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Progestogens for endometriosis: forward to the past

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We performed a MEDLINE and EMBASE search to identify all studies published in the last decade in the English language literature on the use of progestogens for the treatment of endometriosis. Our aim was to clarify the biological rationale for treatment and define the drugs that can be used with their doses, routes of administration, efficacy and tolerability. Progestogens may prevent implantation and growth of regurgitated endometrium inhibiting expression of matrix metalloproteinases and angiogenesis, and they have several anti-inflammatory in-vitro and in-vivo effects that may reduce the inflammatory state generated by the metabolic activity of the ectopic endometrium, and the consequent immune response. Oral contraceptives increase the abnormally low apoptotic activity of the endometrium of women with endometriosis. Moreover, anovulation, decidualization, amenorrhoea and the establishment of a steady estrogen–progestogen milieu contribute to disease quiescence. Progestogens are effective in the control of pain symptoms in approximately three out of four women with endometriosis. Their effect does not seem to be inferior to that of other drugs used for the disease. Different compounds can be administered by the oral, intramuscular, subcutaneous, intravaginal or intrauterine route, each with specific advantages or disadvantages. Medical treatment plays a role in the therapeutic strategy when administered over a prolonged period of time. Given their good tolerability, minor metabolic effects and low cost, progestogens must therefore be considered drugs of choice and are currently the only safe and economic alternative to surgery. However, their contraceptive effectiveness limits their use to women who do not wish to have children in the short term.

Key words: endometriosis/oral contraceptives/pelvic pain/progestogens

Introduction

Drugs used in the treatment of endometriosis are not cytoreductive (Prentice, 2001), which belies the common conviction that, if a treatment determines a sufficiently deep hypo-estrogenism and is administered for an adequate period of time, it may induce necrosis, resorption and disappearance of ectopic endometrial foci. However, this cannot be true as quiescent implants have been demonstrated in nearly all women treated with danazol, GnRH agonists and progestogens (Nisolle-Pochet *et al*., 1988). At restoration of ovulation and of physiological levels of estrogens, the endometrium, both eutopic and ectopic, resumes its metabolic activity. As a consequence, medical therapy is symptomatic and pain relapse at treatment suspension is the rule (Vercellini *et al*., 1997a).

Drugs that are administered for relatively few months only, due to their poor tolerability, severe metabolic side-effects or high cost, do not greatly benefit women with symptomatic endometriosis. Progestogens alone or combined with estrogens are instead generally well-tolerated, have a more limited metabolic impact than danazol or GnRH agonists, are inexpensive and may be used on a long-term basis (Vercellini *et al*., 1997a; Moore *et al*., 2003; Prentice *et al*., 2003).

After more than 20 years on the sidelines, progestogens are gradually regaining popularity as a treatment for endometriosis. Hence we considered it interesting to perform a review of the most recent biological and clinical studies on the topic published in the last decade. Reports that appeared before 1993, generally deemed of suboptimal quality, are considered in a previous overview (Vercellini *et al*., 1997a). A qualitative and quantitative analysis of comparative trials with pooling of results is not among the aims of the present narrative review, and reference is suggested to the Cochrane Collaboration meta-analyses (Moore *et al*., 2003; Prentice *et al*., 2003).

Materials and methods

Several different strategies were adopted to identify all English language medical papers published on progestogen treatment for

Table I. Experimental biological effects of progestogens used for the treatment of endometriosis: literature data, 1993–2003

Drug	Biological effects	Source
Medroxyprogesterone acetate	Inhibition of angiogenesis via stimulation of plasminogen activator inhibitor synthesis *in vitro*	Blei *et al*. (1993)
	Progesterone receptor-mediated down-regulation of endometrial RANTES gene transcription *in vitro*	Zhao *et al.* (2002)
	Inhibition of nuclear factor K-B transcription activity *in vitro*	
Dienogest	Normalization of peritoneal fluid cell number *in vivo*	Katsuki *et al*. (1998)
	Decrease in peritoneal macrophages interleukin-1β production *in vivo*	
	Increase in peritoneal fluid cells natural killer activity *in vivo*	
	Inhibition of rat endometrial cell protein kinase C activity *in vitro*	
	Inhibition of angiogenesis *in vivo*	Nakamura *et al*. (1999)
	Induction of prolactin production by human endometrial stromal cells *in vitro*	Okada *et al*. (2001)
	Inhibition of proliferation of human endometrial stromal cells *in vitro*	
Oral contraceptive[a]	Decreased expression of Ki-67 protein in the eutopic endometrium of women with endometriosis	Meresman *et al*. (2002)
	Increased endometrial apoptosis in women with endometriosis	
	Decreased expression of Bcl-2 and increased expression of Bax in the eutopic endometrium of women with endometriosis	

[a]Desogestrel 0.15 mg + ethinyl estradiol 0.03 mg.
RANTES = regulated on activation, normal T-cell expressed and secreted; Bcl-2 = B cell lymphoma/leukaemia-2.

endometriosis. We conducted a MEDLINE and an EMBASE search from January 1993 to March 2003 using combinations of medical subject heading terms: endometriosis, pelvic pain, dysmenorrhoea, dyspareunia, progestogens, oral contraceptives, and medical therapy. All pertinent articles were retrieved and additional reports were then identified by systematically reviewing all references. In addition, books and monographs on endometriosis published in the last 10 years were consulted. Proceedings of scientific meetings were also included.

Two authors (G.P. and G.F.) abstracted data on standardized forms. An initial screening of the title and abstract of all articles was performed to exclude citations deemed irrelevant by both observers. The year of publication, type and design of the study, experimental setting, clinical characteristics of subjects, and treatment schedule were recorded.

In the biological section, only studies on novel anti-inflammatory or immunomodulatory effects were considered, excluding those focusing on the already well-known properties of progestogens in terms of progesterone receptor-inducing and anti-mitotic activities, as well as induction of secretory changes and decidualization. The search was limited to progestogens currently used in the treatment of endometriosis. In the clinical section, only the effect on pain were considered, as it has been repeatedly and definitively demonstrated that there is no beneficial effect of any medical therapy on endometriosis-associated infertility (Candiani *et al*., 1990; Hughes *et al*., 1993; Olive and Pritts, 2001).

Results

Biological rationale for the use of progestogens in the treatment of endometriosis (Table I)

Progestogens may inhibit the implantation and growth of regurgitated endometrium via various biological mechanisms. During the menstrual cycle in response to serum level variations of ovarian steroids, the endometrium produces various bioactive growth factors and cytokines, which are essential elements of paracrine communication. The latter determines the expression of matrix metalloproteinases (MMP), enzymes which mediate tissue remodelling during the menstrual cycle. Endometriotic disease arises as a consequence of retrograde menstruation, and MMP seem to contribute to the implantation and growth of ectopic endometrium in the peritoneal cavity. Although the risk of developing endometriosis is generically associated with exposure to ovarian steroids, paracrine factors produced locally may modify steroidal action on multiple genetic targets, including MMP (Osteen *et al*., 2002). Growth factors associated with estrogens and inflammatory cytokines stimulate intensely the expression of MMP and can add to the capacity of endometrial fragments for invading the peritoneal surface and establishing ectopic implants. Contrarily, paracrine factors associated with the effect of progesterone during initial pregnancy inhibit expression of MMP and, in an experimental model, prevent growth of ectopic endometrium (Osteen *et al*., 2002).

Once implanted, ectopic endometrium produces angiogenetic factors to induce the formation of new capillaries from existing vessels. In the adult, angiogenesis is limited to few tissues, including uterus and ovaries, but occurs commonly during tumour growth and in other diseases such as endometriosis. The first step of angiogenesis involves local degradation of the basement membrane and extracellular matrix by proteolytic enzymes such as plasminogen activator and MMP as described above (Hyder and Stancel, 1999). An anti-angiogenetic action of medroxyprogesterone acetate (MPA) has been repeatedly demonstrated. In fact, MPA suppresses plasminogen activator activity by means of stimulation of plasminogen activator inhibitor synthesis (Blei *et al*., 1993; Schatz and Lockwood, 1993) (Table I).

Dienogest is a synthetic steroid used as a progestogen in oral contraceptive (OC) pills and its possible clinical application in the treatment of endometriosis is currently being studied. In an experimental model, it has been demonstrated that dienogest also inhibits angiogenesis (Nakamura *et al*., 1999), reduces the volume of autologous transplanted endometrium in rats, increases the natural killer activity of peritoneal fluid cells, decreases the number of inflammatory peritoneal fluid cells, and decreases interleukin-1β production by peritoneal macro-

phages (Katsuki *et al*., 1998). Furthermore, Okada *et al*. (2001) analysed the direct effects of dienogest in the differentiation and proliferation of in-vitro human endometrial stromal cells. After 12 days in the presence of œstradiol and dienogest, the endometrial stromal cells have shown morphological differentiation and started to produce prolactin, a typical marker of decidualization. Prolactin production induced by dienogest is dose-dependent and is almost completely inhibited by the addition of RU 486, a progesterone antagonist. Furthermore, as demonstrated by the uptake of thymidine, dienogest causes a dose-dependent inhibition of stromal endometrial cell proliferation. This inhibitory effect is partially abolished by RU 486.

Once the regurgitated endometrium has disrupted the peritoneal basal membrane, reached the submesothelial collagen matrix, and induced angiogenesis, it resumes its metabolic activity, generating an inflammatory condition. An inflammatory pelvic exudate is a common finding in women with endometriosis and is expressed as an increase in the volume of peritoneal fluid as well as in number of leukocytes, and an elevated concentration of proteases. Haney and Weinberg (1988) were the first to prove the anti-inflammatory action of progestogen therapy. In 16 infertile women with endometriosis, administration of 30 mg/day of MPA for 4 months significantly reduced the volume of the peritoneal fluid, the number of leukocytes and the revised American Fertility Society (R-AFS) classification (American Fertility Society, 1985).

The anti-inflammatory properties of MPA in women with endometriosis may be due to reduction of chemokine synthesis. RANTES (regulated on activation, normal T-cell expressed and secreted) is a chemokine synthesized by stromal eutopic and ectopic endometrial cells, circulates in the peritoneal fluid, and acts as a chemoattractant for monocytes and activated T cells, the two predominant leukocytes in peritoneal fluid of women with endometriosis (Zhao *et al*., 2002). Indeed, RANTES concentration and bioactivity are elevated in peritoneal fluid of patients with the disease. The prolonged administration (8 days) of MPA to cultures of endometrial stromal cells causes a reduction of 36% in luciferase activity and of 50% in RANTES protein synthesis, whereas a briefer treatment (2 or 4 days) does not produce significant effects. The administration of MPA for 8 days increases expression of progesterone receptor (PR). Both effects are blocked by RU 486. A prolonged progestogen exposure induces a down-regulation of gene transcription of in-vitro endometrial RANTES. Such an effect is PR-dependent and is partially mediated by a nuclear factor (Zhao *et al*., 2002). According to Zhao *et al*. (2002), the efficacy of progestogen therapy in endometriosis-associated pelvic pain could therefore be due to inhibition of RANTES production and suppression of the pelvic inflammatory response.

The effect of OC on regulation of in-vitro endometrial cell growth has recently been studied by Meresman *et al*. (2002) in biopsy specimens obtained from 13 women with endometriosis and 13 controls. Apoptosis (or programmed cell death) of the endometrium is regulated by steroid hormones and is controlled by the expression of several regulatory genes. The proto-oncogene B cell lymphoma/leukaemia-2 (Bcl-2) blocks apoptosis, whereas the Bax protein antagonizes its survival activity. The Bcl-2/Bax ratio predetermines susceptibility of cells to apoptotic inducers. Eutopic epithelial and stromal endometrial cells from patients with endometriosis show an augmented survival capability probably caused by an abnormally high effect of Bcl-2. Exposure to a monophasic OC for 30 days significantly increases endometrial apoptosis in comparison with pre-treatment levels, both in epithelial and stromal cells, producing values similar to those observed in the endometrium from women controls without endometriosis (Meresman *et al*., 2002). In fact, OC administration reverses the abnormal increment in Bcl-2 expression in patients with endometriosis, and induces a major increase in the Bax protein expression. Furthermore, endometrial cell proliferation in subjects with the disease is significantly reduced by exposure to an OC.

The anti-angiogenetic, anti-inflammatory and immunomodulatory effects, down-regulation of endometrial cell proliferation and increase in apoptotic activity, all constitute a convincing rational basis for the use of progestogens, alone or combined with estrogens, in the treatment of endometriosis.

Clinical effect of progestogens and estrogen–progestogens in women with symptomatic endometriosis (Table II)

Oral route

Medroxyprogesterone acetate. MPA is a 17-hydroxy derivate progestogen with moderate androgenic activity and minor effects on the lipoproteic asset. Its oral use in the treatment of symptomatic endometriosis has recently been evaluated in two randomized controlled trials.

Harrison and Barry-Kinsella (2000) allocated 100 infertile women with endometriosis to treatment with MPA 50 mg/day for 3 months or placebo. No difference between groups was detected in score variations of the R-AFS classification (American Fertility Society, 1985) at repeat laparoscopy at the end of therapy. Six pregnancies occurred in the placebo group and one in the MPA group. However, pain symptoms were reduced more significantly in the latter group than in the former. In addition, 85% of symptomatic women allocated to MPA deemed such therapy effective in improving overall well-being, versus 41% in those allocated to placebo. Both groups reported minimal side-effects (in 10% of the MPA-treated patients and 2% of the ones given placebo).

In a double-blind, double-dummy study, Bergqvist and Theorell (2001) compared a 6 month treatment with nasal nafarelin, 400 μg/day versus oral MPA, 15 mg/day. Of the 48 women initially recruited, 18 dropped out (six in the nafarelin group, 12 in the MPA group) principally due to anxiety–depressive disturbances. The results showed a considerable reduction in pain symptoms scores with no significant differences between study groups. The anxiety depression score worsened during use of nafarelin. All other psycho-social parameters as well as overall emotional balance improved

Table II. Options for treatment of symptomatic endometriosis with progestogens or estroprogestogens: literature data, 1993–2003

Drug	Schedule	Pain relief[a]No. (%)	Main side-effects (%)	Source
Medroxyprogesterone	50 mg/day p.o. for 3 months	35/40 (87)	Localized pain, acne, acetate, vasodilatation (7)	Harrison and Barry-Kinsella (2000)
	30 mg/day p.o. for 6 months	NR	NR	Bergqvist and Theorell (2001)
	150 mg/3 months i.m. for 12 months	36/40 (90)	Spotting (65), bloating (63), weight gain (53)	Vercellini *et al.* (1996)
Cyproterone acetate	10 mg/day p.o. for 20 days/cycle for 6 months	7/7 (100)	Oligomenorrhoea (86), spotting (14)	Moran *et al.* (1996)
	12.5 mg/day p.o. for 6 months	34/45 (75)	Bloating (32), spotting (28), weight gain (19)	Vercellini *et al.* (2002)
Dydrogesterone	40 mg/day p.o. for 12 days/cycle for 6 months	4/11 (36)	NR	Overton *et al.* (2000)
	60 mg/day p.o. for 12 days/cycle for 6 months	7/10 (70)	NR	
Dienogest	2 mg/day p.o. for 6 months	18/29 (62)	Acne (38), hot flushes (24), headache (17)	Moore *et al.* (1999)
	4 mg/day p.o. for 6 months	18/35 (52)	Acne (31), hot flushes (23), breast tenderness (20)	
	2 mg/day p.o. for 6 months	88/101 (87)	Loss of libido (21), fatigue (10), increased appetite (9)	
	2 mg/day p.o. for 6 months	88/97 (91)	Increased appetite (37), loss of libido (34), hot flushes (19)	
Lynestrenol	10 mg/day p.o. for 6 months	11/22 (50)	Hot flushes (59), sweating (41), acne (23)	Regidor *et al.* (2001)
Norethisterone acetate	5 mg/day p.o. for 6 months increasing by 2.5 mg up to 20 mg/day	48/52 (92)	Breakthrough bleeding (58), breast tenderness (12), weight gain (6)	Delale and Muneyyirci-Karacan (1998)
	10 mg/day p.o. for 6 months	46/48 (96)	NR	Moore *et al.* (1999)
Tibolone	2.5 mg/day p.o. for 12 months	10/11 (91)	NR	Fedele *et al.* (1999)
Nestorone[b]	150 µg/day for 7 months, s.c. implant	NR	NR	Ylänen *et al.* (2003)
	200 µg/day for 7 months, s.c. implant	NR	NR	
	400 µg/day for 7 months, s.c. implant	NR	NR	
Levonorgestrel	20 µg/day IUD for 12 months	12/20 (60)	Bloating (35), weight gain (25), headache (20)	Vercellini *et al.* (1999)
	20 µg/day IUD for 12 months	11/11(100)	Headache (36), breast tenderness (36), weight gain (36)	Fedele *et al.* (2001)
OC[c]	Cyclic administration p.o. for 6 months	17/23 (74)	Spotting (25), headache (21), breast tenderness (18)	Vercellini *et al.* (1993)
OC[d]	Cyclic administration p.o. for 12 months	32/46 (70)	NR	Parazzini *et al.* (2000)

[a]The rate of dysmenorrhoea at the end of treatment is considered or, if this was not reported, of any pelvic pain.
[b]The overall pain relief rate, after pooling of data from the three study groups, is 81%. Crude numbers are not reported.
[c]Desogestrel 0.15 mg + ethinyl estradiol 0.02 mg.
[d]Gestodene 0.75 mg + ethinyl estradiol 0.03 mg.
p.o. = post-operative; NR = not reported.

during the study period with no significant differences between groups.

Evidence that MPA is more efficacious than placebo but no less efficacious than GnRH agonists in reducing pain and in improving health-related quality of life, suggests its use in women with symptomatic endometriosis. However, erratic bleeding episodes may be more frequent and prolonged with MPA compared with other progestogens. Furthermore, the optimal dosage of the drug still needs to be determined.

Cyproterone acetate (CPA). This derivative of 17-hydroxyprogesterone, with anti-androgenic and anti-gonadotrophic properties, was first used in the treatment of endometriosis by Fedele *et al*. (1989) at the dosage of 27 mg/day.

Subsequently Moran *et al*. (1996) evaluated the efficacy of a 6 month treatment with CPA at a reduced dosage (10 mg/day for 20 days followed by 10 days with no treatment) in seven women affected by mild-to-severe symptomatic endometriosis. Dysmenorrhoea was considerably relieved in all the subjects, with oligomenorrhoea reported by six and spotting by one. A repeat laparoscopy at the end of treatment demonstrated minimal residual lesions in five women and absence of disease in two.

A similar dosage (12.5 mg/day) but administered continuously was recently tested by Vercellini *et al*. (2002) in a randomized study that compared its effects to those of an OC, (desogestrel 0.15 mg and ethinyl estradiol 0.02 mg) given continuously for 6 months. Ninety women were recruited with moderate-to-severe pelvic pain that recurred after conservative surgery for symptomatic endometriosis. The main outcome of the study was patients' degree of satisfaction, which was deemed important in order to be able to consider their point of view in the evaluation of drug efficacy, as well as the impact of side-effects. Six women in the CPA arm and nine in the OC arm dropped out due to side-effects (n = 9), treatment inefficacy (n = 4), or loss to follow-up (n = 2). At 6 months, dysmenorrhoea, deep dyspareunia and non-menstrual pelvic pain were considerably reduced. In addition the health-related quality of life, psychological profile and sexual satisfaction improved significantly, with no major differences between groups. Metabolic and subjective side-effects were limited. According to an intention-to-treat analysis, 33/45 (73%) women in the CPA group and 30/45 (67%) in the OC group were satisfied with the treatment received. Both schemes used have therefore been shown to be an effective, safe and inexpensive treatment for pain recurring after conservative surgery for endometriosis. CPA may be used when subjective and metabolic effects of estrogens need to be avoided, or in women unwilling to use contraception because of cultural or religious objections. On the other hand, the continuous use of a low dose monophasic OC is most probably the preferred option to prevent the effects of estrogen deprivation in women for whom a long period of therapy is expected.

Dydrogesterone. Overton *et al*. (1994) studied dihydrogesterone administered according to an atypical modality for the treatment of symptomatic endometriosis. They considered that continuous administration of progestogens inhibits ovulation, thus excluding therapy for all women wanting children. A triple-arm randomized study was designed, which considered 43 women wanting children allocated to dihydrogesterone 40 mg/day or 60 mg/day or to placebo administered for 12 days/cycle in the post-ovulatory phase for 6 months. Combining the results obtained with both doses of progestogen, dihydrogesterone did not prove more effective than placebo in reducing pain symptoms during treatment [odds ratio (OR) 0.8; 95% confidence interval (CI), 0.2–3.3] or at the end of the 12 month follow-up (OR 1.2; 95% CI, 0.2–5.6). Such results confirm that continuous oral progestogen therapy, by suppressing ovulation and creating a stable hormonal milieu, is essential in order to achieve a satisfactory analgesic response.

Dienogest. Dienogest is the first of the so-called hybrid progestogens that, based on their unique chemical structure, combine pharmacodynamic properties typical of progesterone derivatives (i.e. excellent tolerability, anti-androgenic action, diminished anti-gonadotrophic effect, a primarily peripheral modality of action, dosage in the range of milligrams) with those of modern 19-norprogestins that have a 17α-ethinylic group (strong progestogen action on the endometrium, short half-life, high bioavailability after oral administration, low hepatic, toxicological and genotoxicological impact, and adequate control of uterine bleeding if combined with œstrogens) (Foster and Wilde, 1998; Oettel *et al*., 1999; Zimmermann *et al*., 1999). Dienogest does not accumulate in serum although high serum concentrations are obtained after oral administration of only 2 mg, and does not reduce sex hormone-binding globulin (SHBG) serum levels (Kuhl, 1996).

Data on the efficacy of dienogest in the treatment of symptomatic endometriosis are scanty. Moore *et al*. (1999) collected the results of three clinical studies conducted on a total of 267 patients with symptomatic endometriosis A 6 month treatment with dienogest at the oral dose of 2–4 mg/day was shown to be as effective as danazol, GnRH agonists and other progestogens in terms of improving dysmenorrhoea and pelvic pain, as well as regression or disappearance of endometriotic implants. According to the authors, the advantage of dienogest lies in its safe profile, which includes good tolerability and fewer side-effects compared with most treatments commonly used.

Dienogest seems to constitute a promising alternative in the therapeutic horizon for patients with endometriosis. Nonetheless, in order to draw final conclusions there is a need for more robust data originating from adequately designed clinical studies.

Lynestrenol. Effects of a 6 month treatment with the progestogen lynestrenol (10 mg/day post-operatively) were compared with those of the GnRH leuprolide depot formulation (3.75 mg monthly s.c. injections) in a randomized study conducted on 48 women who had undergone operative laparoscopy for endometriosis (Regidor *et al*., 2001). The GnRH agonist produced a more pronounced regression of lesions and of R-AFS scores (American Fertility Society, 1985) at a repeat laparoscopy, a deeper hypo-estrogenism (mean serum 17β-oestradiol levels, 28 ± 9 versus 43 ± 59 pg/ml), as

well as a greater reduction of dysmenorrhoea, dyspareunia and chronic pelvic pain compared with the progestogen. Because treatment with leuprolide cannot be prolonged for more than a few months, the authors suggest the use of lynestrenol as a second-line drug to maintain the beneficial effects obtained with the GnRH agonist.

Norethisterone acetate. Norethisterone acetate (or norethindrone acetate, NETA) is a strong progestogen derivative of 19-nortestosterone. Its efficacy was studied by Muneyyirci-Delale and Karacan (1998) in 52 women with symptomatic and laparoscopically confirmed endometriosis. NETA was started at the beginning of the menstrual cycle at a daily dose of 5 mg, which was increased by 2.5 mg up to 20 mg/day until amenorrhoea was achieved. Treatment was continued for 6 months to >1 year. Dysmenorrhoea regressed in 48/52 (92%) subjects and chronic pelvic pain in 25/28 (89%). At the end of treatment, 49/52 (94%) women had few or no symptoms. Breakthrough bleeding was experienced by 30 (58%) patients, causing four (8%) to drop out. One other patient suspended therapy for severe breast tenderness, and three patients for inefficacy. Overall, treatment was successful in 44/52 (84%) recruited subjects.

Moore *et al*. (1999) compared the effect of a 6 month oral treatment with dienogest 2 mg/day (n = 119) versus NETA 10 mg/day (n = 48). Pain relief at the end of therapy was similar, being obtained in 88/97 (91%) of the former group and 46/48 (96%) of the latter.

NETA offers various advantages for the long-term treatment of endometriosis. This progestogen allows good control of uterine bleeding as compared with other compounds, has a positive effect on calcium metabolism by producing greater increases in bone mineral density than alendronate, and at low dosages has no negative effects on the lipoprotein profile (Riis *et al*., 2002).

NETA administered continuously to treat endometriosis is approved by the United States Food and Drug Administration and the Italian Ministry of Health.

Tibolone. Tibolone is a synthetic steroid with weak estrogenic, progestinic and androgenic activity. The effect of tibolone on the endometrium is inhibitory, as the progestinic–androgenic activity is prevalent. *In vitro*, tibolone is metabolized by endometrial Δ_4 isomerase/dehydrogenase to its Δ_4 metabolite, which is characterized by strong progestinic activity. This explains its endometrial tissue-specific progestinic effect as well as a positive effect on calcium metabolism.

Fedele *et al*. (1999) compared the effects of treatment with transdermal estradiol (50 mg twice weekly ± cyclic MPA 10 mg/day) to those of tibolone (2.5 mg/day p.o.), given for a minimum of 12 months to 21 women with residual pelvic endometriosis after bilateral oophorectomy with or without hysterectomy. Residual endometriosis was found in the bowel wall in four subjects, in the rectovaginal septum in six and deep in the retroperitoneal pelvic space in six. All women were symptomatic before definitive surgery. Moderate-to-severe pain recurred in four subjects in the transdermal estradiol arm versus one in the tibolone arm. These results suggest that tibolone may be considered the drug of choice as postmenopausal replacement treatment for women with pelvic endometriosis. In addition, tibolone may constitute an optimal choice as add-back therapy in selected candidates for prolonged treatment with GnRH agonists (Lindsay *et al*., 1996).

Intramuscular route. The depot formulation of MPA (DMPA) has been widely evaluated for contraceptive purposes and is currently being used by ~12 million women worldwide (Kaunitz, 1994). The administration modality is extremely convenient and consists of a single 150 mg intramuscular injection every 3 months. The increase in risk of breast cancer in users of DMPA is not superior to that of OC (Skegg *et al*., 1995). Literature data do not suggest that depressive symptoms may develop or worsen during use of DMPA (Westhoff *et al*., 1995) whereas there is conflicting evidence regarding the development of bone demineralization secondary to hypoestrogenism in chronic users.

Results from the first formal study on the use of DMPA in patients with endometriosis were published by Vercellini *et al*. (1996). The progestogen was compared with an association of a monophasic oral contraceptive with low dose danazol (50 mg/day). After a 1 year treatment, 29/40 women (72%) allocated to DMPA were satisfied versus 23/40 (57%) of those randomized to receive the OC plus danazol. A significant reduction in pain symptoms evaluated with a visual analogue and multidimensional scale has been observed in both groups. However, patients in the combined OC/danazol group complained of a greater frequency and severity of dysmenorrhoea, which is a logical consequence of cyclic administration. Both treatments induced a similar, significant reduction in serum high density lipoprotein (HDL) cholesterol levels, whereas an increase in low density lipoprotein (LDL) cholesterol levels was only observed in subjects allocated to the OC plus danazol treatment. The incidence of side-effects was greater in DMPA users. In these, the mean delay in appearance of a regular menstrual cycle after suspension was 7 months to a maximum of 1 year.

The efficacy of DMPA as a therapy for endometriosis was recently confirmed in a non-controlled study on 19 patients with severe symptomatic disease (Arowojolu, 2000). In addition to the substantial reduction in pain symptoms, DMPA induced a significant regression of ectopic foci at follow-up laparoscopy, with complete resolution of visible implants in 66% of study subjects.

DMPA is an effective, safe, and extremely economic alternative for the treatment of symptomatic endometriosis. However, because of some of its characteristics, candidates for treatment need to be selected carefully. In fact, prolonged delay in resumption of ovulation is a contraindication to use of DMPA in women wanting children in the near future. Additionally, uterine breakthrough bleeding may be prolonged, repeated and troublesome to correct. Furthermore, treatment cannot be interrupted in the event of side-effects, rendering clinical management complicated when these are severe or scarcely tolerable. Its indication of choice is residual symptomatic endometriosis following definitive surgery. In such

circumstances, there are no problems regarding conception or irregular uterine bleeding, and use of DMPA allows a simple and well-tolerated suppression of persistent foci after non-radical operations with no need to opt for daily administration of drugs or further surgery.

Subdermal route

Nestorone® is a synthetic progestogen proposed for contraception. It is used parenterally as it is almost inactive after oral administration. It is devoid of androgenic side-effects and it inhibits ovulation when delivered by transdermal implants or vaginal ring. Large doses of Nestorone suppress ovulation and determine hypo-oestrogenism. Ylänen *et al*. (2003) allocated 21 patients with symptomatic endometriosis after conservative surgery to treatment with Nestorone subdermal implants for 7 months at the dose of 150 μg/day ($n = 7$), 200 μg/day ($n = 7$), or 400 μg/day ($n = 7$). The implants were removed due to persistent bleeding and pain in one case only. Two other subjects requested removal for non-medical reasons. Amenorrhoea was achieved in only four of the women, and spotting was the rule in the others. Relief of menstrual pain was reported by 81% of the patients, without significant differences in pain score reductions between the three study groups. Most of the women experienced side-effects (insomnia, depression, mood changes, in 57%; hot flushes, sweating, vaginal dryness, in 45%; acne in 38%; headache in 29%). Improved general well-being was reported by 48% of the subjects, no change by 29%, and deterioration by 24%. No significant changes were observed in total, HDL and LDL cholesterol serum concentration. One month after treatment withdrawal, pain scores approached the baseline values.

Although Nestorone has a beneficial effect on pain associated with endometriosis, the need for insertion of multiple subdermal implants (and hence subsequent removal), together with the high incidence of side-effects during treatment, may limit its popularity as a long-term treatment for endometriosis.

Intrauterine route

Dysmenorrhoea is by far the most frequent symptom reported by patients with endometriosis. Menstrual pain is obviously abolished during amenorrhoea secondary to medical treatments that induce anovulation and hypo-estrogenism. However, when side-effects or poor tolerability require interruption of oral or parenteral drug therapies, pain symptoms frequently recur. Consequently, the identification of safe and effective alternatives to prolong treatment constitutes an essential element in the current clinical research on symptomatic endometriosis. In this regard, the possibility of aiming the therapeutic action of drugs at specific organs, thus reducing the general metabolic impact, is a subject of great interest. An intrauterine device (IUD) releasing 20 μg/day of levonorgestrel, a potent progestogen derived from 19-nortestosterone, may induce amenorrhoea in different ways compared with standard treatments and may relieve menstrual pain. In fact, the local administration of levonorgestrel has a profound effect on the endometrium, which becomes atrophic and inactive, although ovulation is generally not suppressed.

Vercellini *et al*. (1999) inserted a levonorgestrel IUD in 20 parous women who had recurrent moderate or severe dysmenorrhoea after conservative surgery for endometriosis and did not want more children. One IUD was expelled and one was removed because of intolerable side-effects. One woman was lost to follow-up. The menstrual pattern in the remaining 17 subjects was characterized by amenorrhoea in four cases, hypomenorrhoea or spotting in eight, and normal flow in five. Blood loss was measured with a semiquantitative method and was decreased during the 12 months of study, as was dysmenorrhoea which was evaluated according to visual analogue and verbal multidimensional scales. Four women were very satisfied with treatment, 11 were satisfied, two were uncertain, and three were dissatisfied.

A levonorgestrel IUD was recently used also in the treatment of persistent rectovaginal endometriosis in 11 patients undergoing non-radical conservative surgery (Fedele *et al*., 2001). One year after insertion, dysmenorrhoea, which had been moderate or severe in all cases, and non-menstrual pelvic pain were absent. Of notable interest was the reduction of deep dyspareunia, from moderate or severe in eight cases prior to IUD insertion, to absent or mild in all subjects throughout treatment. Rectal tenesmus was also substantially alleviated. Furthermore transrectal ultrasound scans demonstrated a progressive reduction in size of rectovaginal lesions. The results of this study are clinically important because they prove the efficacy of a progestogen in a type of lesion generally considered as non-responsive to medical therapy. Relief of deep dyspareunia and rectal tenesmus seems to be due not only to size reduction of the fibronodular rectovaginal plaques, but also to decrease of the intra- and perilesional inflammatory condition, and confirms the effect of treatment also on organic symptoms.

Intrauterine administration of levonorgestrel with a possible direct distribution to pelvic tissues would imply a local concentration greater than its plasma levels. This could translate into a superior effectiveness with limited side-effects, also due to the absence of the hepatic first pass following oral administration of the drug. However, the results of the studies conducted by Vercellini *et al*. (1999) and Fedele *et al*. (2001) show that these expectations were partially incorrect. The side-effects observed are typically associated with the intake of levonorgestrel (weight gain, acne, seborrhoea, breast tenderness, abdominal bloating) and suggest a systemic action deriving from uterine absorption of the drug. This seems logical in relation to the florid endo-myometrial vascularization.

The 'pill': beyond simple contraception

For many years OC have been extensively used in clinical practice for the reduction of pelvic pain and dysmenorrhoea associated with endometriosis. Although their effectiveness has been recognized by all gynaecologists, only a limited number of formal studies have quantified their effects or

compared these with those obtained during administration of other drugs.

In the 1990s, GnRH agonists were considered the therapeutic reference standard for medical treatment of endometriosis. To test this notion, we compared the efficacy of a 6 month treatment with a monophasic OC (desogestrel 0.15 mg and ethinyl estradiol 0.02 mg, 28 patients) administered cyclically versus goserelin depot (3.6 mg s.c. every 28 days, 29 patients) (Vercellini *et al*., 1993). At the end of treatment, a significant reduction in deep dyspareunia was observed in both groups, with goserelin assessed as superior to the OC. Non-menstrual pain was diminished without differences between treatments. Women taking the OC experienced a significant reduction in dysmenorrhoea. With respect to the latter symptom, a comparison with GnRH is impracticable due to amenorrhoea secondary to hypo-estrogenism. Symptoms recurred unaltered 6 months after drug withdrawal.

Parazzini *et al*. (2000) investigated whether a GnRH agonist (triptorelin 3.75 mg i.m. every 28 days, 47 patients) administered for 4 months before starting treatment with a cyclic OC would improve results compared with the immediate use of an estrogen–progestogen combination (gestodene 0.75 mg and ethinyl estradiol 0.03 mg, 55 patients) for 12 months. One year after randomization, the two treatment modalities showed similar relief of pelvic pain in women with endometriosis. No data are available to support the belief that estrogen-progestogen combinations are to be considered as second-line drugs. When a long-term use is indicated, an OC may be prescribed without need of 'preparation' with a GnRH agonist.

OC used cyclically are the only treatment for endometriosis that permits monthly uterine bleeding. Dysmenorrhoea is known as the most frequent and most severe complaint in women with this disease. The symptom may therefore not subside completely during administration of an OC. Recent studies have demonstrated that women with menstrual-related problems during cyclic use of an OC may benefit from a shift to continuous administration (Sulak *et al*., 1997; 2002). Although elimination of the 7 day interval is recommended by various experts, there are no specific data regarding women with endometriosis. Consequently, we prescribed a monophasic OC (desogestrel 0.15 mg and ethinyl estradiol 0.02 mg) continuously to 50 patients with dysmenorrhoea recurring after conservative surgery for endometriosis, and not responding to the cyclic use of the same OC (Vercellini *et al*., 2003b). During the 2 year study period, 38% of women reported amenorrhoea, 36% spotting and 26% breakthrough bleeding. The mean score of menstrual pain, evaluated according to a 100-mm visual analogue scale, showed a reduction from 75 $\pm$ 13 to 31 $\pm$ 17. Moderate or severe side-effects were reported by 14% of the women. At final evaluation 26% of subjects were very satisfied, 54% satisfied, 2% uncertain, 16% unsatisfied and 2% very unsatisfied.

When cyclic use of OC does not resolve pain associated with monthly bleeding, continuous administration might constitute a simple, effective, safe and well-tolerated option for long-term treatment in women not wanting children.

Progestogens as post-operative adjuvant treatment

In spite of the lack of evidence demonstrating necrosis and disappearance of residual foci following medical treatments after surgery for endometriosis, the urge to prescribe such treatments seems to be overzealous. These schemes, which have clearly been derived from oncological practice, have a clinical significance only if prolonged over an extended period of time in women not wanting children immediately. Again, progestogens and estrogen–progestogen combinations constitute the only reasonable alternative for endometrial suppression of longer duration with respect to the conventional, arbitrary 6-month period.

In a randomised controlled study, Muzii *et al*. (2000) demonstrated that administration of a low dose monophasic estrogen–progestogen combination after operative laparoscopy for symptomatic endometriosis significantly reduces the cumulative probability of pain recurrence and increases the symptom-free period, compared to postsurgical expectant management.

Results of a randomized, controlled multicentre European trial on 142 patients showed that oral administration of dienogest for 4 months following conservative surgery for endometriosis is as effective as the GnRH triptorelin depot taken for the same period of time (Cosson *et al*., 2002). The degree of pain symptoms reported was similar in the two groups, as was the proportion of satisfied subjects at the end of treatment (86% in the dienogest arm versus 80% in the triptorelin arm). Spotting was more frequent in the former group (62 versus 25%) and vasomotor symptomatology more frequent in the latter (10 versus 61%).

When dysmenorrhoea is the main symptom of a patient undergoing surgical treatment for endometriosis, the insertion of a slow-releasing levonorgestrel IUD at the end of the procedure may substantially reduce the frequency and severity of post-operative pain. We conducted a randomized study on 40 women with symptomatic endometriosis and scheduled for operative laparoscopy (Vercellini *et al*., 2003a). Recurrent moderate or severe dysmenorrhoea was observed within a year of surgery in 2/20 (10%) women in the laparoscopy plus medicated IUD group and in 9/20 (45%) of those allocated to laparoscopy only. Hence, a medicated IUD needs to be inserted intraoperatively in three patients in order to avoid recurrence of dysmenorrhoea in one of them. One year after randomization, 75% of subjects allocated to the medicated IUD versus 50% of those allocated to surgery only were satisfied with the treatment received.

Conclusions

Progestogens are effective in controlling pain symptoms in approximately three out of four women with endometriosis. Their effect does not seem to be inferior to that obtained with other drugs habitually used in treating the disease. Medical treatment plays a role in the overall therapeutic strategy only if it can be administered over a prolonged period of time. Given their good

tolerability, minor metabolic effects and low cost, progestogens must therefore be considered the drugs of choice.

The effectiveness of progestogens is probably partly due to their proven anti-inflammatory effect. Most pelvic lesions associated with endometriosis are secondary to the strong inflammatory state caused by the metabolic activity of ectopic endometrium and to the resulting immune response. Furthermore, patients with endometriosis experience heavier menstruations than women without the disease (Vercellini *et al*., 1997b). The reduction of menstrual flow observed with the use of OC or the levonorgestrel IUD can limit pelvic contamination caused by transtubal reflux.

Progestogens are currently the only safe and inexpensive alternative to surgery. However, their contraceptive effectiveness limits their use to women who do not wish to have children in the short term.

The role of laparoscopy in the medical treatment of endometriosis needs to be radically reconsidered. In fact, direct observation of the pelvis is not essential before starting therapy because non-surgical diagnosis has proven sufficiently reliable (Eskenazi *et al*., 2001). The guidelines provided by the American College of Obstetricians and Gynecologists (1999) as well as by the Royal College of Obstetricians and Gynaecologists (2000) suggest that, in the absence of adnexal masses, the administration of estrogen–progestogen combinations can be undertaken without the need for preliminary laparoscopy. Finally, experience shows that a repeat laparoscopy is not important from either a clinical or an experimental standpoint because this only monitors what is inevitable: we do not need laparoscopy to know that endometriosis implants have survived therapy. Endometriosis is not a cancer and the systematic use of endoscopic follow-up should be removed from clinical practice.

Future perspectives

Experimentation of products with greater tolerability should be just one of the future objectives of clinical research on progestogens in the treatment of endometriosis. Given the need for long-term treatments, the minimum effective dosage needs to be identified in order to reduce the metabolic impact. Furthermore, we will need to consider alternative administration modalities, such as intravaginal (which should allow much higher pelvic concentrations of the drug as opposed to serum concentrations) and subcutaneous (which avoids the hepatic first pass). The role of adding estrogen in limiting erratic bleeding should be defined. The medical treatment of rectovaginal lesions, which have always been mistakenly considered the exclusive domain of the surgeon, should be studied. Finally, we should not forget the option the doctor has, under the current legislation, of prescribing galenical preparations to be dispensed by the pharmacist. This makes it possible to use progestogens that are no longer covered by international patents and to administer them in the most appropriate dosage, thus avoiding the limits imposed by pharmaceutical industries.

Progestogens applied to endometriosis, after an honoured career in the past, now seem to have an even brighter future ahead, with great benefits for the multitude of patients who suffer from this chronic and sometimes disabling disease.

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