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Correlation of Steroid Receptor Status and Clinical Course of Endometriosis: An Immunohistochemical Study

Endometriozisde Steroid Reseptör ile Klinik Gidişin Karşılaştırılması: İmmun Dokukimyasal Bir Çalışma

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Özet: Endometriozisin klinik olarak gidişi ve steroid reseptör durumu arasındaki ilişkiyi belirlemek amacıyla estrogen reseptör (ER) ve progesteron reseptör (PR) için immün dokukimyasal boylar; endometriozisli 15 hastanın endometriotik lezyonlarının (n: 17) ve endometriumlarının (n: 3) formalinde fikse edilip parafinde bloklanan kesitlerine uygulandı. Onbeş hastanın yedisine preoperatif hormonal sağaltım yapıldı. Endometriumların tamamında ve 17 endometriotik lezyonun 16'sında, bezlerde ve stromada ER ve PR için spesifik nükleer boyanma gözlendi. Boyanma şiddeti (1+-3+) ve yaygınlığı (1+-4+) semikantitatif olarak belirlendi. Preoperatif hormonal sağaltımlı hastalarla, diğerleri arasında anlamlı bir boyanma ayrımı gözlenmedi. Ovaryumdaki (n: 7) ve ovaryum dışındaki (n: 10) endometrial implantlar benzer boyanma paterni gösterdi. Sonuç olarak; belirgin klinik bulgusu olan endometriozisli hastaların endometriotik lezyonlarında immün dokukimyasal yöntemle estrogen ve progesteron reseptörlerinin üniform olarak bulunduğu saptanmıştır. Preoperatif hormonal sağaltım ile reseptörlerde anlamlı bir azalma izlenmemiştir.

Anahtar Sözcükler: Endometriosis, steroid reseptörleri, estrogen reseptörü, progesteron reseptörü

Summary: *In an attempt to establish a correlation between steroid receptor status and the clinical course of endometriosis, immunohistochemical stains for estrogen reseptor (ER) and progesterone receptor (PR) were performed on formalin-fixed, paraffin-embedded sections of endometriotic lesions (n:17) and eutopic endometrium (n:3) from 15 patients with severe, recurrent endometriosis. Seven of the 15 patients received preoperative hormonal therapy. Specific nuclear staining for ER and PR was observed in the glands and stroma of all eutopic endometria and 16/17 endometriotic lesions. Intensity (1+-3+) and extent (1+-4+) of staining were assessed semiquantitatively. There were no significant differences in staining between patients who did and did not receive preoperative hormonal therapy. Ovarian (n:7) and extraovarian (n:10) implants also showed similar staining patterns. We conclude that estrogen and progesterone receptors are uniformly detectable by immunohistochemistry in endometriotic lesions of patients with severe, recurrent endometriosis and that there is no significant downregulation of receptors by preoperative hormonal therapy.*

Key Words: *Endometriosis, steroid receptors, estrogen receptor, progesterone receptor*

Endometriosis is a commonly encountered gynecologic disease which often presents with pain, dyspareunia, abnormal uterine bleeding, dysmenorrhea and infertility. It is responsible for 14 % to 21 % of all gynecologic surgical procedures performed for treatment of infertility (1). Although medical or conservative surgical therapies are effective for a short period of time, many patients have a recurrence within 6 to 12 months after cessation of therapy (2, 3). Understanding the steroid receptor status of endometriosis appears to be fundamental to any attempts to improve the results of therapy (4-6). The presence of estrogen receptors (ER) and progesterone receptors (PR) in these lesions has been previously documented, but there are conflicting findings regarding the distribution and levels of these receptors (5, 7-13). This may be due in part to the unreliability of biochemical studies in detecting ER and PR in lesions where the relative amounts of stromal, glandular and fibrous components can be quite variable.

In an attempt to elucidate the relationship between steroid receptor status and the clinical course of endometriosis, a study of endometriotic tissue from patients with a well documented clinical follow-up was performed using paraffin section immunohistochemistry in order to accurately localize the source of the receptors. The ER and PR status was correlated with the course of the disease, location of endometriosis, effect of preoperative hormone therapy and, in infertility cases, the ability to conceive following therapy. The ER and PR content of endometriotic lesions was also compared with that of eutopic endometrium from the same patient when available.

Materials and Methods

Lesions from 15 patients who were operated on for endometriosis were retrospectively studied. The patients' age ranged from 23 to 43 years. Operations were performed during the time interval of 1977 - 1992 (by RM) at the Methodist Hospital and Baylor College of Medicine. Ten patients were selected based on the primary complaint of infertility, and five patients were selected on the basis of pain. The staging of endometriosis was determined using the American Fertility Society revised classification (14).

Medical therapy during the 3-6 months immediately preceding the operation was defined as preoperative medical therapy (N=4). Medical therapy prescribed prior to 7 months preceding the operation was defined as remote medical therapy (N=4). Medications included Danazol 400-800 mg daily (N=4), Depo Provera 40 mg (N=1), Depo Lupron 3.75 mg (N=2) IM and Zoladex 3.6 mg (N=1) SC each month. Some patients (N=6) received postoperative medical therapy for 2-11 months. These medications included Depo Lupron 3.75 mg each month (N=4), Danazol 400-800 mg daily (N=2), and Depo Provera 150 mg monthly (N=1). Table 1 summarizes these cases.

The following sites of disease were studied: ovary (N=7), colon (N=5), and from the omentum, urinary blader, umbilicus, uterosacral ligament and the anterior cul-de-sac peritoneum (N=1 each). The ER and the PR content of the endometriotic lesions was also compared with that of the eutopic endometrium for the same patient when available.

The tissue samples were fixed in 10% neutral buffered formalin, routinely embedded in paraffin, and 5 μm serial sections were cut of each block. One of these sections was stained with H&E for routine histologic examination and dating of the endometrial tissue, using the criteria of Noyes et al. (15). Immunohistochemical staining for ER was performed on deparaffinized sections using a modification of the procedure of Cheng, et al. (16). Briefly, following digestion in pre-warmed pronase (0.03g/50ml PBS; Sigma Chemical Co., St Louis, MO) at 37 C for 5 minutes, primary antibody (Abbott Laboratories, North Chicago, IL, 1: 5) was applied overnight at room temperature. Biotinylated secondary antibody (rabbit anti-rat, 1:400) and avidin-biotin complex (Vector Elite ABC, Vector Laboratories, Inc. Burlingame, CA) were applied for one hour at room temperature. Progesterone receptor staining was performed using a PR kit (Cell Analysis Systems, Inc., Elmhurst, IL).

Histologic and immunohistochemical ER and PR slides were examined by three investigators (DD, RB, IR) who were blinded to patient outcomes. Nuclear staining was graded for distribution and intensity as follows:

Distribution:	1+=1/100-1/10	2+=1/10-1/3	3+=1/3-2/3	4+=>2/3
Intensity:	1+=weak	2+=moderate	3+=strong	

Following that, the mean values of ER and PR distribution and intensity in both glands and stroma were

calculated for comparison between the following subgroups:

1. Eutopic versus proliferative and inactive endometriotic lesions
2. Cases with and without preoperative or remote hormonal therapy
3. Ovarian versus extraovarian endometriotic lesions
4. Infertile cases which conceived, versus those which failed to conceive.

Results

The histologic appearance of endometriosis was classified as proliferative and inactive; none of the lesions were secretory. Inactive glands were defined as showing no evidence of proliferative or secretory activity (12). Samples from the 7 patients who had preoperative or remote hormonal therapy were predominantly inactive (6 out of 8 samples). Only 2 had proliferative lesions: one followed Zoladex and the other Danazol therapy. Samples from the 8 patients with no history of preoperative or remote hormonal therapy were predominantly proliferative (6 out of 9 lesions). Only 3 had inactive lesions. All 3 eutopic endometrial tissue sampled as controls were proliferative.

The clinical findings are summarized in Table I. Three out of 10 infertile patients (30%) conceived within 12 months of completion of their surgical and/or hormonal therapy. All but one of the 6 cases (7 operations) where postoperative follow-up was available showed recurrent severe disease postoperatively; the only patient who showed regression to mild endometriosis had Depo Provera preoperatively, and Danazol and Depo Lupron postoperatively. Long-term follow-up was not available after ten of the operations.

Results of immunohistochemical staining for ER and PR are presented in Table II. All eutopic endometrial tissue and endometriotic lesions, with the exception of one, showed positive staining for ER and PR within the nuclei of both glandular and stromal components (Figs. 1, 2). Only one case showed negative staining for ER and PR in the glands but positive staining for both receptors in stroma. Progesterone receptor distribution and intensity of immunostaining was generally higher than that of estrogen receptors in endometriotic lesions (Fig. 1). Although the glands and stroma had the same amount of ER content, the stroma had a higher PR intensity than the glands (Table II). Eutopic endometrium revealed the same levels of ER and PR distribution positivity in both glands and stroma, however, the intensity for PR was higher than that for ER both in glands and stroma (Table II, Fig. 2).

The intensity of positive immunostaining for ER and PR (Pi-ER and Pi-PR respectively) in eutopic endometrium and endometriotic lesions is summarized in Table III. Glandular and stromal ER, as well as glandular PR levels, were slightly higher in eutopic endometrium than in endometriotic lesions, and they were slightly higher in proliferative than in inactive endometriotic lesions. The variations in stromal Pi-PR between different sample groups were insignificant. Patients who had remote hormonal therapy had comparable intensity of glandular and stromal ER to those who had preoperative hormonal therapy, but both groups had slightly lower levels than in patients who did not receive any hormones. There was no significant difference in PR between those groups with and without preoperative or remote hormonal therapy. Slightly higher levels of ER and PR were found in extraovarian lesions as compared to ovarian lesions. Fibroblastic cells in ovarian endometriotic lesions showed weak positive staining for ER and PR, while in extraovarian lesions, only endometriotic glands and stroma stained positively (Fig. 3).

Endometriotic lesions of infertile patients who subsequently conceived had slightly lower ER staining than those of patients who did not conceive, but the PR staining was comparable.

Discussion

Since endometriosis is a systemic disease (4), it is often followed by recurrences. Hormonal therapy is widely used and focuses on the premise that these lesions depend on ovarian steroids for maintaining their growth (3, 13, 17). It has been suggested that the hormonal therapy may create a pseudohypogonadotropic state or decrease the number of estrogen and progesterone receptors in endometriotic foci (3, 6, 13, 18-23). Danazol, estrogen/progestogen combinations, progestogens and Gonadotropin-releasing hormone analogues (GnRHa) are widely used for this purpose. However, many studies have shown high recurrence rates as well as no significant difference among the different treatment modalities (2, 3, 20, 21, 24-26).

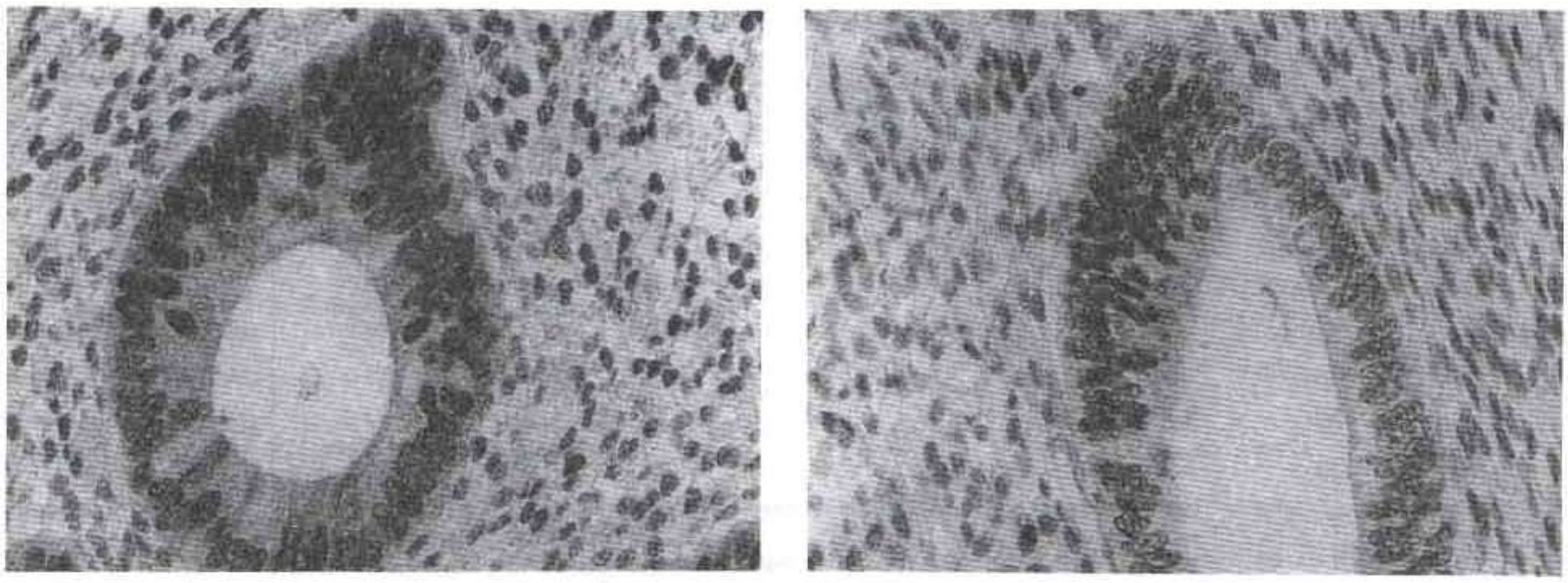

Figure 1. Endometriotic lesions showing higher progesterone receptor in glands and stroma (A), as compared to estrogen receptor (B) (DAB-Methyl Green, X440).

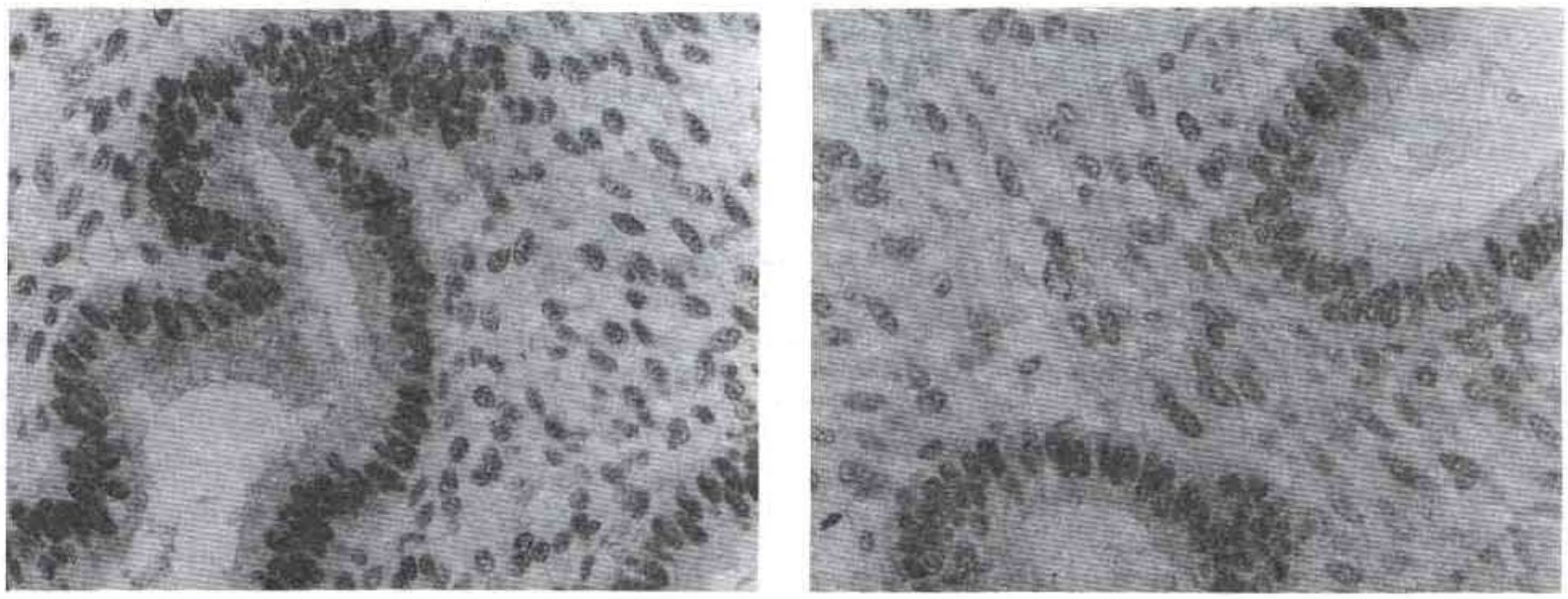

Figure 2. Eutopic endometrium showing higher progesterone receptor in glands and stroma (A), compared to estrogen receptor (B) (DAB-Methyl Green, X440).

Figure 3. Ovarian endometriotic lesions showing positive staining reaction for PR in ovarian fibroblastic cells as well as in endometriotic glands and stroma (DAB-Methyl Green, X220).

Table I. Clinical Findings in Patients with Severe Endometriosis

Case No	Biopsy Site	Recurrence	Surgery Type	Infer-tility	Hormonal Therapy: Remote or (*) Preoperative	Postoperative Hormones	Concep-tion	Postoperative follow-up
1a	Omentum	RS	Excision	–	–	–		Recurrence, severe
1b	Colon	RS	HBSO	–	–	Depo Lupron 3.75 mg/month 3 mos		ND
2	Colon	RS	HBSO	–	–	–		ND
3	Urin bladder	RS	Excision	+	–	–	–	ND
4	Umbilicus	S	Excision	–	–	Depo Lupron 3.75 mg/month x 6 mos		ND
5	Ovary	RS	HBSO	–	–	–		ND
6	Ovary	S	Excision	+	–	–	–	ND
7	Ovary	S	LSO, Cyst resection	+	–	–	+	ND
8	Ovary	RS	Excision	+	–	Danazol 400 mg/day x 2 mos	–	Recurrence, severe
9	Colon	RS	HBSO, excision of endometriosis colon	–	Danazol 800 mg/day x 6 mos, 3.5 years prior	–		ND
10	Ovary	RS	RSO, Excision	+	Danazol 800 mg/day x 6 mos 4 yrs prior	–	–	ND
11	Ovary	RS	RSO, Excision	+	Depo-Provera 40 mg/month x 6 mos, 7 mos prior	Danazol 800 mg/day x 11 mos, Depo Lupron 3.75 mg/month x 6 mos	–	Regression to mild
12	Colon	RS	Hysterectomy, rectosig. resection	+	Zoladex, 3.6 mg/montnh x 6 mos, 3 years prior	Depo provera 150 mg/month x 6 mos	–	ND
13	Uterosacral ligament	RS	Excision	+	Depo Lupron 3.75 mg/month x 6 mos*	–	–	Recurrence, severe
14a	Ovary	RS	Excision	+	Danazol 600 mg/day x 6 mos*	–	–	Recurrence, severe
14b	Anterior cul-de-sac	RS	Excision	+	Depo Lupron 3.75 mg/month x 4 mos*	–	+	Recurrence, severe
15	Colon	RS	Excision	+	Danazol 800 mg/day x 3 mos*	Depo Lupron 3.75 mg/month x 6 mos	+	Recurrence severe

RS = Recurrent severe endometriosis
HBSO = Hysterectomy, Bilateral Salpingo-oophorectomy
RSO = Right Salpingo-oophorectomy
S = Severe endometriosis without previous recurrence
LSO = Left Salpingo-oophorectomy
ND = No data

Table II. Results of Immunohistochemical Staining for ER and PR*

Case no	Histologic date	Hormonal therapy prior to operation**	ER		PR	
			glands	stroma	glands	stroma
Endometriosis						
1.a	Proliferative	None	3+,1+	4+,2+	4+,2+	4+,3+
1.b	Proliferative	None	4+,1+	4+,2+	3+,2+	4+,3+
2	Proliferative	None	4+,2+	3+,1+	4+,3+	4+,3+
3	Proliferative	None	4+,1+	4+,1+	4+,3+	4+,3+
4	Proliferative	None	4+,1+	4+,2+	4+,3+	4+,3+
5	Proliferative	None	4+,2+	4+,1+	4+,3+	4+,3+
6	Inactive	None	4+,1+	4+,1+	4+,2+	4+,3+
7	Inactive	None	4+,1+	4+,1+	4+,2+	4+,2+
8	Inactive	None	3+,1+	4+,1+	3+,2+	4+,3+
9	Inactive	3.5 yrs	4+,1+	4+,1+	4+,2+	4+,3+
10	Inactive	4 yrs	–	1+,1+	–	4+,2+
11	Inactive	7 mos	4+,1+	4+,1+	4+,2+	4+,2+
12	Proliferative	3 yrs	4+,1+	4+,2+	4+,3+	4+,3+
13	Inactive	Preoperative	4+,1+	3+,1+	4+,3+	4+,3+
14.a	Inactive	Preoperative	4+,1+	4+,1+	4+,2+	4+,3+
14.b	Inactive	Preoperative	4+,1+	3+,1+	4+,2+	4+,1+
15	Proliferative	Preoperative	1+,1+	1+,1+	4+,2+	4+,3+
Eutopic Endometrium						
1	Proliferative		4+,1+	4+,1+	4+,3+	4+,3+
2	Proliferative		4+,3+	4+,1+	4+,3+	4+,3+
3	Proliferative		4+,2+	4+,1+	4+,3+	4+,3+

* First numbers indicate distribution, second indicate intensity of staining
** Time relapsed since cessation of hormonal therapy prior to current surgery

Table III. Mean ER and PR Glandular/Stromal Distribution/Intensity

	Eutopic	Endometriotic Lesions		Hormonal Therapy			Site of lesions		Infertile cases	
	Endometrium	Proliferative	Inactive	Negative	Remote	Preoperative	Ovarian	Extraovarian	Conceived	Nonconceived
MERGDPo	4.000	3.500	3.444	3.777	3.000	3.250	3.285	3.600	3.000	3.375
MERGIPo	2.000	1.250	0.888	1.222	0.750	1.000	1.000	1.100	1.000	0.875
MERSDPo	4.000	3.500	3.444	3.888	3.250	2.750	3.571	3.400	2.666	3.500
MERSIPo	1.000	1.500	1.000	1.333	1.250	1.000	1.000	1.400	1.000	1.125
MPRGDPo	4.000	3.875	3.444	3.777	3.000	4.000	3.285	3.900	4.000	3.375
MPRGIPo	3.000	2.625	1.888	2.444	1.750	2.250	1.857	2.500	2.000	2.125
MPRSDPo	4.000	4.000	4.000	4.000	4.000	4.000	4.000	4.000	4.000	3.500
MPRSIPo	3.000	3.000	2.444	2.888	2.500	2.500	2.571	2.800	2.000	2.750

E= Estrogen
P= Progesterone
R= Receptor
G= Glandular
S= Stromal
Po= Positivity
M= Mean
I= Intensity
D= Distribution

Since the hormonal dependency of endometriosis is mediated by ER and PR (27), understanding the steroid receptor status of endometriosis is fundamental to improving the results of the medical therapy (4-6). Several studies have confirmed the presence of estrogen and progesterone receptors in endometriotic lesions (5, 7, 8, 10-13). However, the findings of these studies were often inconsistent. Biochemical and histochemical studies were reported to show much lower concentrations in endometriotic tissue than in the normal endometrium, and in several cases one or both receptors were absent (7, 8, 10, 11). Our study confirms some recent immunohistochemical studies which demonstrated that almost all endometriotic lesions have estrogen and progesterone receptors to a variable degree (5, 12). Dunselman and associates, also using immunohistochemical methods, have found that there was no difference in ER and PR content between eutopic and ectopic endometrial tissue in their rabbit model of endometriosis (27). Endometriotic tissue usually contains more fibroblastic elements and less glands and stroma than eutopic endometrium (28), and since biochemical assays require homogenization, the difference in receptor content may be due to the amount of glands and stroma in the homogenate (12). Immunohistochemistry provides the advantage of evaluating all of the cells individually (5, 12, 27). Although some biochemical and histochemical studies demonstrated cytoplasmic location for these receptors, recent immunohistochemical studies, including ours, indicate that ER and PR are confined to the nuclei of glandular and stromal cells (5, 8-13, 27, 29).

The distribution and intensity of staining for ER and PR seems to be different among proliferative endometriotic tissues, inactive endometriotic tissues and eutopic endometrium. Bur and associates (12) reported moderate to strong ER positivity in proliferative lesions and variable (weak to strong) positivity in inactive lesions. Our results indicate that glandular and stromal ER and glandular PR levels are slightly higher in eutopic endometrium than in endometriotic lesions, and they were slightly higher in proliferative than in inactive endometriotic lesions (Table III). These findings appear to be consistent with the steroid hormone dependency of endometriotic lesions and eutopic endometrium.

The effect of hormonal therapy is not clear. Lessey et al. (5) and Melega et al. (13), reported a significant reduction in the steroid receptor content of endometriotic tissue in cases which had preoperative hormonal therapy. These patients showed much lower ER and PR content in both the glands and stroma, relative to untreated patients. Melega also found that in 21 % of patients, the endometriotic foci were epidermal growth factor receptor (EGFr) positive and ER negative, after Danazol and GnRHa therapy. They suggested that EGFr may have a role in maintaining growth of endometriotic tissue. Our study showed reduced levels of ER in the seven patients who received preoperative or remote hormonal therapy (Table III). However, the

difference between these patients and the untreated patients was not significant. Six cases who had preoperative hormonal therapy continued to show ER and PR in the glands and stroma; the stroma in an additional case stained positively for ER and PR, but the glands were scant as a result of therapy and did not stain. The presence of ER and PR in all hormonally treated cases in our study may also explain the tendency of this group to develop frequent recurrence of endometriosis.

Low or absent steroid receptors were linked to hormonal therapy by some authors, suggesting that such patients may not be ideal candidates for this treatment (4, 6, 30). However, all our cases had high levels of ER and PR, and five of the six patients who showed postoperative recurrence were hormonally treated. Since we had postoperative follow-up after the seven current operations of six cases, the high incidence of recurrence in hormonally treated patients suggests that lesions with high levels of ER and PR tend to recur after surgical and/or medical therapy. This observation is consistent with the findings of Bergqvist and Fernö, who reported higher PR levels in recurrent lesions than in primary endometriotic tissues (29).

The location of endometriotic lesions was reported to be a factor that effects their ER and PR status. The higher receptor content of ovarian implants relative to that of extraovarian lesions may be due to increased exposure of the former to steroids (5). In the present series, however, ER and PR levels in extraovarian lesions were slightly higher than the levels in ovarian lesions. Bergqvist and Fernö also reported higher levels of ER in peritoneal endometriotic lesions than in ovarian lesions (29). These findings suggest that the location of a lesion does not have a significant effect on its receptors (Table III).

Many patients with endometriosis present with infertility problems, and 31-65 % conceive after surgical and/or medical treatment (19, 24, 31, 32). Although ER levels in lesions of infertile patients who subsequently conceived were slightly lower than those of infertile patients who did not conceive, the PR levels of these two groups were comparable (Table III). Further studies must be conducted in order to clarify the importance of ER and PR content in endometriotic tissue with respect to prospects for pregnancy.

In conclusion, all the endometriotic lesions studied had ER and PR to a variable degree. Although hormonal therapy reduces steroid receptor content in endometirotic tissue, the difference may not be as significant as previous studies indicate. Lesions which have a higher ER and PR content tend to show recurrence after surgical and/or hormonal therapy. The location of endometriotic tissue does not seem to have an effect on ER and PR levels in these lesions. At this point, it is not clear as to whether or not there is a relationship between ER and PR content in endometriotic tissue and prospects of achieving successful pregnancy in cases of infertility.

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