could be due to the fact that as menopause approaches, decreased number of ovarian follicles and their increased resistance to gonadotrophic stimulation, results in a low level of estrogen, which cannot keep the normal endometrium growing. Lesser number of patients was seen in the higher ages may be due to earlier evaluation, detection as well as management of the disease.

Distribution of cases according to Clinical features

In the present study ,menorrhagia cases 32.73% (36) is the most common presenting complaint followed by 15.45 % (17) , 10 % (11), 9.09 % (10),6.36 % (7), 4.55%(5), 2.73%(3),1.82%(2), 0.91%(1) in the group of polymenorrhagia, post-menopausal bleeding, intermittent bleeding P/V ,menometrorrhagia and polymennorhea, irregular uterine bleeding and metrorrhagia & oligomenorrhea, bleeding after coitus, bleeding p/v and hypomenorrhea, and spotting respectively. Bleeding patterns were comparable with **Parveen Azim et al 2011 [9]** who observed that the most frequent clinical feature was polymenorrhagia (35%), gestational bleeding (27%), menorrhagia (18%), metrorrhagia (9%) and postmenopausal bleeding (6%).

Jairajpuri ZS et al 2013 [6] concluded that the most common clinical presentation was represented by menorrhagia (41%). Various patterns on histopathology were secretory endometrium(28.99%) the commonest, followed by proliferative endometrium (24.92%).

Agrawal S et al (2014) [7] observed that most common clinical presentation of abnormal uterine bleeding was menorrhagia in 49% cases followed by menometrorrhagia in 22% cases, metrorrhagia in 16.75% cases and postmenopausal bleeding in 10% cases.

Most of the previous study showed menorrhagia as the chief complaint as observed in our study but **Kumari A et al 2016 [10] in their** study found postmenopausal bleeding (PMB) was the most common mode of presentation because as in their study, study place is the Regional Cancer Centre, this might be a cause of increased number of PMB cases.

In the present study, 90.91% cases belong to non neoplastic followed by 9.09% cases belong to neoplastic. Maximum number of the cases in n**eoplastic** were studied (9) 90 % in the age of >60years, followed by (1) 10% in the age of 51 to 60and so on. Similar pattern was observed in n**on-neoplastic**, maximum number of the cases were found (44)44% in the age of 31 to 40years, followed by (24)24% in the age of 21 to 30. This observation was statistically significant (P=0.001**S**). In **Neoplastic cases,** endometrioid carcinoma of age was 65.5±6.78 yrs. (mean ± SD). In Non-neoplastic, in proliferative phase endometrium cases of age was 36.09±9.28 yrs.(mean ± SD), secretory phase endometrium (36.17± 5.64 yrs.), endometrial hyperplasia (38±6.38 yrs), chronic endometritis (40.25±7.35yrs.), disordered proliferative endometrium (44.13±8.72yrs.), non typical endometrial hyperplasia (54±6.93yrs.), this difference of age were observed statistically significant.

Bindroo S et al 2018 [11] observed that endometrial hyperplasia was seen mostly in the age group 41-50 years (27 cases). Two cases of endometrial carcinomas were presented after age 60 years.

Kumari A et al 2019 [10] in this study, the incidence of benign cases was 49%, premalignant 9% and malignant condition 42%, respectively. Out of 42 malignant cases, 37 (88.09%) were cervical cancer, 3 (7.14%) endometrial carcinoma, 1 (2.38%) vulval cancer and 1 sarcoma of uterus.

Distribution of cases according to Histopathological examination

According to **Histopathological examination,** we have found that 50% cases belong to proliferative phase endometrium followed by 16.36% cases belong to secretory phase endometrium,14.55% cases belong to chronic endometritis, disordered proliferative endometrium 7.27 % and endometrioid carcinoma 7.27% and so on.

Distribution of cases according to Neoplastic and Non neoplastic

In **neoplastic,** endometrioid carcinoma 7.27% ,single case adenocarcinoma and poorly differentiated malignant neoplasia. In non-**neoplastic** the most common histological pattern in AUB was 50% cases belong to proliferative phase endometrium, followed by 16.36% cases belong to secretory phase endometrium.

Distribution of cases according to ER and PR Expression

Steroid hormones, including ovarian steroid hormones progesterone and estrogen, play vital roles in the development of benign endometrium and endometrial cancer via their receptors. Estrogens act as a promoter of growth and proliferation of the endometrium via estrogen receptors, while progesterone acts as an estrogen antagonist in endometrial maturation and inhibition of proliferation [12]. The endometrium is very sensitive to sex hormones, and thus a shift in the balance of estrogens and progesterone can cause the development of endometrial cancer[13].The glandular epithelium from which the cancer arises is hormone responsive, expressing both PRs (PR-A and PR-B) and ERs (ER-α and ER-β). Establishing the diagnosis of molecular subtype of EC with limited markers, namely ER/PR, expression similar to breast cancer, may be useful to determine the treatment and prognosis, especially in developing countries.

In the present study, ER were positive in 60 % and PR were positive in 27.27%. In neoplastic lesion, maximum number of the cases 90% found were positive for ER& PR expression. As compared to in non-neoplastic, maximum number of the cases (57%) were observed positive ER expression while 21% were observed PR positive expression. This observation was statistically significant (P=<0.001S)**.**

Disordered proliferative endometrium 87.5%, proliferative phase endometrium 76.36%, endometrioid carcinoma 100% (8/8), endometrial hyperplasia 100% (2/2) and secretory phase endometrium 27.78% (5/18) increased **ER receptor expression** was noted. Endometrioid carcinoma showed the expression of **PR receptors** 8/8 (100%), endometrial hyperplasia 2/2 (100%), non typical endometrial hyperplasia 1/1(100%), adenocarcinoma 1/1(100%), secretory phase endometrium10/18(55.56%), disordered proliferative endometrium 2/8 (25%), proliferative phase endometrium. 6/55(10.91%) .

Mecintosh ML et al 2018 [14] observed that in endometrial tissues, a higher proportion of subjects had ER-positive staining by IHC in postmenopausal relative to proliferative phase premenopausal participants respectively, for glandular tissue [26/29 (90 %) positive vs. 13/23 (57 %)] and in the stroma [21/29 (72 %) positive vs. 9/23 (39 %)], with both *P* values ≤0.02, whereas for PR (glandular or stromal tissue) there was no difference in the frequency of positive staining by menopausal status. Our findings were in concordance with them.

Tanushree Satpathy et al (2018) [15] in their study on Indian population, ER were positive in 84.7% and PR were positive in 76.7%. HER-2/Neu expression in this study showed different histopathological pattern of endometrium in AUB. **Mohapatra K et al 2019 [16]** observed that PR expression was seen in 22 (62.9%) cases and showed significant association with tumor grade, myometrial invasion and histological type. All of the hormone receptors had prognostic value for survival. Both these sudies support observations of our study.

Singh P et al [17] did study on patients with clinical diagnosis of AUB conclude that the relationship between ER, PR receptor expression concentration in AUB-E group will help in providing evidence based treatment and prevent from surgical procedures like hysterectomy and endometrial ablation. With these insight regarding role of ER,PR receptors , this study give better understanding of the etiopathogenesis in our patients of AUB and help in providing more appropriate treatment options.

Conclusion

In present study, we find out spectrum of aetiological factors and the clinical presentation of AUB as per age distribution and found out changing pattern of disease. We observe that menorrhagia is the most common presenting complaint. ER and PR receptors IHC examination results were correlated well with histopathological examination. In our study, we found that early-stage, well differentiated endometrial carcinomas usually retain expression of both receptors whereas advanced stage, poorly differentiated tumors lack one or both of these receptors. Our study indicate that conventional histological examination alone may not help in guiding therapy. We sincerely advice inclusion of ER, PR level evaluation along with histopathology examination should be done in all cases of AUB at appropriate time for early definitive diagnosis.

References

1. Davis E, Sparzak PB. Abnormal Uterine Bleeding. 2023 Sep 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 30422508.
2. Practice Bulletin No. 136: Management of Abnormal Uterine Bleeding Associated With Ovulatory Dysfunction. Obstetrics & Gynecology 122(1):p176-185,July 2013. | DOI:10.1097/01.AOG.0000431815.52 679.bb
3. Singh G, Puckett Y. Endometrial Hyperplasia. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books /NBK560693/

4. Zhang, Y., Zhao, D., Gong, C. et al. Prognostic role of hormone receptors in endometrial cancer: a systematic review and meta-analysis. World J Surg Onc **13**, 208 (2015). https://doi.org/10.1186/s12957-015-0619-
5. Doraiswami S, Johnson T, Rao S, Rajkumar A, Vijayaraghavan J, Panicker VK. Study of endometrial pathology in abnormal uterine bleeding. J Obstet Gynaecol India. 2011 Aug;61 (4):426-30. doi: 10.1007/s13224-011-0047-2. Epub 2011 Sep 22. PMID: 22851826; PMCID: PMC3295868
6. Zeeba S. Jairajpuri, S. Rana and S. Jetley Atypical uterine bleeding-Histopathological audit of endometrium A study of 638 cases Al Ameen J Med Sci 2013; 6(1):21-28
7. Shweta Agrawal, Asha Mathur and Kusum Vaishnav histopathological study of endometrium in abnormal uterine bleeding in women of all age groups in western rajasthan (400 cases) International Journal of Basic and Applied Medical Sciences 2014 Vol. 4 (3) September-December, pp. 15-18.
8. Damle RP, Dravid NV, Suryawanshi KH, Gadre AS, Bagale PS, Ahire N. Clinicopathological Spectrum of Endometrial Changes in Perimenopausal and Post-menopausal Abnormal Uterine Bleeding: A 2 Years Study. J Clin Diagn Res. 2013 Dec;7(12):2774-6. doi: 10.7860/JCDR/2013/6291.3755. Epub 2013 Dec 15. PMID: 24551634; PMCID: PMC3919318.
9. Parveen Azim, Muhammad Mumtaz Khan, Naveed Sharif, Ehsan Gul Khattak Evaluation of abnormal uterine bleeding on endometrial biopsies isra medical journal 2011 dec volume 3 issue 3 pp 84-89
10. Priti Kumari,Harsha S. Gaikwad, **Banashree Nath** Endometrial Cut Off Thickness as Predictor of Endometrial Pathology in Perimenopausal Women with Abnormal Uterine Bleeding: A Cross-Sectional Study Obstetrics and Gynecology International 2022 January, Volume 6 pp1-6 Article Carlson MJ, Thiel KW, Yang S, Leslie KK. Catch it before it kills: progesterone, obesity, and the prevention of endometrial cancer. Discov Med. 2012 Sep;14(76):215-22.PMID:23021376; PMCID: PMC3964851ID5073944 ,| https://doi.org/10.1155/2022/5073944
11. Bindroo s, Garg M, Kaur T Histopathological spectrum of endomerium in abnormal uterine bleeding. International journal of reproduction contraception obstetrics and gynecology 2018 sept. Vol 7 no.9 pp 3633-7
12. Marquardt RM, Kim TH, Shin J-H, Jeong J-W. Progesterone and Estrogen Signaling in the Endometrium: What Goes Wrong in Endometriosis? *International Journal of Molecular Sciences*. 2019; 20(15):3822. https://doi.org/10.3390/ijms20153822
13. Carlson MJ, Thiel KW, Yang S, Leslie KK. Catch it before it kills: progesterone, obesity, and the prevention of endometrial cancer. Discov Med. 2012 Sep;14(76):215-22. PMID: 23021376; PMCID: PMC3964851
14. MacKintosh ML, Crosbie EJ. Prevention Strategies in Endometrial Carcinoma. Curr Oncol Rep. 2018 Nov 13;20(12):101. doi: 10.1007/s11912-018-0747-1. PMID:30426278; PMCID: PMC6244901
15. Tanushree Satpathy, Binapani Satpathy, Prasanna Kumar Satpathy Clinicopathological Evaluation of Abnormal Uterine Bleeding with Special Reference to Estrogen Receptor (ER), Progesterone Receptor (PR)2 and HER-2 / NEU Status Annals of Pathology and Laboratory Medicine, 2018 May Vol. 5, Issue 5, pp 399-403
16. Mohapatra, K., Shivalingaiah, S.C. Immunohistochemical Expression of ER, PR and HER2/neu in Endometrial Carcinoma. Indian J Gynecol Oncolog **17**, 54 (2019). https://doi.org/10.1007/s40944-019-0298-x
17. Singh P, Chaurasia A, Dhingra V, Misra V. Expression of ERα and PR in Various Morphological Patterns of Abnormal Uterine Bleeding-Endometrial causes in Reproductive Age Group. J Clin Diagn Res. 2016 Aug; 10 (8):EC06-9.