Maturitas 65S (2009) S23–S27

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

The place of dydrogesterone in the treatment of endometriosis and adenomyosis

Karl-Werner Schweppe*

Department of Obstetrics and Gynecology, Ammerland Clinic GmbH, Academic Teaching Hospital of the University of Göttingen, Lange Strasse 28/D-26655 Westerstede, Germany

ARTICLE INFO

Article history:
Received 15 September 2009
Received in revised form 9 November 2009
Accepted 9 November 2009

Keywords:
Endometriosis
Adenomyosis
Progestins
Dydrogesterone
Bleeding disorders

ABSTRACT

Oral progestins have been reported to be effective in the treatment of endometriosis. The mode of action is still a matter of debate, but it may involve modulation of mitotic activity, local growth factors and growth factor receptors, as well as other paracrine mechanisms and anti-inflammatory reactions. Other treatments such as danazol and GnRH-agonists are effective with regard to relief of symptoms and regression of the endometriotic implants, but are associated with high recurrence rates and a wide range of side effects. Progestins are therefore indicated in the symptomatic management of pain, bleeding disorders and other symptoms caused by endometriosis when long-term medication or repeated courses of treatment are indicated. The relationship between costs and efficacy is good, and the side effects are tolerable in most cases. Dydrogesterone is particularly suitable in cases where the woman desires to become pregnant and to prevent bleeding problems. Only very limited data are available concerning the use of progestins in adenomyosis and no conclusions can be drawn.

1. Endometriosis

Oral progestins without an estrogen component were first reported to be effective in the treatment of endometriosis more than 40 years ago. Various progestins have been used, including derivatives of natural progesterone (e.g. dydrogesterone, medroxyprogesterone acetate [MPA]) and C-19-nortestosterone derivatives (e.g. norethisterone, lynestrenol, desogestrel), which have different profiles regarding their potency on the hypothalamic-pituitary axis, their metabolic processes, and their effects on breast tissue and genital organs. The secretory transformation of estrogen-primed uterine endometrium is their common characteristic, an effect for which different dosages are necessary. Progestins reduce the frequency and increase the amplitude of pulsatile gonadotropin-releasing hormone (GnRH) release, which results in a reduction of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion. With the exception of dydrogesterone, continuous application therefore leads to a suppression of ovarian steroidogenesis with anovulation and low serum levels of ovarian steroids. This hypoestrogenic status causes decidual transformation of the eutopic endometrium and also, to some degree, of ectopic lesions. However, in order to induce decidual transformation with resultant necrosis and resorption of the implant, a concomitant estrogen effect is required [1]. As continuous progestin therapy results in low serum estradiol levels, breakthrough bleeding is common.

2. Effects on target tissue

The mode of action of progestins on the endometriotic implant is still a matter of debate. Early studies postulated that the effects were mediated via steroid receptor mechanisms, as observed in the uterine mucosa. Only one study was published, which examined the morphological features of endometriotic implants in 18 patients after treatment with dydrogesterone 20 mg/day for 2–5 months or 60 mg/day for 2 months [2]. Secretory changes in the glands and decidualisation of the stroma were judged as no response in 4 cases; the remaining 14 cases were considered to have had a moderate or good response as shown by a lack of growth and secretion within the ectopic foci (with or without involutionary changes). Later studies, however, raised some doubts about this hypothesis. Endometriotic foci contain only very low, or even non-existent, levels of progesterone receptors [3], and enzyme systems differ widely between eutopic and ectopic endometrial tissues [4]. Progestins reduce the synthesis of their own receptors, which results in diminished sensitivity of the implants during long-term treatment. Morphological studies have revealed different effects after long-term (9 months) progestin treatment, with some implants remaining unchanged, some showing arrested epithelium and some having abortive secretory reactions, although decidual reactions and necrosis were not observed [5]. Comparative ultrastructural examinations between eutopic and ectopic endometrium have also revealed significant differences during the menstrual cycle; changes in the endometriotic foci appear to be delayed compared with the uterine endometrium, with the foci remaining proliferative in the luteal phase [6]. This insensitivity to the influence of progestins (so called progesterone blockage) may

* Tel.: +49 4488 503230; fax: +49 4488 503999.
E-mail address: Schweppe@Ammerland-Klinik.de.

0378-5122/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2009.11.011

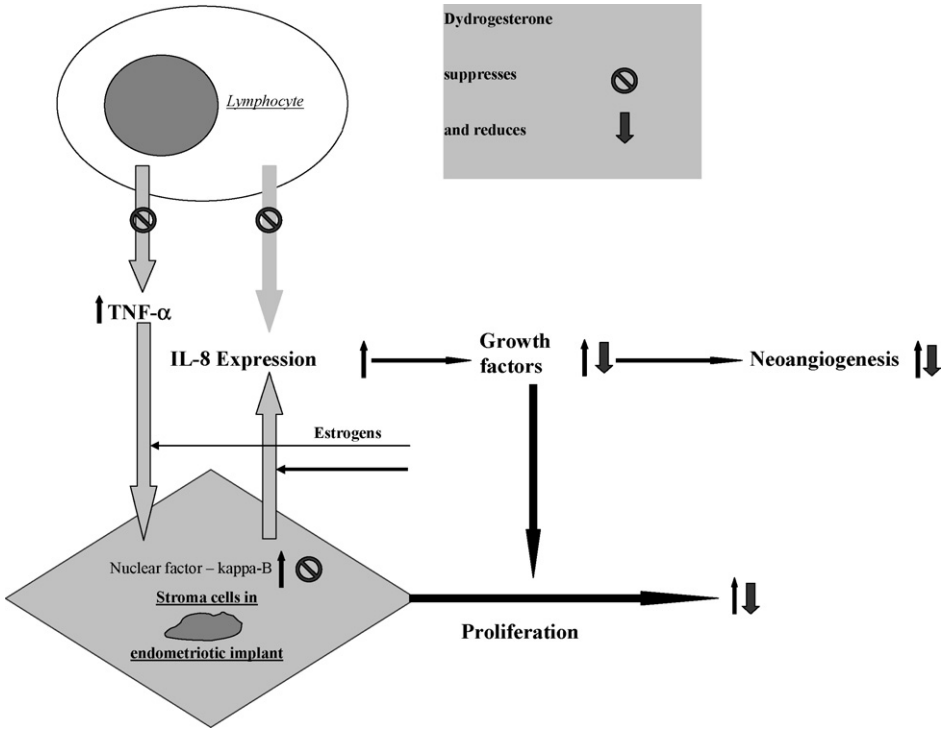

Figure 1. Influence of progestins on TNF-alpha and interleukin-8-induced inflammatory reactions in lymphocytes and proliferation of endometriotic stroma cells [9,10].

be caused by specific changes in enzyme systems [7], in addition to low or reduced receptor concentrations. The enzyme 17β-hydroxysteroid-dehydrogenase type 2 is lacking in endometriotic foci and cannot be activated by progestins. This results in permanent increased proliferation during the menstrual cycle as estradiol is not inactivated [8]. In addition, there is disruption of aromatase activity in ectopic implants. Thus, more estradiol is produced by the endometriotic foci in the conversion of androgens to estrogens.

Inflammatory reactions caused by endometriotic implants are significant in disease progression and cause pain symptoms. An anti-inflammatory mechanism by which the growth of endometriosis is controlled by progesterone and progestins has recently been proposed by Horie et al. [9]. Tumor necrosis factor (TNF)-alpha and estradiol induce the proliferation of endometriotic stroma cells via nuclear factor (NF)-kappa-β, whereas progestins reduce TNF-alpha-induced NF-kappa-β activation (Fig. 1). Dydrogesterone has also been shown to modulate immune responses via suppression of interleukin (IL)-8 production in lymphocytes [10]. The increase in nitric oxide production seen with dydrogesterone may also play an important anti-inflammatory role [11].

To date, details regarding the mechanism of action and the morphological changes induced by progestins are only partly understood. Moreover, it remains unclear as to whether the mode of action varies between the different types of progestins.

3. Clinical experiences

Oral administration of various progestins in low dosages (5–60 mg/day) has been shown to have a range of beneficial effects. In general, these results do not differ considerably from those achieved with combined estrogen–progestin therapy (i.e. continuous oral contraceptives). However, progestins have an advantage over combined treatment in that they avoid estrogen-induced side effects. These mainly constitute spotting and bleeding problems, which may be managed by increasing the dosages, giving additional estrogen medication or interruption of treatment for 5–7 days.

Dydrogesterone was first reported to be effective in endometriosis in the 1960s [12]. In this small study involving 13 patients, some improvement was reported in 70% of women. Overall success rates of around 90% were also reported in other small studies and clinical case reports [13–16]. The most important studies assessing the use of oral dydrogesterone for the management of endometriosis are summarized in Table 1 [17–23]. These studies used dydrogesterone at doses of between 10 and 60 mg/day, for various numbers of days per cycle, and were conducted over periods of 3–9 months. The majority of women became symptom-free or experienced a significant reduction in the number/severity of symptoms. Laparoscopic examination in several of the studies supported these findings. Cyclic application of dydrogesterone has also been shown to induce regular menstruation with reduced blood loss and fewer days of bleeding, combined with excellent symptomatic relief, in women suffering from dysmenorrhea [24–29]. Table 2 summarizes the improvement in pain reported in these studies.

Other oral progestins have also been evaluated in women with endometriosis. For example, dienogest 2 mg/day resulted in a significant reduction in endometriosis-related pain [30]. However, spotting was reported in 95% of cases, and this persisted in 60% of women even with increased dosages of 4 and 6 mg/day. In the same study, norethisterone acetate 10 mg/day was associated with breakthrough bleeding and spotting in 25% of women. In a randomized trial of MPA, Telimaa et al. [31] reported a 50% regression rate of ectopic implants and 13% partial regression with scar formation in the treatment group compared with rates of 12% and 6%, respectively, in the placebo group. Similar results were demonstrated in a randomized study comparing high dose medrogestone with danazol [32].

Depot injections are an alternative to oral administration. Intramuscular and subcutaneous injections of MPA given every 3 months have been shown to be very effective in suppressing the signs and symptoms of endometriosis [33–35]. However, a significant drawback to the use of depot preparations is the occasionally prolonged interval to resumption of ovulatory cycles after treatment discontinuation. This mode of administration is therefore