International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 14, No. 5, May 2025 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_14.5.2025.97

ORIGINAL RESEARCH

Studying The Histopathological Results Of Endometrium And Estrogen And Progesterone Expression In Endometrium Of Subjects With AUB

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Received: 04 March, 2025 Accepted: 13 April, 2025 Published: 13 May, 2025

Abstract
Background: AUB (abnormal uterine bleeding) is a common condition seen by Gynecologists. Existing literature data has reported that abnormal uterine bleeding can be attributed to changes in the expression of PR (progesterone receptors) and ER (estrogen receptors) in the endometriumwhich plays a vital role in abnormal bleeding etiology.
Aim: The present study aimed to study the histopathological results of endometrium and estrogen and progesterone expression in the endometrium of subjects with AUB.
Methods: The present study assessed 126 subjects, using endometrial biopsies done within the defined study period. Following histopathological assessment, all the subjects underwent immunohistochemistry assessment for progesterone receptor and estrogen receptor scoring utilizing the Allred scoring system. The data gathered were analyzed statistically.
Results: The study results showed that heavy menstrual bleeding was reported in subjects aged 41-50 years. The majority of subjects had EH (endometrial hyperplasia) without atypia seen in 63% of subjects followed by proliferative endometrium, disordered proliferative endometrium, and secretory endometrium in 21%, 11%, and 5% of subjects respectively. In AUB subjects, mean Allred scores for ER expression in gland and stroma were significantly higher compared to scores for progesterone receptor expression with 6.0±1.1 versus 5.6±1.4 for stroma with p=0.00 and 7.1±1.3 versus 6.5±1.6 for glands with p=0.00. ER expression in the stroma and endometrial glands for various histological patterns of AUB was significantly higher compared to PR in EH without atypia with 6.0±1.14 versus 5.5±1.6 and p=0.001 for stroma and 7.0±1.6 versus 6.4±1.8 and p=0.001 for gland. For other histological patterns, ER expression was higher compared to PR expression, due to smaller cases, a test of significance was not applied.
Conclusion: The present study concludes that an increase in ER expression is evident compared to PR expression in all histological patterns for subjects with abnormal uterine bleeding. ER expression was significantly higher in subjects with endometrial hyperplasia without atypia, suggesting that they might have a role in the etiopathogenesis of endometrial hyperplasia.
Keywords: Abnormal uterine bleeding, endometrial hyperplasia, endometrium, estrogen receptor, progesterone receptor

Introduction

AUB or abnormal uterine bleeding is a wider term that depicts various irregularities associated with the menstrual cycle and involves the amount of blood loss, volume of flow, duration, regularity, and frequency of blood loss which is a common cause for referral to the gynecologist. It can be seen at any age during the reproductive phase and is a common sign of various uterine disorders in the range of non-organic (dysfunctional abnormalities) to organic lesions including carcinoma, dysfunctional

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abnormalities, or polyps as well as systemic diseases or hormonal diseases.[1]

The PALM–COEIN system (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified) helps in the classification of females with AUB in a systematic manner that helps in providing reliable information concerning accurate diagnosis and management.[2]

IHC (Immunohistochemistry) data depicts the presence of steroid receptors in the endometrium of humans depicting that these cells react to steroid hormones as progesterone and estrogen. Concerning AUB (abnormal uterine bleeding), there is a change in the expression of these receptors that might play a vital role in the etiology. With specific monoclonal antibodies, receptor expressions can be assessed at the cellular level and hence, their exact intensity, localization, and distribution in stromal and glandular cells can be studied.[3]

Till today, abnormal uterine bleeding remains one of the most controversial and enigmatic conditions. The pattern and etiology of hormonal receptor expression in the endometrium of subjects with abnormal endometrial bleeding are still not understood well.[4] The present study aimed to study the histopathological results of endometrium and estrogen and progesterone expression in the endometrium of subjects with AUB.

Materials and methods

The present observational descriptive study was aimed at studying the histopathological results of endometrium and estrogen and progesterone expression in the endometrium of subjects with AUB. The study subjectssamplewere evaluated at Department of Pathology of the Institute. Verbal and written informed consent were taken from all the subjects before participation.

The study assessed 126 female subjects with abnormal uterine bleeding who presented to the Institute within the defined study period.The inclusion criteria for the study were female subjects in the age range of 18-50 years and presented to the Institute within the defined study period. The exclusion criteria for the study were hysterectomy cases, post-menopausal females, and cases of inadequate specimens.

The data of the study subjects was gathered in the defined study period. The specimens collected were sent to the Department of Pathology in 10% neutral buffered formalin as the storage media. Gross findings were recorded following the standard protocol. The specimens were then processed and embedded in 4-micron thick sections that were cut and stained using eosin and hematoxylin stain and observations were recorded.

All the cases underwent immunohistochemistry assessment for progesterone and estrogen receptors using commercially available kits and following instructions of the manufacturer. The specimens from the control group for ER PR were from ductal breast cases which were ER and PR positive.IHC (immunohistochemistry) findings were recorded and categorized based on standard protocol.

The scoring for immunohistochemistry sections was done utilizing the scoring system that utilizes the calculations for intensity score (IS) and PS (proportion score) as depicted in Table 1. The data gathered were analyzedstatistically using SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk. NY, USA) for assessment of descriptive measures, Student t-test, ANOVA (analysis of variance), Turkey post hoc analysis, and Chi-square test. Pearson correlation coefficient was used to assess correlation in various parameters. The results were expressed as mean and standard deviation and frequency and percentages. The p-value of <0.05 was considered.

Results

The present observational descriptive study was aimed at studying the histopathological results of endometrium and estrogen and progesterone expression in the endometrium of subjects with AUB. The present study assessed 126 subjects where endometrial biopsies were assessed that were done within the defined study period. The study subjects were in the age range of 24-50 years with a mean age of 41.4±5.7 years. Among 126 cases, the majority of subjects were under the age of 40 years. The most common presenting symptom was menorrhagia or heavy menstrual bleeding seen in 70 subjects and irregular bleeding in 40 subjects, prolonged bleeding and dysmenorrhea were seen in 10 and 6 subjects respectively.

On assessing the Allred scores (PS+IS) in study subjects with AUB, Allred scores 3 and 4 were seen in no subject with ER expression in gland and stroma. Score 3 was seen in 3% (n=4) cases of PR expression in the gland and 14% (n=8) subjects with PR expression in the stroma. Score 4 was seen in 5% (n=6) and 10% (n=12) subjects with PR expression in gland and stroma respectively. Allred scores of 5, 6, and 7 were higher in ER and PR expression in stroma compared to ER and PR expression in the gland. An Allred score of 8 was highest for ER expression in the gland as seen in 64% (n=78) subjects followed by 51% (n=62) subjects with PR expression in the gland, 8% (n=10) subjects with ER expression in the stroma, and 3% (n=4) subjects with PR expression in the stroma (Table 2).

It was seen that for expression of progesterone and estrogen receptors in the endometrial gland and stroma in study subjects, for glands, the mean Allred score for ER expression was 7.1±1.3 and the mean Allred score for PR expression was 6.5±1.6. Expression of progesterone and estrogen receptors in the endometrial gland and stroma in study subjects, mean Allred score for ER expression for stroma was 6.0±1.1 and mean Allred score for PR expression was

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5.6±1.4. The difference was statistically significant with p=0.00 (Table 3).

The study results showed that for expression of progesterone and estrogen receptors in an endometrial gland in different histological AUB patterns in study subjects, for hyperplasia without atypia, mean Allred scores for ER and PR expression were 7.0±1.6 and 6.4±1.8 respectively. For disordered proliferative endometrium, mean Allred scores for ER and PR expression were 7.0±0.9 and 6.9±0.8, for the secretory phase, mean Allred scores for ER and PR expression were 7.4±0.3 and 6.4±0.3, and for proliferative phase, mean Allred scores for ER and PR expression was 7.44±0.3 and 7.06±0.9. The scores were higher for ER expression compared to PR expression which was statistically significant with p=0.001 (Table 4).

Concerning the expression of progesterone and estrogen receptors in endometrial stroma in different histological AUB patterns in study subjects, mean Allred scores for ER and PR expression were 6.0±1.4 and 5.5±1.6 respectively, for disordered proliferative endometrium, it was 5.5±0.2 and 5.5±1.0 respectively, for secretory phase, it was 6.8±0 and 6.4±0.3 respectively, and for proliferative phase, it was 6.44±0.6 and6.29±1.0 respectively depicting was statistically significant difference with p=0.001 (Table 5).

S. No	PS (proportion score)	Positive cells (%)	IS (intensity score)	Staining intensity
1.	**Negative**	0		
2.	**1**	>1	0	None
3.	**2**	1-10	1	Weak
4.	**3**	11-33	2	Intermediate
5.	**4**	34-66	3	Strong
6.	**5**	>67		
	Total score= PS+IS (sum of proportion score and intensity score)			
	0-2	Negative		
	2-8	Positive		

Table 1: Allred scoring system for evaluation of estrogen and progesterone receptor

S. No	Allred score (PS+IS)	ER expression in the gland n (%)	ER expression in stroma n (%)	PR expression in the gland n (%)	PR expression in stroma n (%)
1.	**3**	0	0	4 (3)	8 (14)
2.	**4**	0	0	6 (5)	12 (10)
3.	**5**	4 (3)	14 (12)	4 (3)	8 (7)
4.	**6**	2 (2)	48 (39)	16 (13)	42 (34)
5.	**7**	38 (31)	50 (41)	30 (25)	48 (39)
6.	**8**	78 (64)	10 (8)	62 (51)	4 (3)

Table 2: Allred scores (PS+IS) in study subjects with AUB

S. No	Categories	Mean Allred score for ER expression	Mean Allred score for PR expression
1.	**Glands**	7.1±1.3	6.5±1.6
2.	**Stroma**	6.0±1.1	5.6±1.4
3.	**p-value**	**0.00**	

Table 3: Expression of progesterone and estrogen receptors in the endometrial gland and stroma in study subjects

S. No	Categories	Mean Allred score for ER expression	Mean Allred score for PR expression
1.	**Hyperplasia without atypia**	7.0±1.6	6.4±1.8
2.	**Disordered proliferative endometrium**	7.0±0.9	6.9±0.8
3.	**Secretory phase**	7.4±0.3	6.4±0.3
4.	**Proliferative phase**	7.44±0.3	7.06±0.9
5.	**p-value**	**0.001**	

Table 4: Expression of progesterone and estrogen receptors in an endometrial gland in different histological AUB patterns in study subjects

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S. No	Categories	Mean Allred score for ER expression	Mean Allred score for PR expression
1.	Hyperplasia without atypia	6.0±1.4	5.5±1.6
2.	Disordered proliferative endometrium	5.5±0.2	5.5±1.0
3.	Secretory phase	6.8±0	6.4±0.3
4.	Proliferative phase	6.44±0.6	6.29±1.0
5.	p-value	0.001	

Table 5: Expression of progesterone and estrogen receptors in endometrial stroma in different histological AUB patterns in study subjects

Discussion

The present study assessed 126 subjects where endometrial biopsies were assessed that were done within the defined study period. The study subjects were in the age range of 24-50 years with a mean age of 41.4±5.7 years. Among 126 cases, the majority of subjects were under the age of 40 years. The most common presenting symptom was menorrhagia or heavy menstrual bleeding seen in 70 subjects and irregular bleeding in 40 subjects, prolonged bleeding and dysmenorrhea were seen in 10 and 6 subjects respectively. These data were comparable to the previous studies ofDoraiswamiS et al[5] in 2011 and Shaheen S et al[6] in 2005 where authors assessed subjects with demographic data comparable to the present study with abnormal uterine bleeding as seen in the present study.

Concerning the assessment of the Allred scores (PS+IS) in study subjects with AUB, Allred scores 3 and 4 were seen in no subject with ER expression in gland and stroma. Score 3 was seen in 3% (n=4) cases of PR expression in the gland and 14% (n=8) subjects with PR expression in the stroma. Score 4 was seen in 5% (n=6) and 10% (n=12) subjects with PR expression in gland and stroma respectively. Allred scores of 5, 6, and 7 were higher in ER and PR expression in stroma compared to ER and PR expression in the gland. An Allred score of 8 was highest for ER expression in the gland as seen in 64% (n=78) subjects followed by 51% (n=62) subjects with PR expression in the gland, 8% (n=10) subjects with ER expression in the stroma, and 3% (n=4) subjects with PR expression in the stroma. These results were comparable to the studies of Qureshi A et al[7] in 2010 and Upadhyaya I et al[8] in 2009 where Allred scores (PS+IS) comparable to the present study were also reported by the authors in their respective studies in subjects with abnormal uterine bleeding.

The study results showed that for expression of progesterone and estrogen receptors in the endometrial gland and stroma in study subjects, for glands, the mean Allred score for ER expression was 7.1±1.3 and the mean Allred score for PR expression was 6.5±1.6. Expression of progesterone and estrogen receptors in the endometrial gland and stroma in study subjects, mean Allred score for ER expression for stroma was 6.0±1.1 and mean Allred score for PR expression was 5.6±1.4. The difference was statistically significant with p=0.00. These findings were in agreement with the results of Chakraborty S et al[9] in 2005 and Majeed NM et al[10] in 2017 where expression of progesterone and estrogen receptors in the endometrial gland and stroma reported by authors in their studies was comparable to the results of the present study.

It was seen that for expression of progesterone and estrogen receptors in an endometrial gland in different histological AUB patterns in study subjects, for hyperplasia without atypia, mean Allred scores for ER and PR expression were 7.0±1.6 and 6.4±1.8 respectively. For disordered proliferative endometrium, mean Allred scores for ER and PR expression were 7.0±0.9 and 6.9±0.8, for the secretory phase, mean Allred scores for ER and PR expression were 7.4±0.3 and 6.4±0.3, and for proliferative phase, mean Allred scores for ER and PR expression was 7.44±0.3 and 7.06±0.9. The scores were higher for ER expression compared to PR expression which was statistically significant with p=0.001. These results were in line with the findings of Singh P et al[11] in 2020 and Chakravarthy VK et al[12] in 2013 where expression of progesterone and estrogen receptors in an endometrial gland in different histological AUB patterns similar to the present study was also reported by the authors in their respective studies.

On assessing the expression of progesterone and estrogen receptors in endometrial stroma in different histological AUB patterns in study subjects, mean Allred scores for ER and PR expression were 6.0±1.4 and 5.5±1.6 respectively, for disordered proliferative endometrium, it was 5.5±0.2 and 5.5±1.0 respectively, for secretory phase, it was 6.8±0 and 6.4±0.3 respectively, and for proliferative phase, it was 6.44±0.6 and6.29±1.0 respectively depicting was statistically significant difference with p=0.001. These findings correlated to the results of Jiang W et al[13] in 2016 and Mostafa AM et al[14] in 2018 where expression of progesterone and estrogen receptors in the endometrial stroma in different histological AUB patterns reported by the authors in their respective studies were comparable to the results of the present study.

Conclusions

Considering its limitations, the present study concludes that an increase in ER expression is evident compared to PR expression in all histological patterns for subjects with abnormal uterine bleeding. ER

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expression was significantly higher in subjects with endometrial hyperplasia without atypia depicting that they might have a role in etiopathogenesis for endometrial hyperplasia.

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