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The Treatment of Endometriosis

AND OTHER DISORDERS AND INFECTIONS

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THE TREATMENT OF ENDOMETRIOSIS

— AND OTHER DISORDERS AND INFECTIONS

Edited by Y. Boutaleb and A. Gzouli

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Foreword

Whilst preparing for the XIIIth World Congress of Fertility and Sterility, I could not help reflecting on the possibility that perhaps the Palais de Congrès might not be completed in time – and that for the first time in the history of the IFFS, the Congress might have to be held in tents! However, I need not have worried: after a very rapid construction schedule, this splendid new building was finished shortly before the Congress opened – and provided an ideal setting for the distinguished gathering of scientists from all over the world that met in Marrakesh for the IFFS Congress.

I should like to thank all those who took part in the XIIIth World Congress: their presentations made an important contribution to our growing understanding of all aspects of reproductive medicine, an understanding which is helping to develop new approaches to therapy around the world.

Finally, I should like to pay a special tribute to Dr Jean Cohen and Professor Robert Harrison, from the IFFS Committee, who together went to so much effort to ensure the success of the scientific program. I am indebted to them for their help – and I trust that these published Proceedings will provide a useful record of this very important scientific occasion.

Y. Boutaleb
President of the Congress

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SECTION 1

Endometriosis: diagnosis and treatment

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Hormonal aspects in endometriosis and endocrine pathogenesis

A. Kauppila, L. Rönnberg and S. Telimaa

INTRODUCTION

Despite extensive research, the real histogenetic origin of endometriosis and the factors promoting its initiation have remained unclear[1]. There is a substantial body of evidence, however, to suggest that the growth and persistence of endometriosis lesions must be dependent on, and controlled by ovarian steroid hormones. The arguments supporting this are derived from clinical observations, animal experiments, biochemical studies on the endocrine properties of endometriosis tissue and therapeutic trials using hormonal compounds.

CLINICAL AND HISTOPATHOLOGICAL OBSERVATIONS

The finding that endometriosis appears only in fertile-aged women and disappears after natural or surgical menopause provided the primary evidence for its close dependence on the hormonal activity of the ovaries. In addition, the clinical symptoms, the most prominent of which is dysmenorrhea, appear cyclically.

The ectopic endometrium is characterized in histopathological examination by findings typical of the intrauterine endometrium, including presentation of endometrial glands, endometrial stroma, fibrosis and hemorrhage. In contrast to the normal endometrium, however, it exhibits stromal hemorrhage, dense stromal fibrosis and the formation of cysts[2]. An ectopic endometrium may present proliferative, secretory and sometimes even mild hyperplastic changes during different phases of the menstrual cycle, and decidualization during pregnancy, but these features are usually weaker than in the normal endometrium.

Unlike the situation in the normal endometrium, there are marked gland-to-gland variations in the histomorphological responses of the endometriosis tissue to endogenous ovarian hormones, and the internal structures of endometriosis are therefore highly irregular in both the follicular and

luteal phases of the cycle, as observed in light microscopy[3,4] and electron microscopy[5,6].

The histopathological heterogeneity explains why the intrauterine and ectopic endometrium exhibit menstrual phase synchrony in only 65% of cases[3]. Dyssynchrony was recorded in 17%, and a lack of any signs of a cyclic menstrual phase pattern in 18%. Some authors have found even more discordant morphological patterns[4,5].

The remnants of endometriosis persist during the postmenopausal years in the form of fibrous adhesions and hemosiderin-bearing histiocytes as a sign of an old hemorrhage[2]. These findings also prove that hormonal support is vitally important for the persistence of endometriosis.

Histopathological examinations demonstrate that polymorphism is characteristic of endometriosis, indicating that such tissue differs from the endometrium in its hormonal regulation.

EXPERIMENTAL APPROACHES

The hormonal relationships existing in endometriosis have also been investigated under experimental conditions using animals as recipients of endometriosis tissue grafts.

Surgically induced intraperitoneal endometriosis implants in castrated monkeys survived for at least 4 weeks without any hormonal support, but did not grow[7]. At 12 weeks, the implants in untreated animals were atrophic or burnt out, whereas those in monkeys treated with steroid hormones (estrogen, progesterone or their combination) were fresh and viable. The female steroid hormones thus appeared not to be necessary for the initiation of endometriosis, but they were necessary for its maintenance and growth, with no apparent difference prevailing between estradiol alone, progesterone alone or their combination in this respect. In another experiment viable ectopic endometria with a pattern of active growth persisted for up to 37 months in monkeys receiving estrone alone[8].

The necessity for ovarian hormone support to maintain endometriosis was also demonstrated by inducing endometriosis in New Zealand White rabbits by transplanting pieces of endometrial tissue to various sites on the peritoneum[9]. Following the 8-week induction period, the animals were treated with gonadotropin-releasing hormone (GnRH) analog, danazol or oophorectomy. Substantial regression of endometriosis was achieved in each group and it was in inverse relation to the degree of ovarian suppression.

Where these experiments with monkeys and rabbits employed autologous endometrial transplants, the use of homozygous mouse mutants, Nude mice (with a deficient T-lymphocyte system) as receipients for the grafts allows the transplantation of human endometrial tissues[10]. This heterotransplantation of human intrauterine endometrium and ectopic endometriosis tissues was performed subcutaneously. The two tissue types were histopathologically similar after some weeks, resembling human endometriosis tissue, so that the origin of the graft could no longer be identified. The two tissue types also responded to different hormonal stimuli in similar ways. It was typical

for the grafts of both tissue types (normal and ectopic endometrium) to be surrounded and invaded by fibrous tissue in a manner often observed in human endometriosis.

BIOCHEMICAL CHARACTERIZATION

Steroid hormone action in the target cells is transmitted via intracellular estrogen, progestin and androgen receptors, which are also present in the endometriosis tissue (Table 1), as confirmed using the biochemical hormone-ligand binding technique[11–16]. Steroid autoradiography[17], the histochemical fluorescein-labeled steroid hormone-binding technique[18] and immunohistochemistry with monoclonal antibodies to estrogen and progestin receptors[19] have confirmed the presence of these receptors in endometriosis lesions.

The concentrations of estrogen and progestin receptors in the endometriosis tissue were low in relation to the intrauterine endometrium[13,15], a difference which may be due to the replacement of stroma by fibrotic tissue inside and outside endometriosis lesions and/or a real loss of receptors.

Endometriosis tissue estrogen and progestin receptor concentrations and 17-HSD activity (17β-hydroxysteroid dehydrogenase, a progestin-specific enzyme) did not change during the menstrual cycle, as shown in an identical manner using ligand binding techniques[15] or immunohistochemical identification and semi-quantification of estrogen and progestin receptors[19]. This situation is in contrast to that in the normal endometrium, and suggests defects in the intracellular mechanisms transmitting steroid hormone action. In line with these observations, the endometriosis tissue estrogen and progestin receptor concentrations measured by the ligand binding assay and the 17-HSD activity did not change during treatment with danazol, medroxyprogesterone acetate (MPA)[15] or gestrinone[16]. Lessey *et al.*[19], who evaluated the receptors in the stromal and glandular cells separately, observed in four patients that danazol and MPA reduce estrogen and progestin receptor concentrations in both cellular types of endometriosis (Figure 1). The reason(s) for the discrepancies in the results regarding danazol and MPA treatment may be methodological and/or related to the heterogeneity of endometriosis. It is possible that immunohistochemical staining intensity in the untreated patients (controls) had been measured from the freshest, most active endometriosis lesions, possessing estrogen and progestin receptors in relatively high concentrations, and these receptors may have retained their ability to react to steroid hormones. The tissue homogenates used in the

Table 1 Estrogen and progestin receptors in endometriosis tissue

	Estrogen receptors		*Progestin receptors*	
Author	*n*	*%*	*n*	*%*
Tamay *et al.*[11]	7	86	7	86
Bergqvist *et al.*[12]	20	30	9	22
Jänne *et al.*[13]	47	30	47	80
Vierikko *et al.*[15]	52	73	53	94

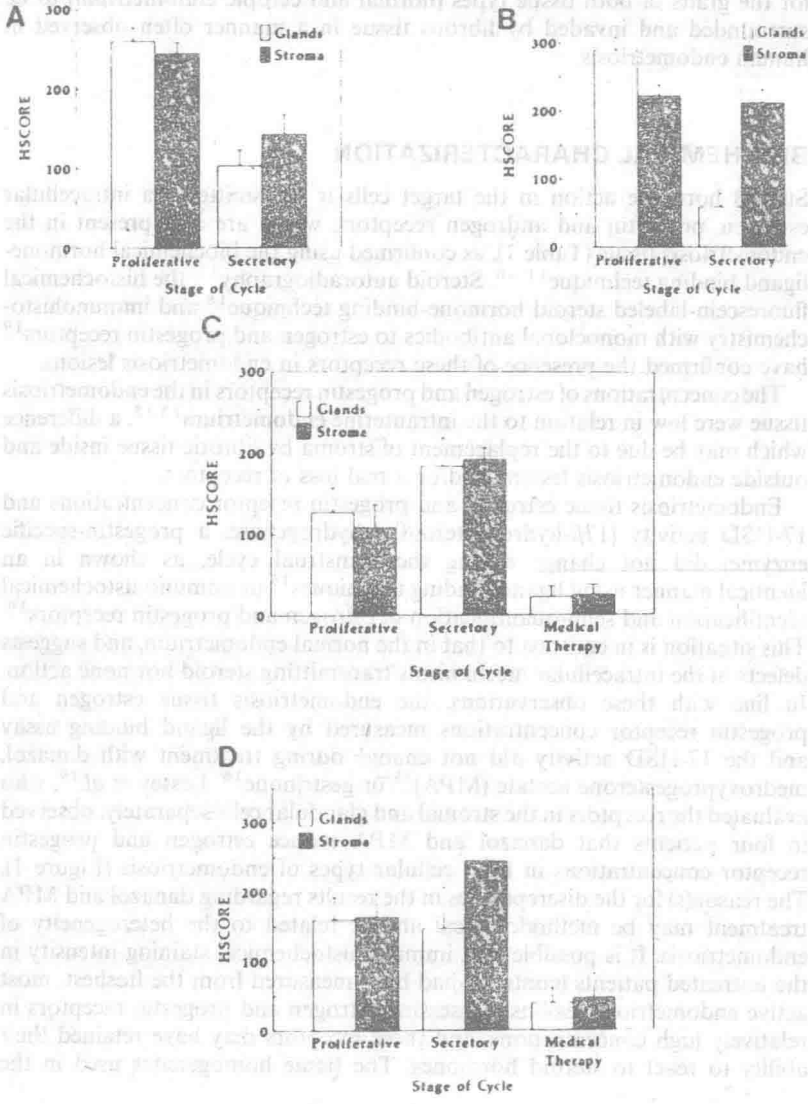

Figure 1 Relationship of estrogen receptor (A) and progestin receptor (B) content of glandular epithelium and stroma to the stage of the cycle in normal endometrium using immunohistochemical analysis and mean HSCORE (± SEM: $n = 34$). Mean HSCORE (a value designated the HSCORE was derived by summing the percentages of cells stained at each intensity multiplied by the weighted intensity of staining) of estrogen-receptor-staining (C) and progestin-receptor-staining (D) in glandular epithelium and stroma in endometriotic implants during the menstrual cycle ($n = 12$) and after medical therapy ($n = 4$), using immunohistochemical staining with H222 antibody and B39 antibody, respectively. The data are from the article of Lessey *et al.*[19]. Reproduced with the permission of the authors and the publisher, the American Fertility and Sterility Society

biochemical method very probably contained predominantly old endometriosis tissue.

The differences between normal endometrium and endometriosis tissue observed in the steroid hormone binding tests are evidently indicative of a difference in hormonal regulation between endometriosis and the normal endometrium.

THERAPEUTIC TRIALS WITH STEROIDAL DRUGS AND GnRH ANALOGS

A large number of uncontrolled trials have shown various progestins, including MPA, danazol, gestrinone and GnRH analogs, to be effective for the treatment of endometriosis as regards alleviation of the symptoms and resolution of the lesions[20]. There are also two recent placebo-controlled trials which evaluated the efficacy of steroidal drugs for this purpose (Tables 2 and 3). Thomas *et al.*[21] demonstrated the ability of gestrinone to eliminate endometriosis lesions or prevent their growth and progression, while other works[22,23] confirmed that danazol and high-dose MPA (100 mg daily) are able to alleviate the clinical symptoms secondary to endometriosis and partly or totally resolve endometriosis lesions in some but not all patients, without any difference being evident between the drugs. The unpredictable responses are possibly related to the heterogenous histomorphology of endometriosis, which consequently leads to different reactions of the lesions to hormonal drugs.

The mechanisms of the action of the steroidal drugs administered for endometriosis are not known exactly. In the normal endometrium, estrogens induce mitogenic cellular changes and proliferative effects, whereas progesterone and synthetic progestins antagonize these actions by suppressing

Table 2 Effects of 6-month therapy with gestrinone[21] on endometriosis lesions. Comparison with placebo. Laparoscopical evaluation before and at the end of therapy

	Disease	
	Eliminated	*Deteriorated*
Gestrinone treatment	61%	0%
Placebo treatment	24%	47%

Table 3 Effects of 6-month therapy with danazol and high-dose MPA[22]. Laparoscopical evaluation before and 6 months after the end of the therapy

	Changes in endometriosis score	*Total resolution*
Danazol treatment	from 35 to 17	33%
MPA treatment (100 mg daily)	from 30 to 17	50%
Placebo treatment	from 26 to 30	12%

estrogen and progestin receptors and causing endometrial atrophy during long-term therapy.

Direct progesterone-mediated endometrial effects, as in the normal endometrium, may be partly responsible for the regression of endometriosis, while another alternative would be ovarian suppression by the hormones, leading to a discontinuation of estrogen support for endometriosis. Ovarian suppression may indeed be the main mechanism in the therapeutic action of the compounds, since the GnRH analog, which achieves a 'biochemical oophorectomy', is as effective as the steroidal drugs for resolving endometriosis implants[20].

The fact that hormonal treatment with drugs inducing endometrial atrophy and/or ovarian quiescence is effective in most patients with endometriosis supplies further arguments to show that ovarian steroid hormones are the dominating factor for the maintenance, growth and resolution of endometriosis. The development of fibrosis in endometriotic implants and the structures surrounding the lesions may reduce the vascularity and detract from the nutritional conditions of the lesion. Morphological changes in the course of endometriosis (replacement of the stroma with fibrous tissue) may regulate the sensitivity of lesions to exogenous hormones[10] and explain the histopathological heterogeneity and unpredictability affecting hormonal treatment.

CONCLUSIONS

It is evident that the hormones regulating the functions of the normal endometrium also control the activity of endometriosis tissue, but there are marked differences between these two endometrial tissue types in the hormonal relationships, as observed in the histopathological and biochemical characterization of endometriosis tissue. Experimental results suggested that the specific stroma of endometrial tissues are crucially important for their capacity to respond to different hormonal influences[10]. Replacement of the stroma by fibrous tissue may explain the histopathological heterogeneity of endometriosis and the unpredictable and varied responses of endometriosis tissue to hormonal therapy.

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