



IMMUNOHISTOCHEMICAL STUDY OF HORMONAL RECEPTORS IN ENDOMETRIUM OF WOMEN WITH DYSFUNCTIONAL UTERINE BLEEDING: A PROSPECTIVE CROSS-SECTIONAL STUDY AT A TERTIARY CENTER

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ABSTRACT

Dysfunctional uterine bleeding is a major gynecologic problem, with varied treatment options. A significant proportion of these patients undergo hysterectomy. To investigate the hormonal milieu at tissue level, we semi-quantitatively assessed the estrogen and progesterone receptors in the endometrial samples of 50 DUB patients, by Immunohistochemistry.

We observed a significant increase ($p < 0.001$) in the concentration of both estrogen and progesterone receptors in patients with dysfunctional uterine bleeding, compared to normal population. We also noted a significant increase in the endometrial thickness ($p < 0.001$) of patients with simple endometrial hyperplasia.

Our study demonstrates the role of estrogen and progesterone receptors in the etiopathogenesis of dysfunctional uterine bleeding and in the alteration in the morphology of endometrium, such as simple endometrial hyperplasia. We advocate the use of progesterone antagonists and selective progesterone receptor modulators in the treatment of patients with dysfunctional uterine bleeding, especially in those with endometrial hyperplasia, who carry the long term risk of endometrial carcinoma with sustained endometrial estrogenic stimulation.

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INTRODUCTION

Dysfunctional uterine bleeding is one of the major causes of menorrhagia and it's a diagnosis of exclusion.¹ It accounts for 33% of overall referrals to gynecologic practice² & is estimated to occur in 11-14% of reproductive women.³ Over 50% of the patients who undergo hysterectomy for menorrhagia have DUB.⁴ DUB has several complications such as anovulation, infertility and severe anemia.

The basic underlying mechanism of DUB is unopposed estrogenic stimulation leading to excessive endometrial proliferations and hyperplasia⁵, which is a known risk factor for endometrial carcinoma. Hence, a comprehensive understanding of mechanisms of DUB is fundamental to its management. Histological examination of endometrial aspirate is the management of choice in DUB, besides transvaginal ultrasound.⁶ Histological changes in DUB are varied, with little correlation between histology and abnormal bleeding pattern.^{7,8}

Discovery of specific steroid receptors in endometrium, through which the ovarian hormones act, has revolutionized the medical management of DUB patients, with introduction of receptor modulating drugs.⁹ The knowledge of steroid receptors in endometrium is of utmost importance, since it supports the role of hormone receptors in the etiopathogenesis

of DUB^{7,9} and it could start a new era in the hormonal therapy of endometrial cancer.⁷ Steroid receptors can be assayed either quantitatively in tissue homogenates or qualitatively by Immunohistochemistry.¹⁰ Immunohistochemistry helps in direct localization and analysis of receptors in tissues.¹¹

To date, there are very few studies on the pattern of expression of these hormonal receptors in the endometrium of DUB patients. With this aim, we undertook this study in an attempt to establish the role of these hormonal receptors in the etiopathogenesis of DUB and its implications in the management of DUB.

MATERIALS AND METHODS

Tissue sample

A thorough hematologic and endocrinologic workup was done on all women aged between 20 and 50 years, who presented to Obstetrics & Gynecology department with menstrual irregularities. After obtaining detailed clinical & menstrual history and complete general physical examination, transvaginal ultrasound was done to assess the uterine size, endometrial width and echogenic pattern. Those with histologic evidence of uterine pathology and endocrine

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diseases were excluded from the study. 50 women who met the criteria for diagnosis of DUB were selected.

Normal endometrium from 30 normally menstruating women between 30 and 50 years age, who underwent vaginal hysterectomy for prolapsed uterus were selected for control group.

METHODS

The specimen were fixed in 10% neutral buffered formalin and subjected to routine histopathological examination.

The study and control samples were classified according to the histologic appearance as early proliferative (EP), late proliferative (LP), early secretory (ES), late secretory (LS), simple endometrial hyperplasia (SEH) with/ without atypia and complex hyperplasia with/ without atypia.

Immunohistochemical staining

Paraffin sections were taken on poly-L-lysine coated slides and immunohistochemistry was performed using microwave heating and standard streptavidin-biotin-peroxidase complex using Super Sensitive TMIHC detection systems (BioGenex Laboratories, CA, USA). For positive tissue control, endometrial specimens with known ER & PR positivity (that were being used as positive controls for breast cancer specimens) were used and unstained areas other than nuclei in positive tissue control served as negative control. Staining of non-nuclear areas was considered false positive and such slides were considered invalid and the procedure was repeated for such cases.

Immuno-scoring

Semi-quantitative assessment of ER and PR was done based on the distribution and the intensity of staining. We used a scoring system recommended by McCarty *et al.* Positive staining was seen as fine granular staining of nuclei of glands and stroma. A total of 100 cells were counted under oil immersion (x1000). An Immunohistochemical score was calculated by the formula $\sum Pi \times I$, which is sum of percentage of cells for each intensity of staining [Pi= percentage of cells (0-100%), i= intensity (0- absent, 1- weak, 2- moderate, 3- intense)] and the final score ranged from 0 to maximum of 300.

Statistical analysis

Data were analyzed using SPSS version 18. One sample t test was performed to compare endometrial thickness of DUB group with the normal group. Distribution of histopathological patterns across the DUB and Normal groups was compared using Chi square test. Data were normally distributed and changes in ER/PR expression between DUB and Normal groups were analyzed using Independent samples t test. ER/PR expression across various HP patterns was compared using median test in DUB group. Bivariate relationships were determined using Pearson's correlation analysis between ER/PR and independent variables such as age, parity and endometrial thickness.

RESULTS

The clinical profile of DUB patients is summarized in table 1. A significant proportion (44%) of DUB patients were more than 45 years of age. The mean duration of menstrual blood flow among DUB patients was long and all had irregular cycles. 16% were moderately anemic (7-9 gm/dl) and 44% had

mild anemia (9-11 gm/dl). 26% were nulliparous, remaining were biparous or multiparous.

Table 1 Clinical profile of DUB group

Profile	Mean + SD
Age (years)	38.88±6.8
Parity	2±1
Weight (kilograms)	56.24±6.8
Bleeding (days)	8.36±3.9
Cycle duration (days)	27.06±7.5
Hemoglobin (gm/dl)	10.54±1.6

We performed a One Sample t test to compare the endometrial thickness of DUB patients in our study (Table 2) with a reference normal group reported from an earlier study by Chakraborty S *et al.*⁹ There was a significant increase (p<0.001) in mean endometrial thickness (ET) in DUB group (6.70±3.1mm) compared to normal group (Table 3).

Table 2 Ultrasonography and histologic characteristics of DUB groups

Characteristic	Mean + SD
Uterine size (cm)	6.07±1.01
Endometrial thickness (mm)	6.70±3.1

Table 3 One sample t test to compare endometrial thickness of DUB group with normal or control group reported earlier in an Indian Study by S Chakraborty *et al.*⁹ wherein mean endometrial thickness was 4.5mm.

Test value= 4.5 mm						
95% Confidence Interval of the Difference						
	t	df	Sig. (2-tailed)	Mean difference	Lower	Upper
ET (mm)	4.820	49	p <0.001	2.19600	1.2805	3.1115

Changes in HP patterns in Normal and DUB group

There was a significant increase in late proliferative, early secretory and late secretory HP patterns in normal subjects and increase in simple endometrial hyperplasia and early proliferative patterns in DUB group. The linear by linear association and Chi-square ratio was significant ($\chi^2 = 3.91$, p =0.05) (Figure 1, Tables4 & 5).

Table 4 Chi-Square analysis of proportion of HP patterns across DUB (n=50) and Normal groups (n=30)

	EP	LP	ES	LS	S.E.H	AEH	Total
Normal	count 4	7	7	11	1	0	30
	% Total 5.0%	8.8%	8.8%	13.8%	1.2%	.0%	37.5%
DUB	count 7	7	11	14	10	1	50
	% Total 8.8%	8.8%	13.8%	17.5%	12.5%	1.2%	62.5%

EP: early proliferative ES: early secretory S.E.H: Simple endometrial hyperplasia
LP: late proliferative LS: late secretory A.E.H: Atypical endometrial hyperplasia

Table 5 Comparison of changes in distribution of HP patterns across DUB and Normal groups using Chi square test.

	Value	df	P value (2- tailed)
Pearson Chi-Square	5.793 ^a	5	0.327
Likelihood Ratio	6.966	5	0.223
Linear-by-Linear Association	3.914	1	0.048
Number of valid cases			80

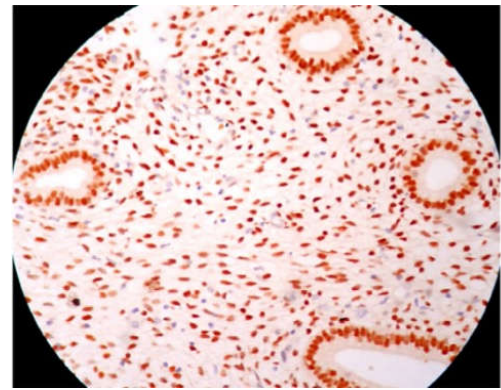
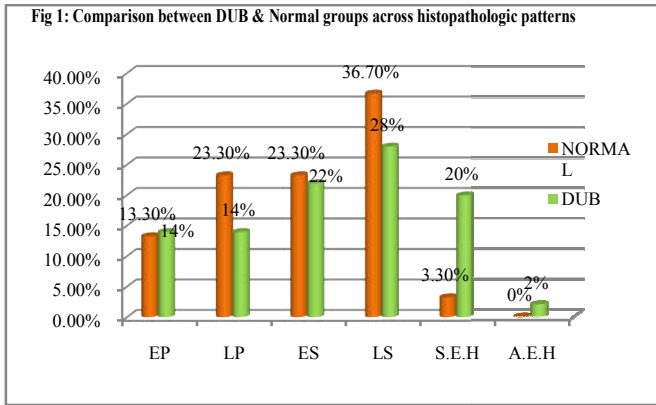


Fig 3 Early Proliferative Phase (ER, x400)

Changes in ER/PR expression in Normal and DUB groups

There was a significant increase in ER and PR receptor expression (all $p < 0.001$) in both the uterine stroma and glands in DUB group as compared to Normal group on independent samples t test (Figure 2, Tables 6 and 7).

Table 6 Comparison of mean values of ER and PR expression in endometrial stroma and glands of subjects with DUB and the Normal using Independent samples t test.

GROUP	ERG	ERS	PRG	PRS
Normal N= 30	95.37±36.3	87.6±32.6	104.67±35.8	124.57±39.5
DUB N= 50	186.38±39.1***	169.22±37.9***	189.08±35.5***	191.08±32.9***

*** $p < 0.001$ using Independent samples t test

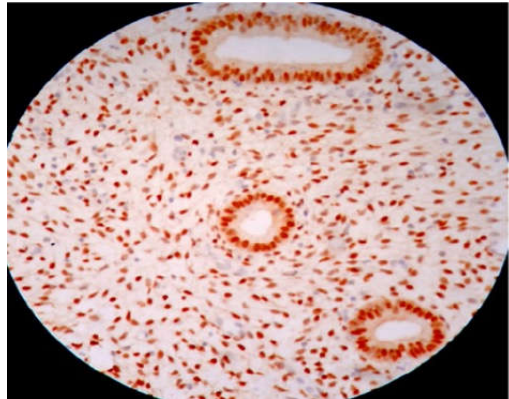


Fig 4 Early Proliferative Phase (PR, x400)

Table 7 Independent samples t test for ER/ PR receptor expression in endometrial stroma and glands in DUB and normal group.

Receptor Status	T	df	Sig. (2-tailed)	Mean difference	SE difference	95% Confidence Interval of the Difference	
						Lower	Upper
ERG	10.351	78	$p < 0.001$	91.013	8.793	73.508	108.519
ERS	9.802	78	$p < 0.001$	81.620	8.326	65.043	98.197
PRG	10.244	78	$p < 0.001$	84.413	8.240	68.009	100.818
PRS	8.104	78	$p < 0.001$	66.513	8.208	50.173	82.854

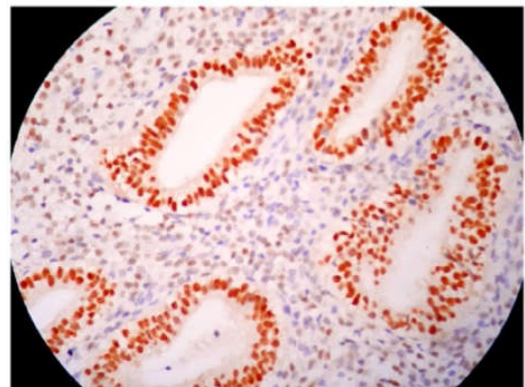
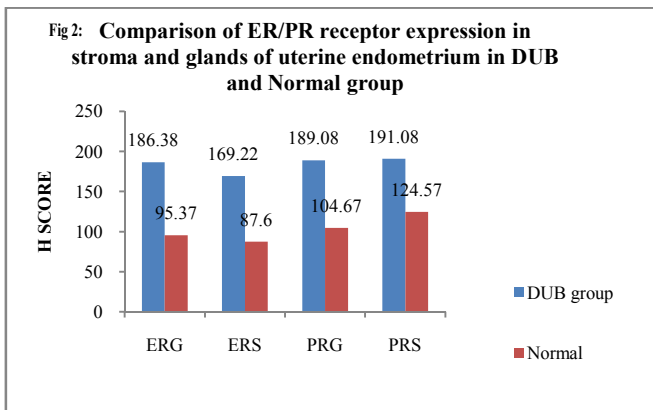


Fig 5 Early Secretory Phase (ER, x400)

ER/PR receptor expression across various HP patterns in DUB (Fig 3 to 14)

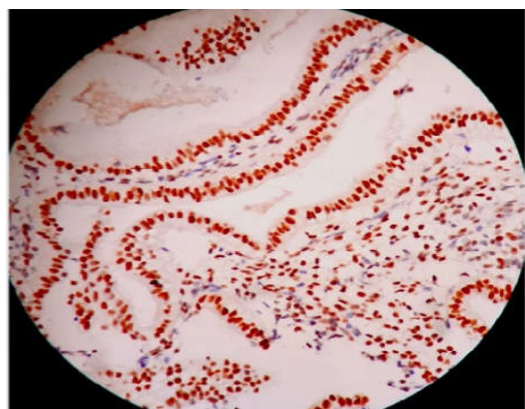


Fig 6 Early Secretory Phase (PR, x400)

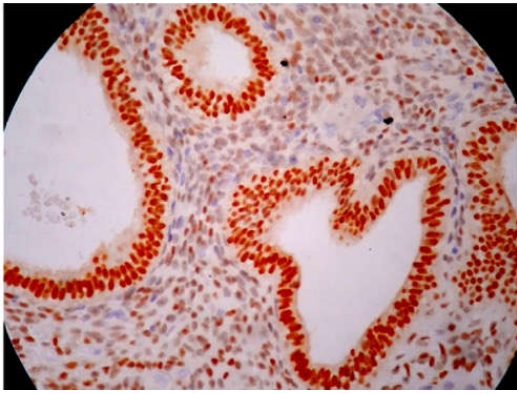


Fig 7 Late Proliferative Phase (ER, x400)

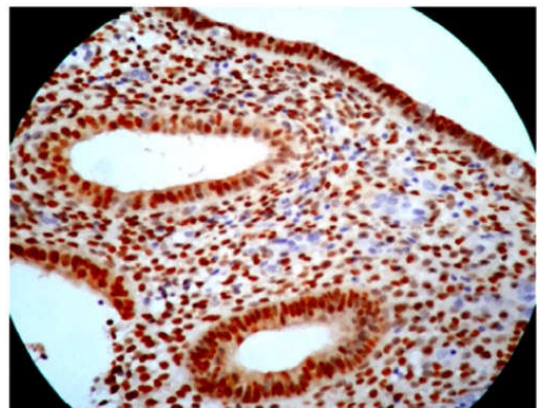


Fig 11 Simple Endometrial Hyperplasia(ER,x400)

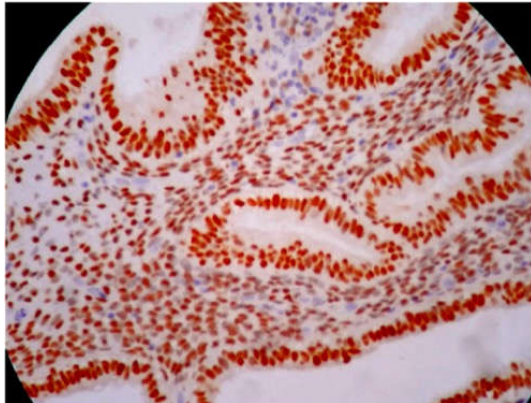


Fig 8 Late Proliferative Phase (PR, x400)

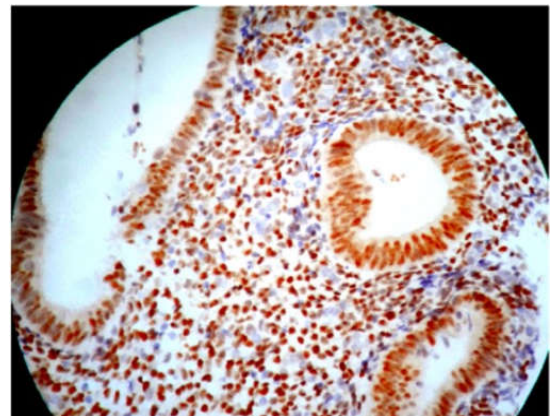


Fig 12 Simple Endometrial Hyperplasia (PR,x400)

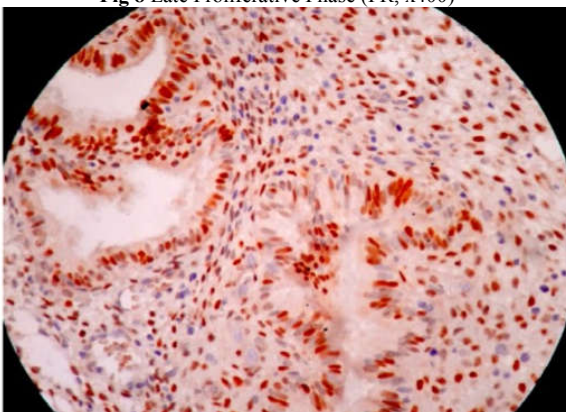


Fig 9 Late Secretory Phase (ER, x100)

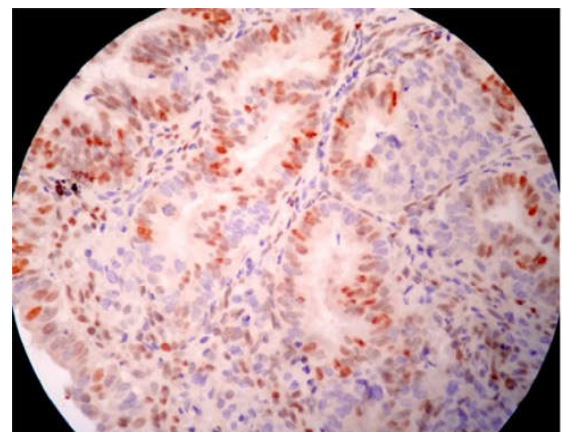


Fig 13 Atypical Endometrial Hyperplasia (ER, x400)

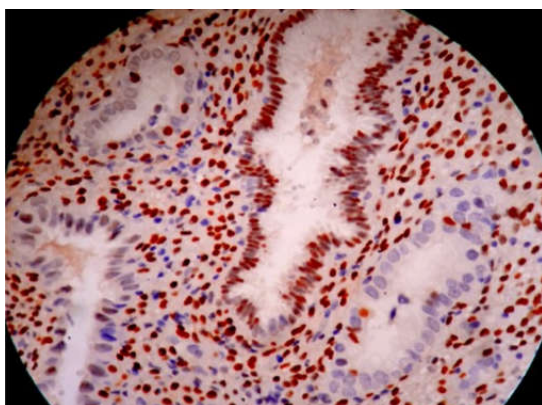


Fig 10 Late Secretory Phase (PR, x400)

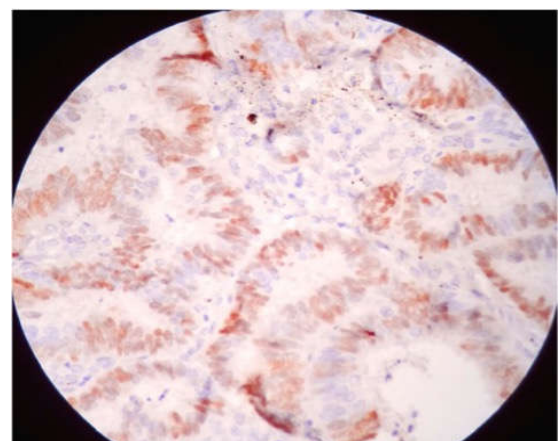


Fig 14 Atypical Endometrial Hyperplasia (PR, x400)

We performed a Non-parametric median test to compare ER/PR receptor expression across various HP patterns in DUB group. Estrogen receptor expression in glands was significantly lesser in LS type more in S.E.H type on median test ($\chi^2= 24.1, p<0.001$)(Tables 8a and 8b).

Table 8a Comparison of ER/ PR receptor expression in various HP patterns in patients with DUB using Median test

HP pattern	Mean± SD			
	ERG	ERS	PRG	PRS
EP (N= 7)	196.71±36.8	174.71±44.8	202.14±45.8	202.57±37.6
LP (N= 7)	200.14±14.9	175.29±14.6	191±21.7	185.14±24.4
ES (N= 11)	195.82±37.4	187.18±37.1	196.09±32.9	199.73±38.7
LS (N= 14)	152.57±19.4	137.93±28.5	167.07±25.3	187.93±31.5***
S.E.H (N= 10)	213.80±40.2***	189.80±31.1	207.5±36.7	189.7±24.4
A.E.H (N= 1)	113	123	131	115
Total (N= 50)	186.38±39.1	169.22±37.9	189.08±35.6	191.08±32.9

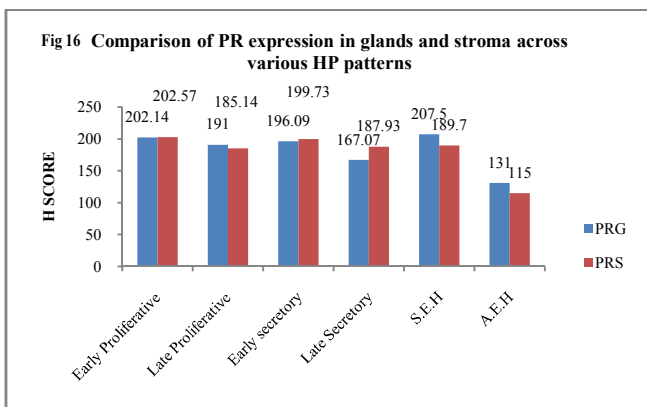
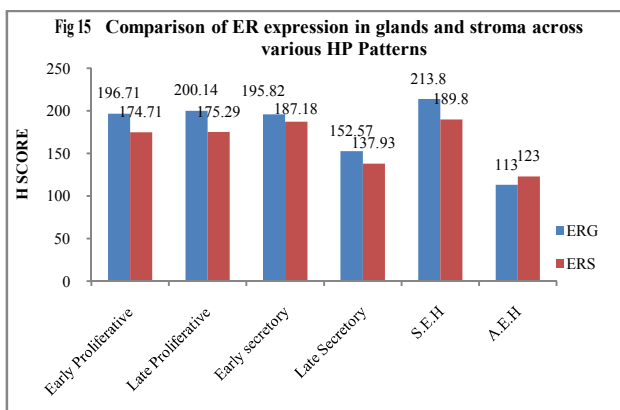
***p<0.001 on Median Chi-Square test

Table 8b Test statistics^c for the above table (Table 8a)

	ERG	ERS	PRG	PRS
Median	187.50	167.00	187.00	197.00
Chi-Square	24.062 ^a	9.730 ^a	8.625 ^b	6.335 ^b
P value	P<0.001	.083	.125	.275

Figures 15 and 16 illustrate trend in the concentration of both ER and PR in glands and stroma of DUB patients across the different phases of menstrual cycle.

There was an increasing trend in ER glands in proliferative phase, and decreasing trend in secretory phase. In late secretory phase, the mean ER and PR scores were significantly lower compared to other phases. The ER stroma was lower than ER glands in all phases PR showed decreasing trend from early to late proliferative phase, thereafter increasing in early secretory phase before falling again in late secretory phase, wherein PR in stroma was higher than that in glands (mean=167.07±25.3). In atypical endometrial hyperplasia, ER and PR were significantly lower than in all other HP patterns.



DISCUSSION

The response of the tissues to steroid hormones depends upon the availability of corresponding receptors in the target organs. These receptors can be analyzed by different methods. Tissue homogenization and biochemical methods are time consuming; complicated and less reliable.¹² Immunohistochemistry allows tissue localization of these receptors in endometrial glands and stroma. Very few studies have been done on Immunohistochemical assessment of hormonal receptors in the endometrium of patients with dysfunctional uterine bleeding. In our study, we investigated the hormonal milieu in the endometrium of patients with dysfunctional uterine bleeding by Immunohistochemistry, by the use of specific monoclonal antibodies against estrogen and progesterone receptors.

In concordance with the results of C Levy *et al*,¹³ S Chakraborty *et al*⁹ and N Gleeson *et al*,⁴ there was an increasing trend in ER and PR in proliferative phase and decreasing trend in secretory phase in DUB group. This was consistent with the findings in normal endometrium by previous investigators.^{7, 14, 15} Our findings confirm the cyclical variation of the steroid receptors. Also we suggest that the estrogen hormone induces the synthesis of both the receptors during the proliferative phase, and the progesterone hormone suppresses the synthesis of these receptors in secretory phase. Histologically we observed predominance of early proliferative pattern, endometrial hyperplasia and increased endometrial thickness in DUB patients compared to normal (Table 13) as in earlier studies.^{16, 17} Since the concentrations of both ER and PR were increased in endometrial glands and stroma of DUB patients, our findings support the role of ovarian steroid hormones in pathogenesis of DUB through increased local concentration of these receptors in endometrium,¹⁸ with subsequent unopposed estrogen effect leading to excess endometrial proliferation and hyperplasia.⁶ This, in addition to uneven breakdown of endometrium may be responsible for increased endometrial thickness in DUB patients.

We demonstrated higher variation in ER of glands than other receptors in simple endometrial hyperplasia ($\chi^2= 24.1, p < 0.001$), which was consistent with findings of Thornton JG *et al*,¹⁹ This might be due to increased proliferation of glands and increased gland to stroma ratio in endometrial hyperplasia.

High concentration of both endometrial estrogen ($p < 0.05$) and progesterone ($p < 0.05$) receptors in late secretory phase in DUB patients compared to normal group in our study, suggests increased synthesis of these receptors induced by high local estrogen concentration during this phase.

The most interesting finding in our study was demonstration of significant increase (all with $p < 0.001$) in both ER and PR in glands and stroma of endometrium in women with DUB compared to normal group. Since serum estrogen and progesterone were normal in our patients, we suggest the role of increased local concentration of these receptors in the etiopathogenesis of DUB.

Earlier studies^{9, 20} have demonstrated down regulation of both ER & PR in atypical endometrial hyperplasia. We report one such case. These findings imply that with the development of atypical hyperplasia, there is down regulation of the hormonal receptors.

Our findings were in contrast to N Gleeson *et al*⁴ and Critchley *et al*,²⁰ who found no significant difference in estrogen and progesterone receptors between dysfunctional uterine bleeding and normal endometrium. This could be due to difference in the method of selection of patients for the study. Both Critchley *et al* and Gleeson *et al* excluded patients with histologic evidence of simple endometrial hyperplasia and endometrial maturation and menstrual dating discordance.

Although we observed peak concentration of ER and PR in endometrial hyperplasia, but not as exaggerated as noted by S Chakraborty *et al*.⁹

To the best of our knowledge, there are no reports available on correlation between the ER/ PR and the endometrial thickness in DUB. Y Ohno *et al* studied relationship of endometrial ER & PR with sonographic appearance of endometrium in normal and pregnant women. They found no significant relationship between the endometrial thickness and ER, PR receptors. In contrast, we demonstrated a significant negative correlation ($p=0.03$) between the endometrial thickness and progesterone receptors in glands.

There is various treatment modalities available for DUB, depending on reproductive status of women and individual's choice. The current most effective treatment strategy for DUB is hormonal therapy. Surgical interventions are reserved for intractable cases. Majority of patients with simple endometrial hyperplasia undergo endometrial ablation or hysterectomy, since they are less amenable to medical management.

A recent development in the management of dysfunctional uterine bleeding is the identification of progesterone antagonists, such as Mifepristone, and selective Progesterone receptor modulators, such as Mesoprogesterin J1042.^{21, 22} Some Progesterone antagonists, such as ZK 137 316 and ZK 230 211 have been studied in experimental models with promising results in inhibition of endometrial proliferation and induction of amenorrhea.²³

CONCLUSION

Immunohistochemical analysis of estrogen and progesterone receptors in endometrium is a very useful adjuvant investigation in the management of DUB patients. We support the role of these receptors in the etiopathogenesis of DUB and consequently the development of simple endometrial hyperplasia, which is a pre-cancerous lesion. Our correlation of ER/PR with sonographic endometrial thickness in DUB implies that the later may help in predicting the behavior of these receptors in endometrium. There are limited reports available on the study of both glandular and stromal hormonal receptors in simple endometrial hyperplasia. We conclude that glandular estrogen receptor is a better predictor of disease behavior than other receptors in these patients. There is a subset of DUB patients with increased concentration of ER & PR, who might benefit from the receptor-targeted drugs, such as progesterone antagonists and receptor modulators. This obviates the need for invasive surgeries. We advocate the use of these drugs in the treatment of patients with dysfunctional uterine bleeding and endometrial hyperplasia. However, this needs to be validated by long term follow-up studies.

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