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Pathology

ROLE OF ESTROGEN RECEPTOR (ER) AND PROGESTERONE RECEPTOR (PR) IN ABNORMAL UTERINE BLEEDING- THE NON STRUCTURAL CAUSES.

Sabari Devi Associate Professor Department Of Pathology Gauhati Medical College And Hospital, Guwahati.

Waziha Ahmed* PGT Pathology Department Of Pathology Gauhati Medical College And Hospital, Guwahati. *Corresponding Author

ABSTRACT

BACKGROUND: Abnormal uterine bleeding (AUB) is defined as any uterine bleeding that is more than the normal volume, of longer duration and varying in regularity or frequency. Nearly 30% of all gynaecological outpatient attendants are for AUB. Understanding the biochemical basis of endometrial responsiveness to hormones in such patients is fundamental to designing a successful medical therapy. Thus Immunohistochemistry was done in this study to evaluate the expression of estrogen receptor (ER) and progesterone receptor (PR) in endometrium in patients with AUB, to find whether evidence based hormonal therapy can be used in patients to prevent unnecessary surgical interventions.

METHODS: The study was done on patients with clinical diagnosis of Abnormal uterine bleeding from Gynaecology Department, Gauhati Medical College and Hospital, Guwahati from December 2017 to November 2018. Endometrial dilatation and curettage samples or hysterectomy specimens of 60 patients, collected or done in the premenstrual phase of the cycle or at random for cases presenting with irregular cycles, was sent to Pathology Department from Gynaecology Department. All histopathological samples were stained with Hematoxylin and Eosin stain (H&E stain) and subsequently immunostaining was done for ER, PR..

RESULTS: 30% cases of AUB were observed in the age group of 36-40 years. 50% cases presented with menorrhagia. Endometrial proliferative pattern was the most common histopathological finding and was seen in 41.67% patients .Statistically significant expression of ER and PR was found in AUB endometrium as compared to control group endometrium.

CONCLUSION: The relationship between ER,PR concentration and altered endometrial histology that was demonstrated in this study suggest the role of these receptors in the etiopathogenesis of Abnormal Uterine Bleeding.

KEYWORDS : Estrogen Receptor, Progesterone Receptor

INTRODUCTION:

Abnormal uterine bleeding (AUB) is defined as any uterine bleeding that is more than the normal volume, of longer duration and varying in regularity or frequency. Nearly 30% of all gynaecological outpatient attendants are for AUB[1].

Dysfunctional uterine bleeding is defined as a type of AUB where no underlying cause can be defined. But with passing time more and more causes are being defined.[2]) therefore diagnosis earlier included in DUB category are now classified[3] under 3 headings.

Disorders of endometrial origin (disturbances of molecular mechanisms responsible for regulation of the volume of menstrual bleeding)

Disorders of hypothalamic-pituitary-ovarian axis.
Disorders of haemostasis (coagulopathy)

These three together are called non-structural causes of abnormal uterine bleeding[4]

FIGO (Federation of International of Gynecologists and Obstetricians) in 2011 came forward with the new nomenclature of AUB instead of dysfunctional uterine bleeding, and a new classification system to define its cause. This classification is named 'PALM–COEIN' system. It stands for polyp, adenomyosis, leiomyoma, malignancy, coagulopathy, ovulatory dysfunction, endometrium, iatrogenic and non classified. The first four are related to visually objective structural uterine abnormalities that can be measured visually with imaging modalities and by histopathological study. The others are non structural and attributed to coagulation disorders and hormonal dysfunction. N stands for no cause detected.[5]

Estrogen and progesterone exert their effect by acting on specific nuclear receptor proteins, Estrogen Receptor (ER) and Progesterone Receptor (PR). These receptors are present in endometrial stromal and glandular cells[6] The estrogen receptor (ER) and progesterone receptor (PR) expression and distribution pattern have been demonstrated to play an important role in normal endometrial functioning[7,8]. Throughout the menstrual cycle, the concentrations of both estrogen receptor (ER) and progesterone receptor (PR) undergo considerable variations in the human uterus,in response to changing hormonal levels , and a variable expression of the steroid receptors in the cells of epithelium and stroma of the endometrium occurs[9,10].

IHC offers exact tissue localization of receptors at cellular and subcellular levels and also helps in assessing their distribution.[11]

This study aimed to study various aetiopathological factors responsible for AUB. To correlate clinical presentation with histopathological studies along with hormone receptor markers ER and PR.

MATERIALS AND METHODS:

The study was done in the Department of Pathology,Gauhati Medical College and Hospital on patients with clinical diagnosis of Abnormal uterine bleeding from Gynaecology Department, Gauhati Medical College and Hospital, Guwahati from December 2017 to November 2018. Endometrial dilatation and curettage samples or hysterectomy specimens of 60 patients, collected or done in the premenstrual phase of the cycle or at random for cases presenting with irregular cycles, was sent to Pathology Department from Gynaecology Department. All histopathological samples were stained with Hematoxylin and Eosin stain (H&E stain) and subsequently immunostaining was done for ER, PR .For IHC, 10 controls control samples were taken from hysterectomy specimen of similar age group presenting with vaginal prolapse. .. The IRS score was calculated as follows: IRS=SI x PP, where SI is the optical staining intensity (graded as 0 = no, 1 = weak, 2 = moderate and 3= strong staining) and PP the percentage of positive-stained cells. The PP was estimated by counting approximately 200 cells and it was defined as 0 = no staining, 1 = <10%, 2 = 11-50%, 3 = 51-80% and 4 = >81.9 [Table]. Unpaired student t' test was performed. P-value ≤ 0.05 was taken as critical level of significance

RESULTS:

The maximum number of cases were seen in the age group of 36-40 years (30%), followed by 41-45 years age group (18.33%).It was found that the most common clinical presentation was menorrhagia(50%), followed by menometorrhagia(23.33%) . Anovulatory cycle was found in 75% of the cases and ovulatory cycle is found in 25 % of the cases. Proliferative endometrium was the most common histopathological finding accounting for 41.67%. followed by secretory endometrium accounting for 25%, non-atypical hyperplasia accounting for 21.67%, disordered proliferative endometrium (6.67%), and the least common histopathological finding was atypical hyperplasia (5 %).

The ER and PR expression in both glands and stroma of the endometrium were significantly higher in AUB group (n=60) as compared to control group (n=10) (p-value < 0.001).

Table 1: Distribution of cases according to bleeding pattern

SYMPTOM	NO. OF CASES	PERCENTAGE
1.Menometorrhagia	14	23.33
2. Menorrhagia	30	50
3.Metorrhagia	7	11.67
4.Polymenorrhagia	5	8.33
5.Polymenorrhea	4	6.67

Table 2: Distribution of cases according to histopathological findings

Histopathological findings	No.of cases	Percentage
1. Proliferative	25	41.67
2. Secretory	15	25
3. Disordered proliferative	4	6.67
4. Non atypical hyperplasia	13	21.67
5. Atypical hyperplasia	3	5

Table 3 : Table showing distribution of cases according to ovulatory and anovulatory cycles:

Cycle	Histopathological Finding	No. of cases	Percentage
Anovulatory	Proliferative endometrium	25	75
	Disordered proliferative endometrium	4	
	Non- atypical hyperplasia	13	
	Atypical hyperplasia	3	
Ovulatory	Secretory endometrium	15	25

Table 4 : Table showing Comparison of ER and PR expression scores in glands and stroma of endometrium in control proliferative (n=5) and AUB proliferative (n=25) groups

ER	Control proliferative (n=5)	AUB Proliferative (n=25)	p-value
Gland	3.8+ 1.28	9.52+2.04	<0.001
Stroma	3.1+1.12	8.62+1.85	<0.001
Total score	6.9+2.50	18.14+3.50	<0.001
PR	Control proliferative (n=5)	AUB Proliferative (n=25)	p-value
Gland	4.0+ 1.28	8.62+1.70	<0.001
Stroma	3.11+1.01	8.40+1.82	<0.001
Total score	7.11+1.82	17.02+2.82	<0.001

The ER and PR expression in both glands and stroma of the endometrium were significantly higher in AUB proliferative (n=25) as compared to Control proliferative (n=5) (p-value < 0.001)

Table 5 : Table showing Comparison of ER and PR expression scores in glands and stroma of endometrium in control secretory (n=5) and AUB secretory (n=15) groups.

ER	Control secretory (n=5)	AUB Secretory (n=15)	p-value
Gland	2.12+0.43	2.82+0.40	0.15
Stroma	1.80+0.59	2.30+1.00	0.35
Total score	3.92+1.04	5.12+1.50	0.32
PR	Control secretory (n=5)	AUB Secretory (n=15)	p-value
Gland	2.42+0.48	3.00+1.17	0.31
Stroma	1.72+0.53	2.82+1.20	<0.001
Total score	4.14+1.28	5.82+2.22	0.015

The PR expression in stroma and PR total score of the endometrium were significantly higher in AUB secretory (n=15) as compared to control secretory (n=5) (p-value < 0.05).

Table 6: Table showing comparison of ER and PR expression in glands and stroma of endometrium in control group(n=10) and study group(n=60)AUB cases.

ER	Control(n=10)	AUB(n=60)	p- value
Gland	3.5+1.50	7.24+2.32	< 0.001
Stroma	2.84+1.26	6.74+3.30	<0.001
Total	6.34+ 2.60	13.98+ 6.70	<0.001
PR	Control(n=10)	AUB(n=60)	p- value
Gland	3.82+ 1.38	6.82+3.30	<0.001
Stroma	2.5+1.03	7.34+3.12	<0.001
Total	6.32+2.25	14.16+6.28	<0.001

The ER and PR expression in both glands and stroma of the endometrium were significantly higher in AUB group(n=60) as compared to the control group(n=10)

DISCUSSION:

In our study the most common age group presenting with AUB is 36-40 years (30%), followed by 41-45 years age group (18.33%).

Devi LS et al (2012), in their study of 50 cases of DUB, also found the highest number of patients in the age group of 36-45 years (54%). They found maximum number of cases in 36-40 years age group (34 %), followed by 20% cases in 41-45 years age group (9), which is in concordance with our study[12]

In the study by Chakravarthy VK et al (2013), the age group of 60 patients ranged from 22 years to 60 years with maximum number of cases in the age range of 31 to 40 years (54.1%). Only 5.8% were found to be more than 50 years[13]

In our study,Menorrhagia was the most common symptom accounting for 50% of patients, followed by Menometrorrhagia accounting for 23.33%.

Saroj A. Bolde et all(2014),[14], found that the commonest clinical feature was menorrhagia(46.86%), which is in accordance with our study.

In our study, Proliferative endometrium was the most common histopathological finding accounting for 41.67%, followed by secretory endometrium accounting for 25%, non-atypical hyperplasia accounting for 21.67%, disordered proliferative endometrium (6.67%), and the least common histopathological finding was atypical hyperplasia (5 %).

Our findings are similar to those of the study by Mahapatra M et al (2015), where, out of 60 cases of dysfunctional uterine bleeding (DUB), most common histopathological finding was found to be proliferative endometrium (43.3% cases), followed by secretory endometrium (23.4% cases), followed by hyperplastic endometrium (21.7% cases). They also found 10% cases to have atrophic endometrium[15]

In the study by Chakravarthy VK et al (2013), the most common histopathologic finding was proliferative endometrium (40%), followed by secretory endometrium (31.6%), followed by Disordered proliferative endometrium (13.3%), followed by Simple cystic hyperplasia (10%), followed by Irregular ripening (3.3 %), followed by Complex hyperplasia (1.6%)[13]

In our study, Anovulatory cycle is found in 75% of the cases and ovulatory cycle is found in 25% of the cases.It is in concordance with the study by Devi LS et al (2012), where, anovulatory cycle was observed in 62% of the cases and 38% of the cases showed ovulatory cycles[12]

In our study, the ER and PR expression in both glands and stroma of the endometrium were significantly higher in AUB group (n=60) as compared to controls (n=10) (p-value < 0.001).

The ER and PR expression in both glands and stroma of the endometrium were significantly higher in AUB proliferative (n=25) (p-value < 0.001), AUB Non-atypical hyperplasia (n=13) (p-value < 0.001), and AUB Disordered proliferative (n=4) (p-value < 0.05) as compared to Control proliferative (n=5).

The PR expression in stroma and PR total score of the endometrium were significantly higher in AUB secretory (n=15) as compared to control secretory (n=5) (p-value < 0.05).

Our findings are in concordance with those of the study by Singh P et al (2016). In the study by Singh P et al, AUB-E (DUB) group when compared with control group showed statistically significant difference for ERα and PR receptor[16]

Ahmed M. Mostafa et all(2018), in their study also observed ER alpha expression is signifi cantly higher in the endometrial glands as compared to stroma while PR expression is signifi cantly higher in the endometrial stroma than the endometrial glands. The endometrial glands of females with abnormal uterine bleeding appeared relatively wider and longer. There was a significant increase in estrogen receptor alpha and progesterone receptor expression in the cells lining the endometrial glands and in the stroma cells in females with abnormal uterine bleeding as compared to the females of the control group.[17]

Our findings are also in concordance with the study by Chakraborty S et al (2004), where the ER and PR levels in both glands and stroma of the endometrium were significantly higher in patients as compared to controls. In women with atypical hyperplasia, they found that the mean score of ER and PR decreased as compared to hyperplasias without atypia.[7]

CONCLUSION:

Immunohistochemical analysis of estrogen and progesterone receptors in endometrium is a very useful adjuvant investigation in the management of AUB patients**.** Further, it validates the use of progesterone antagonists and selective progesterone receptor modulators in the medical management of DUB patients, as opposed to invasive procedures, such as,endometrial ablation or hysterectomy.

PHOTOS:

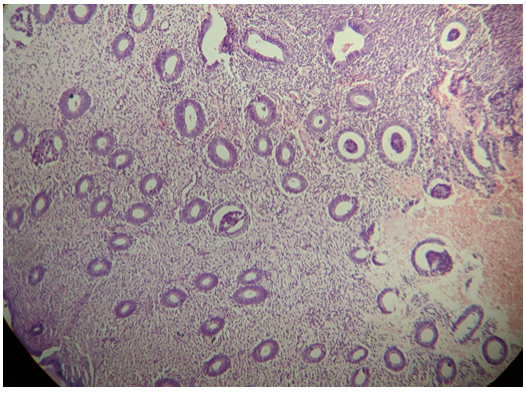

Fig 1: Proliferative endometrium

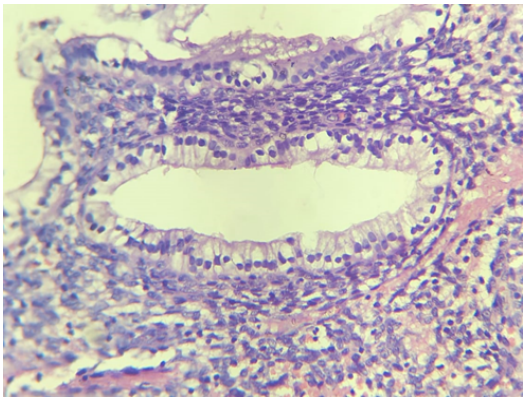

Fig 2: secretory endometrium

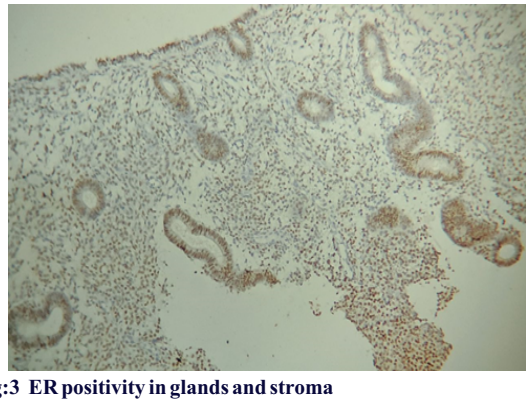

Fig:3 ER positivity in glands and stroma

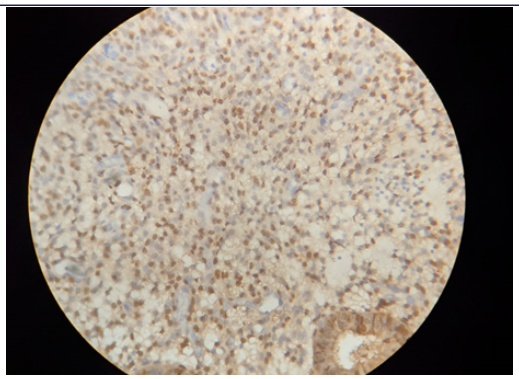

Fig 4: PR positivity in stroma

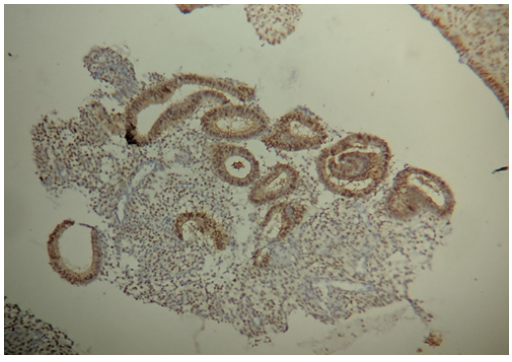

Fig 5: PR positivity in gland

REFERENCES:

1. Dutta D. Textbook of gynecology. 6th ed.; November 2013.
2. Critchley HOD, Maybin JA. Molecular and cellular causes of abnormal uterine bleeding of endometrial origin. Semin Reprod Med 2011;29(5):400–409
3. Munro MG, Critchley HOD, Fraser IS. The flexible FIGO classification concept for underlying causes of abnormal uterine bleeding. Semin Reprod Med 2011;29(5):391–399
4. Dueholm M. Levonorgestrel-IUD should be offered before hysterectomy for abnormal uterine bleeding without uterine structural abnormalities: there are no more excuses! Acta Obstet Gynecol Scand 2009;88(12):1302–1304.
5. Howkins & Bourne Shaw's Textbook of Gynaecology.
6. Clark JH. Female sex steroid receptors and function. Monogr Endocrinol.1979;14:1-12.
7. Chakraborty S, Khurana N, Sharma JB, Chaturvedi KU.Endometrial hormone receptors in women with dysfunctional uterine bleeding.Arch GynecolObstet 2005;272(1):17-22.
8. Mylonas I, Jeschke U, Shabani N, Kuhn C, Balle A, Kriegel S, et al. Immunohistochemical analysis of estrogen receptor alpha, estrogen receptor beta and progesterone receptor in normal human endometrium. ActaHistochem 2004;106(3):245-52
9. M. P. M. L. Snijders, A. F. P. M. Degoeij, M. J. C. Debets-Te Baerts,M. J. M. Rousch, J. Koudstaal and F. T. Bosman. Immunocytochemical analysis of estrogen receptors and progesterone receptors in the human uterus throughout the menstrual cycle and after the menopause. 1992 Mar; 94(2):363-71.
10. Michelle Reid-Nicholson, Pratibha Iyengar, Amanda J Hummer, Irina Linkov, Marina Asher1 and Robert A Soslow. Immunophenotypic diversity of endometrial adenocarcinomas implications for differential diagnosis. Modern Pathology 2006; 19: 1091–1100.
11. Press MF, Udove JA, Greene GL. Progesterone Receptor Distribution in the Human Endometrium. American Journal of Pathology. 1988 April; 131(1): 112-124
12. Devi, L. S., Singh, M. R., Singh, L. R., & Debnath, K. (2012). The histological and histochemical study of endometrium in dysfunctional uterine bleeding. Journal of Medical Society, 26(3), 167.
13. Chakravarthy, V. K., Nag, U., Rangarao, D., & Anusha, A. M. (2013). Estrogen and progesterone receptors in dysfunctional uterine bleeding. IOSR-JDMS, 4(3), 73-6.
14. Bolde, S. A., Pudale, S. S., Pandit, G. A., & Matkari, P. P. (2014). Histopathological study of endometrium in cases of abnormal uterine bleeding. International Journal of Research in Medical Sciences, 2(4), 1378-1381.
15. Mahapatra, M., & Mishra, P. (2015). Clinicopathological evaluation of abnormal uterine bleeding. Journal of Health Research and Reviews, 2(2), 45.
16. Singh, P., Singh, P., Chaurasia, A., Dhingra, V., & Misra, V. (2016). Expression of ERα and PR in Various Morphological Patterns of Abnormal Uterine Bleeding-Endometrial causes in Reproductive Age Group. Journal of clinical and diagnostic research: JCDR, 10(8), EC06.
17. Mostafa AM, Elsaid N, Fawzy RA, Elfeky A. Endometrial Estrogen and Progesterone Receptor Expression in Women with Abnormal Uterine Bleeding in the Reproductive Age. Int J Reprod Med Gynecol. 2018;4(2): 041-046.