

Oestrogen and Progesterone Receptor (ER & PR) Status in Dysfunctional Uterine Bleeding

Aparna Bhattacharyya, Sashilata Kabra, Sabitri Sanyal, M K Sanyal

Dept. of Gyn & Obst (Eden Hospital) and Pathology, Medical college, Calcutta - 700 073.

Summary : A study on estrogen and progesterone receptor (ER & PR) status on the uterine tissue of dysfunctional uterine bleeding cases was carried out in the Department of Pathology and department of Gynecology and Obstetrics of Medical College, Calcutta, to assess the intensity / concentration of the receptors. Uterine tissue from fibroid of uterus having bleeding acted as diseased control. Uterine tissue from prolapse of uterus acted as nondiseased control. Receptor study was done on the paraffin embedded sections of endometrium and myometrium following the immuno-histochemical method using the streptavidinbiotin immunoenzymatic antigen detection system.

The present study did not find any evidence of secretory endometrium in routine histology but found high PR and low ER receptors in glandular, stromal and myometrial nuclei of DUB cases and high ER content in glandular, stromal & myometrial nuclei in cases with bleeding fibroid. The glandular, stromal & myometrial nuclei of the prolapsed uteri showed irregular staining with both ER and PR.

It appears from the study that there is receptor imbalance in the tissue which probably leads to the local nonresponsiveness of the cells to peripheral endocrine signals leading to bleeding in cases of dysfunctional uterine bleeding.

Introduction:

The role of oestrogen and progesterone receptors (ER & PR) has been established to be important prognostic indicator for breast carcinoma (McGuire et al, 1986). Reports are coming up for the utility of assessment of these receptors in the prognosis of uterine adenocarcinoma (Pollow et al, 1983, Ehrlich et al, 1988). But little work has been done on benign pathology of the uterus which is hormone dependent.

Dysfunctional uterine bleeding is an enigma in gynecology whose etiology is still debated. This could be due to lack or excess of estrogen and progesterone or to an abnormality in the relative proportions of these hormones. There are controversial reports about plasma oestradiol, progesterone, LH and FSH levels in women with DUB (Hynes et al, 1979). Thus there is a possibility that a dysfunctional endometrium may arise from a change in the responsiveness of the endometrium, related to an abnormality in the steroid receptors.

The present study has been undertaken to assess the oestrogen and progesterone receptor status in the endome-

trial gland, uterine tissues in cases of dysfunctional uterine bleeding (DUB).

Material and Methods:

The study was carried out in the Department of G & O, and Department of Pathology in Medical College Calcutta during the period of 1996 to 1997.

Fifty cases were selected who were diagnosed, by imaging technique and by other methods of exclusion, to be dysfunctional uterine bleeding (DUB). Twenty five cases were selected who had abnormal uterine bleeding due to fibroid of uterus diagnosed clinically and by imaging technique. They acted as diseased control. Another group of 25 cases were taken as non-diseased control who did not have any history of abnormal bleeding per vaginum and came for treatment for prolapse of uterus.

The study and the control cases were matched for age as far as practicable, and none of the cases were subjected to hormonal therapy.

Histopathology was done on the removed uteri of all these

Table I
Distribution of ER/PR in study and control cases

Cases	No. of cases (Percent)	ER		PR	
		+ve	-ve	+ve	-ve
DUB	14 (100)	4 (29)	10 (71)	10 (71)	4 (29)
Fibroid	8 (100)	6 (75)	2 (25)	2 (25)	6 (75)
Prolapsed uterus	6 (100)	2 (33)	4 (67)	3 (50)	3 (50)

cases to confirm the diagnosis made clinically.

Receptor study was done on the paraffin embedded sections of endometrium and the myometrium from uterus following the immunohistochemical method using the kit of streptavidin-biotin immunoenzymatic antigen detection system for oestrogen and progesterone. The technique involved was sequential incubation of the specimen/section of tissue with unconjugated primary and biotinylated secondary antibody, enzyme labelled streptavidin-biotin and substrate chromogen DAB. A positive staining of the receptor was indicated by yellowish brown staining of the nucleus (Fig.1) A gradation of the staining intensity was done for advantage of study analysis. This was done as follows:

- Strongly positive (+++) - when more than 75% of the nuclei of the glands, stromal cells and the muscle cells showed positive staining. (Fig. 1)
- Weakly positive or irregularly positive (+ / ±) - when the staining was positive in 50 to 75% of the cell

nuclei.

- Negative (-ve) - when less than 50% of the cell nuclei were negative for staining.

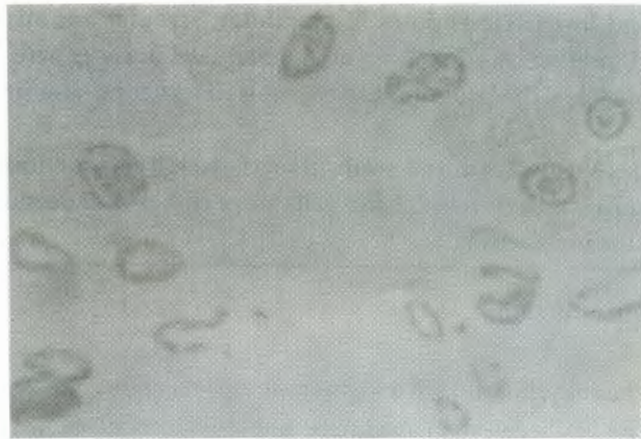


Fig. 1: Section shows endometrial tissue stained with progesterone receptor antibody. The receptor positivity is shown by the yellowish brown colouration of the nuclei of the glandular epithelium stromal cells. Immunostaining for PR x 100.

Table II.
Severity of bleeding vs ER/PR status in DUB and bleeding in fibroid cases

Severity of bleeding	PR (No. of cases)			ER (No. of cases)		
	Strg	WK	Neg	Strg	WK	Neg
DUB - Mild (4 cases)	-	4	-	-	2	-
- Moderate (2 cases)	2	-	-	-	2	-
- Severe (8 cases)	8	-	-	-	-	-
Fibroid						
Uterus - Mild (2 cases)	-	-	-	-	2	-
- Moderate (2 cases)	-	2	-	-	2	-
- Severe (4 cases)	-	-	-	2	2	-

Observations:

Histological sections from cases of DUB showed endometrium having the appearance of proliferative change in most of the cases, none had cystic endometrium. The cases with fibroid also showed proliferative endometrium in most while the cases of prolapse of uterus had atrophic appearance of the endometrium in majority of the cases.

The receptor study of the sections showed that 70% of the DUB cases had intense progesterone receptor positivity. The cases with fibroid had intense positivity for oestrogen in 75% of the cases. Most of the cases with prolapse of uterus showed weak and irregular staining with both oestrogen and progesterone receptors. (Table I)

It has also been observed that in DUB severe bleeding cases showed intense positivity for progesterone receptors and mild to moderate bleeding cases showed weak positivity for oestrogen also (Table II). No such definite relationship with severity of bleeding could be obtained in cases of fibroid of uterus.

Discussion:

The present study has shown that the nuclei of the glandular cells, stromal cells and the muscle cells of uterus showed similar type of intensity of staining with both oestrogen and progesterone receptor staining technique. The progesterone receptor staining was positive in more than 70% of the uteri in DUB cases and oestrogen receptors were positive in 75% of cases with fibroid uteri. The cases with prolapse uteri showed inconsistent results with both oestrogen and progesterone receptors. Severe bleeding uteri showed strong positivity with progesterone receptors in DUB cases.

The glands showing progesterone receptor positivity showed the appearance like proliferative change, in histology.

Lessey et al (1988) have shown that the maximal concentration of ER and PR occurred in the mild and late proliferative phase of the menstrual cycle. ER content

declined throughout the secretory phase. In contrast, the PR underwent unexpectedly complex and dyssynchronous fluctuations during the secretory phase of menstrual cycle. Specifically, the glandular epithelium had diminished PR content while the stroma and the myometrium maintained a significant PR content. PR and probably ER are not concordant in different cell types within the uterus. Thus they had suggested that segregation of function through alteration of receptor content may be an important mechanism in steroid dependent growth and differentiation of target tissues.

Progesterone has been considered an antagonist of oestrogen action. The delicate balance and interactions between these ovarian hormones are essential for the growth and functioning of the uterus. It is generally thought that oestrogen exerts its effects by binding first to a cytoplasmic macromolecule (Rc) to form oestrogen receptor complex (RcE) (O'Malley & Means 1974). This complex undergoes translocation to specific nuclear sites where it stimulates RNA synthesis which in turn is responsible for cell growth and function. It has been proposed by Hsueh et al (1976) that progesterone exerts its action i.e. inhibit oestrogen, by interfering with replenishment of Rc, thereby reducing the number of receptor oestrogen complex that are translocated and retained by uterine nuclei.

Coppens et al (1992) had shown that normal proliferative endometria had strong staining reaction in a large number of glandular cells and stromal cells for the ER and PR antibodies. Also they had shown that there were more positively stained nuclei for ER than for PR in the glandular cells than in the stromal cells. In secretory phase the glandular cells as well as stromal cells showed more number of PR staining cells upto mid secretory phase and in the late secretory phase the ER staining was seen to be poorer than the PR staining and the stromal cells showed more of PR positivity. In contrast to normal proliferative endometria, deficient proliferative endometria showed a decreasing ER/PR ratio i.e. more number of nuclei were stained with PR antibody than with ER antibody. In irregular proliferative endometria, Coppens et al (1992) observed a variable ER and PR distribution and also a variable gland versus stromal ratio.

They also recorded more of progesterone receptors in the stromal as well as glandular nuclei in delayed deficient secretory endometrium and deficient secretory endometrium with co-ordinated apparent delay in cases of DUB.

The present study could not find typical picture of secretory endometrium in routine histology in cases of DUB but found high quantity of PR receptors and low ER receptors in glandular cell nuclei, stromal cell nuclei and muscle cell nuclei. We could also find a direct relation of high PR content of cell nuclei with severity of bleeding in DUB cases in contrast to the controls. Thus it appears that the cells were probably having receptor imbalance which had led to local non-responsiveness of the cells to peripheral endocrine signals leading to dysfunctional uterine bleeding.

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