SPECIAL ARTICLE

Pathogenesis, Diagnosis and Treatment of Genital Endometriosis

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Endometriosis is a slowly progressive, partly studied disease. Its genetic background is partly clarified but its aetiology still remains totally unclear. According to Philipp and Huber[1] it is a disease where endometrial epithelium and stroma are found at a location to which it does not belong. With more advanced pelviscopic procedures endometriosis is detected more frequently and any relation to sterility can easily be traced[2].

In a way, the pathogenesis of endometriosis depends on the local conditions in the minor pelvis where metaplastic growth of endometrium can be induced by specific factors leading to the transformation of endometriotic epithelium and stroma by continuous growth as well as direct invasion.

Also immunological factors seem to influence the pathogenesis of endometriosis. Characteristics of ectopic endometrium are, like in endometrium, the receptor content in a certain percentage. This facilitates the possibility of endocrine therapy. As the development of endometriosis, however, does not depend simply on the endocrine stimulation but primarily on the degree of differentiation and modulation of endometriosis the described phenomena do not serve as therapy in many cases. Ectopic endometrium shows benign infiltrations, especially where the stroma has a so called "histocytological penetrative function"[3].

Pathogenesis

The current theory complexes of the pathogenesis the mechanisms do not explain, but also do not exclude each other.

1. The metastatic theory = implantation theory (haematogenic or lymphogenic) or the invasion theory = adenomyosis
2. Metaplastic theory
   coelom-epithel = mesothel-theory.

We know that in over 90 per cent of women at the time of menstruation, endometrial tissue is flushed into the peritoneal cavity (retrograde menstruation). An increased migration of monocytes results that differentiate into peritoneal macrophages and take up phagocytotic functions.

The question arises why in some women the contact of endometrium and

peritoneum leads to endometriosis and in others this contact does not provoke any implantation of endometrial tissue on the peritoneum, ovary, etc..

Probably, certain immunological and hormonal conditions facilitate the growth of normal or metaplastically produced endometrium. These are on one side growth factors produced by mesenchymal cells, fibroblasts, macrophages and by hormone-secreting cells. The cell proliferation also depends on receptors that are frequently localised at the cell membrane.

It is known that in endometriotic lesions receptors of progesterone and estrogens can be missing. In a number of endometriosis patients on the other side higher numbers of macrophages were determined in intraabdominal fluid than in non-endometriosis patients. Thus, originated our "Macrophage theory" (Fig. 1).

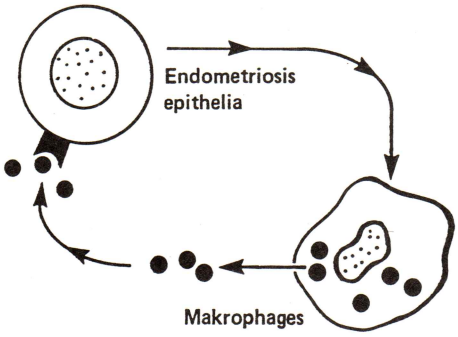

Fig. 1 Schematic presentation of "Makrophage -Hypothesis" for the pathogenesis of endometriosis. Endometrioid tissue enters through retrograde menstruation into the peritoneal cavity and stimulates the migration of makrophages. Growth factors of makrophages (dark points) can stimulate epithelial growth in case a corresponding fms coded receptor is expressed.

In this complex it is thought that certain macrophage populations produce growth factors that promote the growth and proliferation of endometrioid epithelia.

Prerequisites for this theory would be an adequate receptor for macrophages growth factors on the surface of endometriotic epithelia. This receptor is coded by the oncogen "fms" (Fig.2).

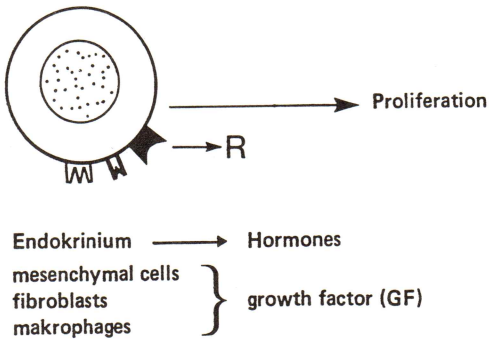

Fig. 2 Schematic presentation of cell varieties that can promote the proliferation of endometrial cells by secretion of hormones or other growth factors (makrophages, fibroblasts). Prerequisite for the efficiency is the expression of corresponding receptors (R) by epithelia.

As each body cell contains the gene, a proof of the corresponding RNA-transcript or of the receptor protein could verify the validity of the theory. At present, we have tried with phosphor labeled "fms" copy probes using the technique of Northernblot analysis to identify corresponding RNA-transcripts.

For a short time we have produced monoclonal antibodies recognizing the receptor protein for macrophage growth factor. In this process in a vicious circle

(Fig.3) endometriotic foci stimulate macrophage migration into the peritoneal cavity. Macrophages themselves produce growth-factors that possibly favour the proliferation of endometriotic epithelia.

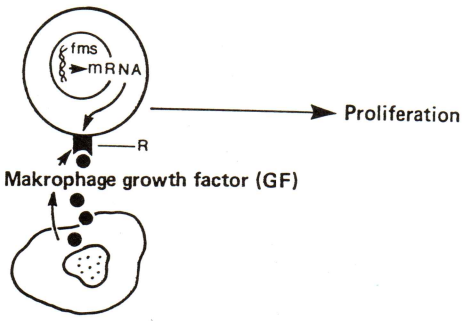

Fig. 3 Scheme for the "Makrophage - Hypothesis" of endometriosis. Dystrophic endometrium provokes the migration of makrophages into the peritoneal cavity, who on the other side secrete growth factors (GF) for the proliferation of endometrioid epithelia. Prerequisite for the efficiency is the expression of a corresponding receptor through epithelia. The specific receptor for makrophages growth is the onkoprotein of the onk-gene fms.

Diagnosis

Endometriosis has a distinct morphology where macroscopically the bloody content of different sized ovarian cysts represent a characteristic sign at pelviscopy or laparotomy. Histologically, the full picture of endometrium is seldom developed. In characteristic cases one sees a small, moderately proliferated endometrium with mucous glands and stroma. Fully secretory developed cells are lacking. In a cytokeratin-stain, epithelia are visible. The dystopic endometrium does not posess the full endocrine activity. In about 30 per cent hormonal receptors are not found. The surrounding stroma contains endometrioid stroma cells.

Is it at all necessary to treat endometriosis at an early stage? Is it really a disease? For the sake of saving a woman from having continuous dysmenorrhea durring her reproductive age it seems necessary to diagnose her early, treat her early and prevent advanced disease.

Diagnostically the following points may be considered :

1. Pains
2. Palpation
3. Speculum presentation
4. Ultrasound diagnosis
5. Pelviscopy with a direct visualisation of foci
6. Histology
7. Success after symptomatic treatment
8. Classification

Pains as symptoms

Dysmenorrhea is the leading symptom of endometriosis. It is found in uterine as well as in extrauterine localisation. Dysmenorrhea carries significant social medical aspects. It belongs in the life of many young women and has always been tolerated as destiny. It still disturbs the life quality of many females for a few days every month. An account of pains in a woman with endometriosis and dysmenorrhoea caused in 34 years during the reproductive period for 5 days every month results in 5

1/2 years of having to tolerate pain. Other symptoms are dyspareunia and chronic abdominal pain. In patients with endometriosis we found 65 per cent pain as a symptom and 35 per cent with no pain. Early diagnosis and treatment seems reasonable.

Palpation

The classic bimanual palpation in endometriosis patients is found negative in 60 per cent of endometriotic patients. Besides the rectal investigation it is the rectovaginal investigation that allows us to diagnose endometriotic conditions.

Speculum presentation

The visualisation of the cervix and the anterior vaginal wall with the duck-mouth speculum allows the localisation of endometriotic foci on the cervix. With endocoagulation at endometriotic foci a correlation with black coloration is seen (Thermocolor-test)[2].

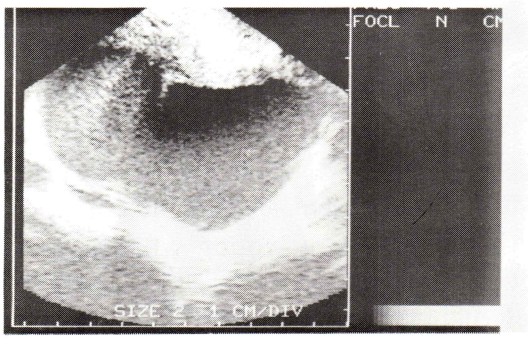

Fig. 4 Vaginosonographical scan of an ovarian endometrioma with cloudy structures easy to be differentiated from other ovarian tumours

Ultrasound diagnosis

The vaginosonographical examination gives espeically good information of endometriotic foci in the ovaries with an exact measurement of endometriomas in diameter (Fig. 4).

Pelviscopy

According to anamnesis and the clinical picture, the patients can be divided into 4 groups :

1. young females with pain and later desire to have children
2. females that have completed their reproductive performance having pain
3. sterile patients and
4. females with symptoms as in endometriosis.

Typical symptoms of endomrtriosis are the lack of blood in the pouch of Douglas and the dark coloration of endometriotic foci at the Thermocolor-test where 100-120° C endocoagulation is applied[2]. Even large endometric foci with 30-50 ml menstrual blood in the pouch of Douglas are sometimes not related to pain in the patients. They produce, however, over the years nuclear abdominal discomfort which we understand accounts for 30-50 ml menstrual blood being absorbed continuously. Pelviscopically an interesting distribution of foci can be found :

1. on the peritoneum
2. in the area of sacro-uterine ligaments
3. on the ovary
4. in the ovary (endometrioma,

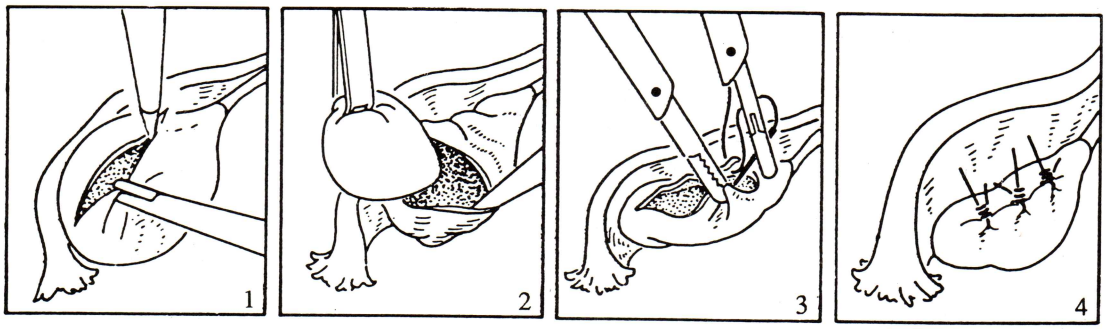

Fig. 5 Ovarian endometrioma presented at operative pelviscopy, consecutive pelviscopic cystpuncture (1), enucleation (2), and adaption of wound margins by endosutures with extracorporal knotting technique (3, 4)

Fig.5)

5. within the uterus = adenomyosis uteri
6. in the tubes (endosalpingitis nodosa)
7. on the bladder roof
8. on the intestines
9. on the spleen
10. on the diaphragm

Histology

As already described, typical endometriotic lesions are small, only slightly proliferated endometrium with some glands and abundant stroma is visible. Figure 6 shows an endometriotic focus in the mesosalpinx in an immune-alkaline phosphate stain of the paraffin section using a monoclonal antibody

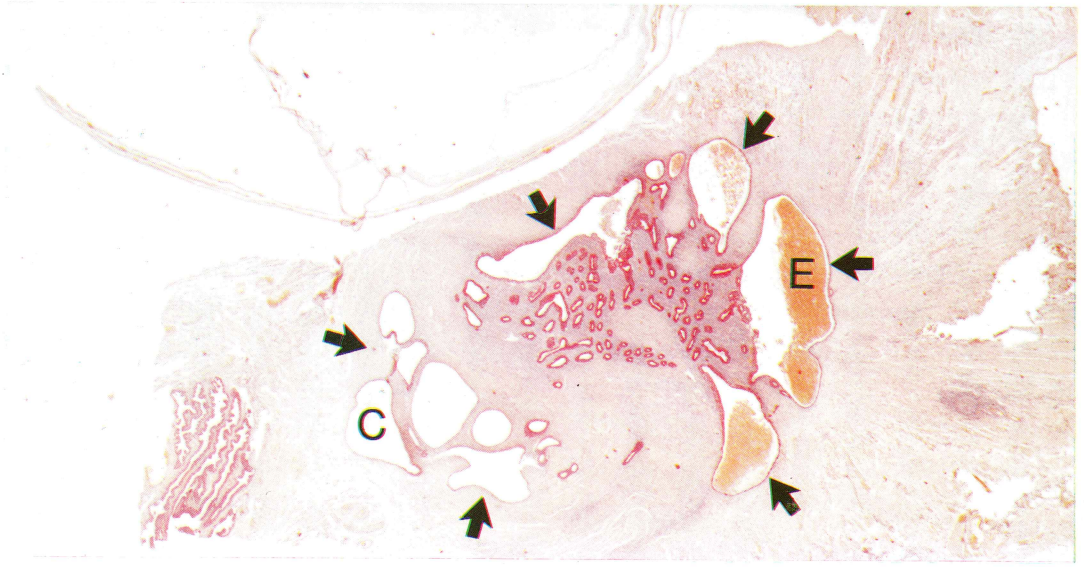

Fig. 6 Immune-histochemical stain of an endometriotic lesion in the Falloppian-tube mesosalpinx. Left: normal tubal mucose. In der endometriotic cysts (C) are many erythrocytes (E). Epithelia are presented in red. 5 µ parffin sections. Immune-alkaline phosphatase reaction with a monoclonal antibody against human epithelia Haemalum-nuclear-counter staining (x 19)

against epithelia. These are selectively shown. The stromal surrounding contains typical endometrial cells, a few haemosiderin carrying macrophages and mononuclear cell. Especially in fresh lesions eosinophilic granulocytes are present. This can be interpreted as a reaction in the sense of an immunological inflammation.

Success after symptomatic treatment

The curative success rate of endocrine treatment with the disappearance of dysmenorrhoea is indicative of the disease.

Classification

The classification is done according to the endoscopic dividing pelvic endometriosis into 3 steps keeping step IV for extragenital endometriosis (Fig.7). The application of the AFS-Scores[4] (American Fertility Society) with a more detailed localisation of the lesions seems only advisible in scientific evaluations. The EEC-classification is identical to the earlier published classification by Acosta[5] and can be directly placed at all operative procedures.

A comparison of the 3 classifications ACOSTA, EEC and AFS is given as follows :

AFS 1-5	= EEC I	= ACOSTA I
AFS 6-15	= EEC II	= ACOSTA II
AFS 16-40	= EEC III	= ACOSTA III
AFS > 40	= EEC IV	= ACOSTA IV

Because of its complexity, the AFS classification is rather difficult for use in routine diagnostic procedures. Endometriosis represents a specific gynaecological disease. The success of treatment depends on good diagnosis as well as application of a combined knowledge of surgery, endocrinology and reproductive biology.

Therapy and Results

As already stated by many authors the surgical removal of endometriotic foci still represents the optimal therapy. Pure endocrine therapy with application of hormones as lynestrenol, danazol, gestrinone preparation or LH-RH superanalogues over 3-6 months leads to a regression of ectopic foci. Pelviscopically this regression can easily be verified by vanishing or disappeared lesions. Therefore, we advise combined diagnostic, surgical and endocrine treatment in 3 steps :

1. Diagnosis including biopsies and surgical destruction of endometriotic implants as radical as possible,
2. endocrine suppression,
3. second-look pelviscopy with continous surgical treatment by pelviscopy or laparotomy if necessary for example : salpingostomy, cystenucleation, etc..

By surgical treatment pelviscopy is applied. If extensive surgical procedures via pelviscopy are not performable a laparotomy is performed. For the second step we advise one of the following 5 treatment modalities (Table 1).

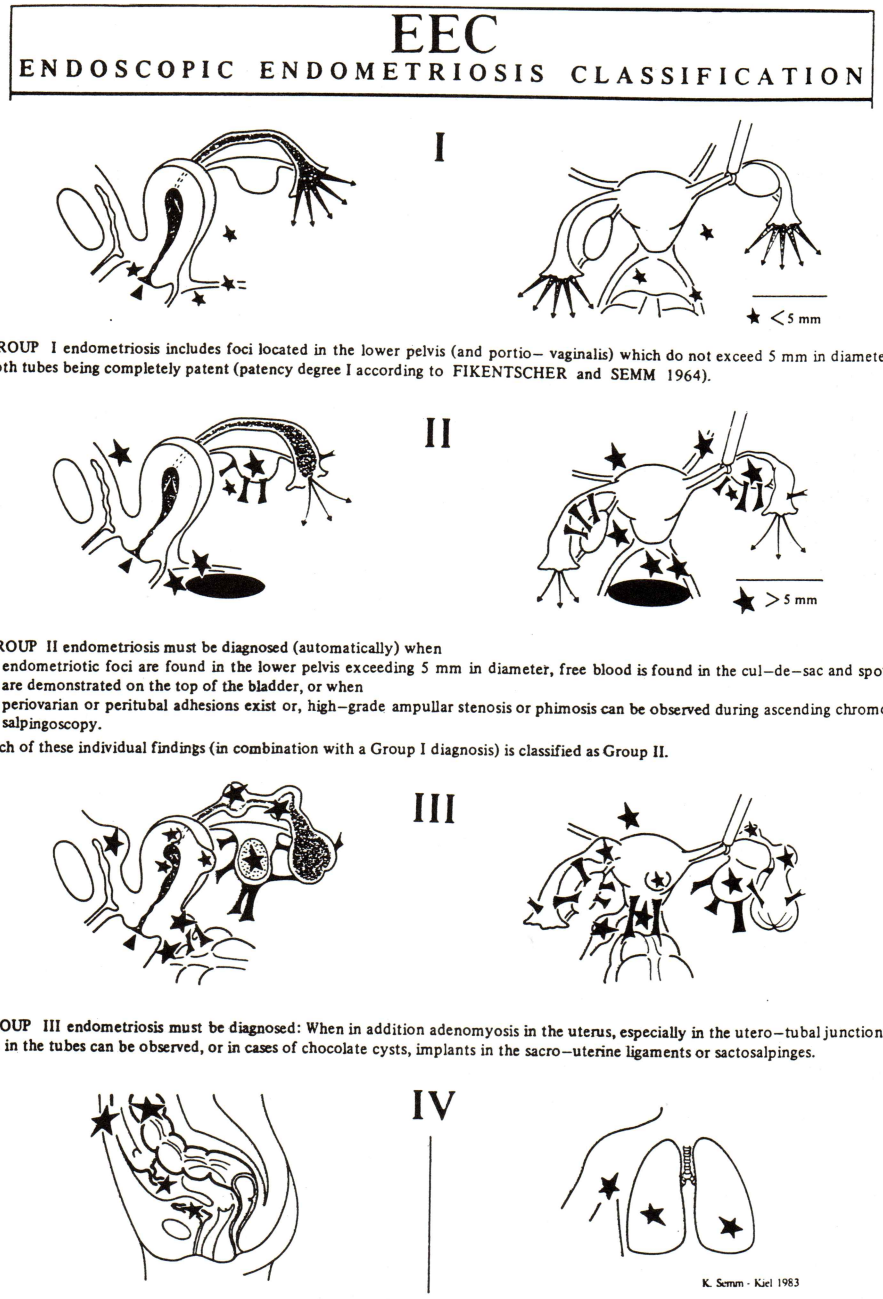

Fig. 7 Endoscopic endometriosis classification (Semm 1984)

Table 1 Endocrine regulation within the 3-step therapy of genital endometriosis over 3-6 months

Lynestrenol (2 x 5 mg daily)
Danazol (3 x 200 mg daily)
Gestrinone (2 x 2.5 mg weekly)
Buserelin (6 x 150 μg daily)*
Zoladex (3.6 mg monthly)

**As example of LH-RH agonist therapy*

In this paper, I would like to compare a recent group of patients treated in this 3-step therapy with the 5 different endocrine modalities in the second step. Gestrinone, Buserelin and Zoladex were given just in this study, while Danazol and Lynestrenol represent treatment modalities, given for many years, with a significantly higher success rate for the Danazol treated patients[6].

Properties of Danazol - mechanisms of action

Danazol, as a synthetic steroid, is an isoxazole of 17-alpha-ethinyl-testosterone (ethisterone), which is well absorbed by the oral route with a circulating half-life of about 15 hours in humans. At least 60 different metabolites have been identified (one of which is 17-alpha-ethinyl testosterone). Their role in the biological effects of Danazol is still controversial. Danazol has multiple effects at various sites of the female reproductive system which are the direct or indirect consequences of its binding affinity to intracellular steroid receptors and its capacity to inhibit multiple enzymes involved in gonadal and adrenal steroidogenesis.

In addition, the interaction of Danazol with the regulation of the immune system may also contribute to its effects. The effects are respectively a reduced release of GnRH, FSH and LH, at the ovarian level an alteration of normal follicular growth with estrogen and progesterone suppression and a direct suppression of endometrium and endometriotic tissue growth. Danazol reduces liver synthesis of the sex hormone binding globulin (SHBG) and displaces free testosterone from this carrier protein, increasing the levels of the bioavailable testosterone, which will further cause atrophy of the endometrial and endometriotic tissues. This agent by inhibiting ovarian enzymes and steroidogenesis also reduces the production of estrogen.

In comparison to other drugs, Danazol reveals the production of a reversible atrophy of the endometrium. It also interacts directly with intracellular steroid receptors present in endometrium. The binding activity of Danazol is high for AR, lower for PR (3 per cent of progesterone) receptors. The direct androgenic activity of Danazol and the increase of free testosterone due to the effect of SHBG also produces further endometrial atrophy.

It is clear that Danzol therapy induces atrophy and regression of endometrium implants as promptly as after the second month of therapy with cellular inactivity and degeneration. The effects of Danazol are multiple and complex and create a hormonal milieu unfavourable for the growth of endometriotic cells. On eutopic as well as ectopic endometrium it produces a marked regres-

sion of the hormone-dependent endometriotic tissue.

Properties of Gestrinone

Gestrinone is an original steroid intended for use as an oral contraceptive agent administered with one or two doses a week. It has been prepared by total synthesis by Roussel-Uclaf in 1965. The biological spectrum of activities is quite original. In vivo as well as in vitro (receptor binding competition) it has shown marked antiprogestative[7] and antihidatory effects and practically no estrogenic effect[8].

Given at a dosage of 5 mg per week the preparation gestrinone was given in 5000 cycles as a contraceptive to women of child bearing age. The Pearl-index was 4, the tolerance satisfactory.

As the main side effects observed in these clinical contraceptive trials were amenorrhoea, decreased breast size and acne, a significant inhibition of endometrial tissue growth was evident. The endometrium of women on gestrinone became markedly atrophic and suggested its possible use in the treatment of endometriosis.

The properties of gestrinone can be summarized as being anti-estrogenic, anti-progestagenic and antiandrogenic as well as showing pituitary inhibition and an effect on the steroid receptor level of the endometrium[8].

Properties of Buserelin and Zoladex

The LH-RH analogues have a 200 folds more potent action than the native peptide and block receptors on the pituitary and ovarian level. Buserelin (3 x 300 µg D-Ser-(Bu^t) -GnRH was given intranasally daily and Zoladex (3.6 mg D-Ser (Bu^t) -GnRH intracutaneously per month. Table 2 and 3 evaluate a group of patients treated between 1985 and 1988 in respect to the effect of therapy and incidence of pregnancies up to 6 months post treatment. No statistically significant differences were found in the group treated with Danazol, Gestrinone, Buserelin and Zoladex. Although side effects in the GnRH analogue groups especially hot flushes seemed to be increased. The twice weekly medication of Gestrinone was well accepted. GnRH analogues appeared to be comparable treatment modalities and could well be used in unsuccessfully treated endometriosis cases with estrogen and

Table 2 Evaluation of 224 patients prior and after 3-step endometriosis therapy (1985-1988)

	Patients	Prior to therapy					after therapy				
	n	0	I	II	III	IV	0	I	II	III	IV
Gestrinone	30	0	10	10	10	0	22	7	0	1	0
Lynestrenol	33	0	14	9	10	0	16	9	7	1	0
Danazol	31	0	12	12	7	0	17	14	0	0	0
Buserelin	80	0	22	31	17	10	49	24	7	0	0
Zoladex	50	0	20	19	10	1	26	14	8	2	0
Tatal	224	0	78	81	54	11	130	68	22	4	0

Table 3 Evaluation of the incidence of pregnancies for 224 patients after the 3-step treatment of genital endometriosis (1985 - 1988)

	Patients	Pregnacies		Abortions and Tubal pregnancies		Living baby rate	
	n	n	%	n	%	n	%
Gestrinone	30	19	63,2	2	6,6	17	56,6
Lynestrenol	33	10	35,3	1	0,3	9	27, 3
Danazol	31	14	45,2	0	0	14	45,2 (1 x twins)
Buserelin	80	43	54	3	3,75	40	50,0
Zoladex	50	21	42	2	4	15	30,0
Tatal	224	78	35	8	18,6	95	42,4

progesterone receptors in the lesions.

Discussion

According to our study a long term application of gestagens, Danazol, Gestrinone and GnRH-analogues result in cellular inactivity and only partly in cellular desintegration. In peritoneum implants after surgico-medical therapy some remaining endometriotic tissue with an induced atrophy was still found. It seems that peritoneal implants respond better on an endocrine therapy than ovarian implants. All applied drugs create a hormonal milieu unfavourable for the growth of endometriotic cells. Only Danazol, however, acts directly at the tissue level of the endometriotic implants itself. Surgical therapy with excision of lesions should always be performed if possible as the first diagnostic step and be followed by endocrine therapy if pelviscopy is available. If only a laparotomy can verify the diagnosis a hormonal pretreatment at suspicion of endometriosis is suggested.

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