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Endometriosis

Current Therapies and New Pharmacological Developments

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Abstract

Endometriosis is a chronic inflammatory condition that is responsive to management with steroids. The establishment of a steady hormonal environment and inhibition of ovulation can temporarily suppress ectopic implants and reduce inflammation as well as associated pain symptoms. In terms of pharmacological management, the currently available agents are not curative, and treatment often needs to be continued for years or until pregnancy is desired. Similar efficacy has been observed from the various therapies that have been investigated for endometriosis. Accordingly, combined oral contraceptives and progestins, based on their favourable safety profile, tolerability and cost, should be considered as first-line options, as an alternative to surgery and for post-operative adjuvant use. In situations where progestins and oral contraceptives prove ineffective, are poorly tolerated or are contraindicated, gonadotrophin-releasing hormone analogues, danazol or gestrinone may be used. Future therapeutic options for managing endometriosis must compare favourably against existing agents before they can be considered for inclusion into current practice. Finally, as reproductive prognosis is not ameliorated by medical treatment, it is not indicated for women seeking conception.

Historically, treatment for endometriosis has been based primarily on the oncological principle of radical removal of lesions, and this remains a mainstay of therapy in patients with bowel and ureteral stenosis or adnexal masses with ultrasonographic doubtful characteristics. However, endometriosis is not a cancerous condition and does not cause intestinal or ureteral strictures in the vast majority of patients. Furthermore, during the past two decades, it has become increasingly evident that the overall magnitude of disease does not correlate with either the frequency and severity of symptoms, or with long-term prognosis in terms of conceptions and recurrences.[1] Hence, a more pragmatic approach to treatment has evolved that is centred more on the patient's needs than on the extent of lesions.[2] That is, treatments for endometriosis should focus on the resolution of symptoms, independently of the *a priori* excision of lesions, because the problems experienced by patients are related to symptoms of the disease and not endometriotic implants *per se*.

In this review, we discuss the general principles on which a pharmacological treatment strategy may be based. We discuss the most frequently used agent classes, their efficacy and tolerability, and describe alternative hormonal and non-hormonal treatment strategies that are in development. For the purposes of this review, we address only the management of pain because it has been shown that medical therapy does not impact on fertility, either when used alone or as a post-operative adjuvant measure.[3-5] Conversely, the efficacy of hormonal drugs on endometriosis-associated algic symptoms has been definitively proven in placebo-controlled randomized studies.[6-9] The present critical analysis of the available evidence is largely based on a recently published literature review on the same issue.[10]

1. Progestins and Estrogen-Progestin Combinations

Hormones used in the medical therapy of endometriosis have definitively been shown to be non-cytoreductive.[11] Upon the restoration of ovulation and physiological levels of estrogens, the endometrium, both eutopic and ectopic, resumes its metabolic activity. Agents that can be administered for long periods of time are necessary, as pharmacological treatment is symptomatic and pain relapse usually occurs at the end of treatment.[12] Medical therapy for endometriosis often needs to be viewed in terms of years, and the use of agents that must be withdrawn after a few months because of poor tolerability, severe

metabolic adverse effects or high cost do not greatly benefit women with symptomatic endometriosis. Hence, progestins (progesterone congeners) and combined oral contraceptives (OCs) have characteristics that make them the ideal pharmacological choices. The main agents that are used in the management of endometriosis and currently available on the market are summarized in table I.

1.1 Oral Administration

1.1.1 Oral Contraceptives

OCs have been extensively used for many years in clinical practice to reduce pelvic pain and dysmenorrhoea associated with endometriosis. Although their effectiveness has been well recognized by gynaecologists, there have been a limited number of formal studies that have quantified their effects or compared them with the use of other agents.[13,14]

Table I. Medical treatment options available for women with symptomatic endometriosis who do not wish to be become pregnant (reproduced from Vercellini et al.,[10] copyright 2008, with permissions from Elsevier)

First-line
Peritoneal disease and endometriotic cysts ≤3 cm
estrogen-progestin combinations used cyclically or continuously[a] (oral or intravaginal use)
Rectovaginal lesions
norethisterone acetate 2.5 mg/day orally used continuously[a]
Second-line
Depot GnRH analogues plus add-back therapy (e.g. oral tibolone 2.5 mg/day)
Alternative progestins (e.g. medroxyprogesterone, desogestrel, cyproterone)
Third-line
Low-dose danazol (e.g. 200 mg/day, oral or intravaginal use)
Gestrinone 2.5 mg orally twice weekly
Specific conditions
Women with dysmenorrhoea as main symptom
levonorgestrel-releasing IUD
Hysterectomized women with residual disease
depot medroxyprogesterone (150 mg intramuscularly every 3–6 months)

a A 7-day interruption is suggested in case of breakthrough bleeding during continuous use.

GnRH = gonadotropin-releasing hormone; **IUD** = intrauterine device.

Gonadotropin-releasing hormone (GnRH) analogues were considered the therapeutic reference standard during the 1990s for medical treatment of endometriosis. We studied the efficacy of a 6-month treatment with a monophasic OC (desogestrel 0.15 mg/ethinylestradiol 0.02 mg, in 28 patients) administered cyclically compared with goserelin depot (3.6 mg subcutaneously every 28 days, in 29 patients).[13] Following treatment, a significant reduction in deep dyspareunia was seen in both groups, with goserelin being superior to the OC. Non-menstrual pain was diminished without any differences between the two treatments. Women treated with the OC experienced a significant reduction in dysmenorrhoea; however, a comparison with GnRH for this symptom is not possible because of amenorrhoea secondary to hypoestrogenism. All symptoms recurred unaltered in both groups 6 months after the discontinuation of drug therapy.

In another study, Parazzini et al.[14] investigated whether a GnRH analogue (triptorelin 3.75 mg intramuscularly 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-progestin combination (gestodene 0.75 mg/ethinylestradiol 0.03 mg, 55 patients) for 12 months. One year after randomization, the two treatment regimens produced similar relief of pelvic pain in women with endometriosis. Accordingly, when long-term use is indicated, an OC may be prescribed without the need for prior therapy with a GnRH analogue.

The efficacy of OCs in providing relief from endometriosis-associated pain was recently confirmed in a randomized, placebo-controlled, double-blind trial.[15] In this study, 100 patients with severe dysmenorrhoea and surgically or ultrasonographically diagnosed endometriosis were allocated to treatment with a monophasic OC (norethisterone 1 mg/ethinylestradiol 0.035 mg) or placebo. After four cyclic treatments, the reduction in total dysmenorrhoea score, assessed by a verbal and visual analogue scale (VAS), was significantly greater in the OC group. A significant difference in favour of OC users was also observed in the relief from non-menstrual pelvic

pain on the VAS. Moreover, endometrioma volume decreased significantly in the OC group but not in the placebo group.

OCs used cyclically represent the only treatment for endometriosis that allows monthly uterine bleeding. Dysmenorrhoea, the most frequent and most severe complaint in women with endometriosis, may therefore not subside completely during OC therapy. There are several studies demonstrating that women with menstrual-related problems during cyclic use of an OC may benefit from a switch to continuous OC administration.[16-18] Elimination of the 7-day interval has been recommended by various experts,[19] although there are limited data available regarding women with endometriosis. We investigated this in a 2-year study, in which a monophasic OC (desogestrel 0.15 mg/ethinylestradiol 0.02 mg) was prescribed for continuous use in 50 patients with dysmenorrhoea recurring after conservative surgery for endometriosis and not responsive to the cyclic use of the same OC.[20] During the study period, 38% of the women reported amenorrhoea, 36% spotting and 26% breakthrough bleeding. The mean score for menstrual pain, evaluated according to a 100-mm VAS, was reduced from 75 ± 13 to 31 ± 17. Moderate or severe adverse effects were reported by 14% of the women, and at final evaluation, 26% were very satisfied, 54% satisfied, 2% uncertain, 16% unsatisfied and 2% very unsatisfied with the treatment.

Therefore, when cyclic use of OCs does not resolve pain associated with monthly bleeding, continuous use may safely provide a simple, effective and well tolerated option for long-term treatment in women who do not wish to become pregnant. A 7-day interruption is recommended in the case of breakthrough bleeding during continuous use of OCs, and allows for the simple management of unexpected bleeding without prescheduling possibly unnecessary withdrawals at regular intervals.

1.1.2 Norethisterone Acetate

Norethisterone acetate (or norethindrone acetate) is a potent progestin derivative of 19-nortestosterone. Its efficacy was reported by Muneyyirci-Delale and Karacan[21] in a study involving 52 women with symptomatic and laparoscopically confirmed endometriosis. Norethisterone acetate was initiated at the start of the menstrual cycle at a dose of 5 mg/day, which was increased by 2.5 mg up to 20 mg/day until amenorrhoea was achieved. Treatment was continued for 6 months to over 1 year. Dysmenorrhoea regressed in 92% of the patients and chronic pelvic pain regressed in 89%. At the end of treatment, 94% of the patients had few or no symptoms. Breakthrough bleeding was experienced by 58% of patients and led to four patients withdrawing from the study. One other patient suspended treatment because of severe breast tenderness, and three because of a lack of efficacy. Overall, treatment was successful in 84% of the women recruited into the study.

A 6-month oral treatment with dienogest 2 mg/day (n = 119) was compared with norethisterone acetate 10 mg/day (n = 48) in a study by Moore et al.[22] Pain relief was reported to be similar in the two groups at the end of the treatment period (88/97 [91%] in the dienogest group and 46/48 [96%] in the norethisterone acetate group).

Norethisterone acetate has a number of advantages in the long-term treatment of endometriosis, including good control of uterine bleeding compared with other agents, a positive effect on calcium metabolism and bone mineral density (BMD), and a lack of negative effects on lipoprotein profiles at low dosages.[23] This may be due in part to the low conversion (0.20–0.33%) of norethisterone acetate to ethinylestradiol.[24]

However, the relationship between long-term systemic progestogen use (including norethisterone acetate) and BMD is a controversial issue. In one study, adolescents using injectable norethisterone enantate as a contraceptive were found to have lower increases in BMD over time compared with users of depot medroxyprogesterone or OCs.[25] Nevertheless, another study involving women >40 years of age showed no evidence of an effect on BMD through long-term use of depot medroxyprogesterone, norethisterone enantate or OCs.[26]

Norethisterone acetate has been approved by the US FDA and Italian Ministry of

Health for continuous administration to treat endometriosis.

1.1.3 Cyproterone

Cyproterone, a derivative of 17-hydroxyprogesterone with anti-androgenic and anti-gonadotropinic properties, was first reported in the treatment of endometriosis by Fedele et al.[27] at a dosage of 27 mg/day. In a subsequent study involving seven women with mild-to-severe symptomatic endometriosis, Moran et al.[28] evaluated the efficacy of a 6-month regimen of cyproterone at a lower dosage (10 mg/day for 20 days followed by 10 days with no treatment). Dysmenorrhoea was considerably relieved in all patients, with oligomenorrhoea reported by six of them and spotting by one. Repeat laparoscopy performed at the end of the treatment showed minimal residual lesions in five of the women and absence of disease in two.

In a randomized study, cyproterone at a similar dosage (12.5 mg/day) but administered continuously was compared with treatment with an OC, (desogestrel 0.15 mg/ethinylestradiol 0.02 mg) used continuously for 6 months, in 90 women with moderate-to-severe pelvic pain that recurred after conservative surgery for symptomatic endometriosis.[29] The main outcome of this study was patients' degree of satisfaction with therapy. At 6 months, dysmenorrhoea, deep dyspareunia and non-menstrual pelvic pain were considerably reduced. In addition, health-related quality of life (HR-QOL), psychological profile and sexual satisfaction all improved significantly, with no major differences between the treatment groups. Metabolic and subjective adverse effects were limited. According to an intention-to-treat analysis, 33/45 (73%) of the women in the cyproterone group and 30/45 (67%) in the OC group were satisfied with the treatment they received.

Cyproterone may be used when it is necessary to avoid subjective and metabolic effects of estrogens, or in women who prefer not to use contraception for cultural or religious reasons. Alternatively, continuous use of a low-dose monophasic OC is probably the preferred option to prevent the effects of estrogen deprivation in women for whom a long period of therapy is anticipated.

1.1.4 Medroxyprogesterone

Medroxyprogesterone is a 17-hydroxy derivative of progesterone that has moderate androgenic activity and minor effects on the lipoprotein profile. Its use as an oral agent for the treatment of symptomatic endometriosis has been studied in two randomized controlled trials.

In the first of these,[30] 100 infertile women with endometriosis were randomized to treatment with medroxyprogesterone 50 mg/day for 3 months or placebo. No difference was detected between groups in the changes in score using the revised American Fertility Society (R-AFS) classification on repeat laparoscopy at the end of therapy.[31] There were six pregnancies in the placebo group and one in the medroxyprogesterone group. However, pain symptoms were reduced more significantly in the medroxyprogesterone group than in the placebo group. In addition, 85% of symptomatic women assigned to medroxyprogesterone therapy deemed it effective in improving overall well-being, compared with 41% of those in the placebo group. Minimal adverse effects were reported in both groups (10% of patients in the medroxyprogesterone group and 2% in the placebo group).

In the second trial, Bergqvist and Theorell[32] compared a 6-month treatment course of nasal nafarelin 400 μg/day with oral medroxyprogesterone 15 mg/day. Of the 48 women initially recruited into the study, 18 withdrew (six in the nafarelin group, 12 in the medroxyprogesterone group) principally because of anxiety-depressive disturbances. The results showed a considerable reduction in pain-symptom scores with no significant differences between the treatment groups. The anxiety-depression score worsened during use of nafarelin, while all other psycho-social parameters as well as overall emotional balance improved during the study period with no significant differences between the two treatment groups.

The use of medroxyprogesterone in women with symptomatic endometriosis is supported by evidence showing that medroxyprogesterone is

more efficacious than placebo, and no less efficacious than GnRH agonists, in reducing pain and improving HR-QOL. However, erratic bleeding episodes may be more frequent and prolonged with the use of medroxyprogesterone compared with other progestogens. Furthermore, the optimal dosage for this agent is yet to be determined.

1.2 Intramuscular and Subcutaneous Administration

The depot formulation of medroxyprogesterone has been widely studied for contraception and is currently used by around 12-million women worldwide.[33] The mode of administration is very convenient and entails a single 150 mg intramuscular injection every 3 months. The increase in risk of breast cancer in users of depot medroxyprogesterone is no greater to that of OCs.[34]

Published data suggest that in long-term users of depot medroxyprogesterone, bone demineralization secondary to hypoestrogenism may develop,[35-38] although this issue is controversial. The recovery of BMD after discontinuation of depot medroxyprogesterone therapy has been observed in long-term users, even after menopause.[39,40] In general, no significant differences were found between former users of depot medroxyprogesterone and never users, although low BMD was observed in women who had been using depot medroxyprogesterone for >2 years.[41] Among post-menopausal women who underwent BMD evaluation at the lumbar spine, a significant change in BMD from –2% to –6% compared with baseline measurements was observed among the nonusers of depot medroxyprogesterone. However, in the group of women who used depot medroxyprogesterone, a change of only –2% was found at the end of the first year, while BMD was almost identical to baseline values in the third year following menopause. No detrimental effect was observed at the femoral neck in former depot medroxyprogesterone users, and BMD was increased significantly compared with nonusers.[39-41] In addition, Crosignani et al.[42] reported that in women with endometriosis, depot medroxyprogesterone 104 mg subcutaneously for 6 months had significantly less impact on BMD than treatment with the GnRH agonist leuprorelin (leuprolide) over the same time period. Moreover, in the case of depot medroxyprogesterone treatment, BMD returned to pre-treatment levels within 12 months of discontinuation, whereas patients who received the GnRH agonist continued to show significant reductions from baseline in BMD at the end of follow-up.

The first formal study on the use of depot medroxyprogesterone in women with endometriosis was published in 1996,[43] and compared depot medroxyprogesterone with the combination of a monophasic OC and low-dose danazol (50 mg/day). After 1 year, 29/40 of the women (72%) who received depot medroxyprogesterone were satisfied with treatment compared with 23/40 (57%) of those who received the OC plus danazol. A significant reduction in pain symptoms, evaluated with a visual analogue and multidimensional scale, was observed in both patient groups. However, patients in the combined OC plus danazol group experienced a greater frequency and severity of dysmenorrhoea, which is a logical consequence of cyclic administration. Both treatments produced similar, significant reductions in serum levels of high-density lipoprotein (HDL) cholesterol, whereas an increase in low-density lipoprotein (LDL) cholesterol was only observed in the group treated with OC plus danazol. The incidence of adverse effects was greater in depot medroxyprogesterone users. The mean delay in appearance of a regular menstrual cycle after suspension of depot medroxyprogesterone therapy was 7 months to a maximum of 1 year.

The efficacy of depot medroxyprogesterone for the treatment of endometriosis was confirmed in two randomized controlled trials,[42,44] to investigate a new subcutaneous formulation of depot medroxyprogesterone 104 mg and to assess its noninferiority to leuprorelin 11.25 mg chosen as the standard comparator. The agents were administered during a menstrual cycle and again after 3 months, with the overall treatment period being 6 months. In one trial, 300 women with surgically diagnosed endometriosis were recruited in

Europe, Asia, Latin America and New Zealand,[42] and in the other trial, 274 subjects with similar characteristics were recruited in Canada and the US.[44] The subcutaneous preparation of depot medroxyprogesterone was found to be statistically equivalent to leuprorelin in reducing pain symptoms both at the end of the 6-month treatment phase and at 12-month follow-up. Patients in the group that received depot medroxyprogesterone showed significantly less BMD loss than those in the leuprorelin treatment group. BMD returned to pre-treatment levels 12 months after treatment in the depot medroxyprogesterone group but not in the GnRH analogue group. Depot medroxyprogesterone was associated with fewer hypoestrogenic symptoms than leuprorelin, but with more irregular bleeding. In one study,[42] the continuation rate was 90% in the group receiving the subcutaneous depot formulation of medroxyprogesterone group and 93% in the leuprorelin group, whereas in the other study[34] the percentages were 65% and 74%, respectively. There were improvements in total productivity and HR-QOL in both groups.

Depot medroxyprogesterone is therefore an effective, well tolerated and economic alternative for the treatment of symptomatic endometriosis. However, candidates for treatment must be selected carefully because of some of this agent's characteristics. In fact, prolonged delay in the resumption of ovulation is a contraindication to the use of depot medroxyprogesterone in women desiring pregnancy in the near future, although the delay in return of fertility is the same as for other contraceptives at 16 months after discontinuation. In addition, uterine breakthrough bleeding can be prolonged, repeated and difficult to correct. Moreover, it is not possible to interrupt treatment in the event of adverse effects, which complicates clinical management in patients in whom these effects are severe or barely tolerable. The preferred indication for use of depot medroxyprogesterone is in patients with residual symptomatic endometriosis following definitive surgery. In such circumstances, future conception or irregular uterine bleeding are not issues, and the use of depot medroxyprogesterone permits a simple and well tolerated treatment for the suppression of persistent foci after non-radical surgery without the need for daily drug administration or further surgery.

1.3 Intrauterine Administration

Levonorgestrel is a potent progestin that is derived from 19-nortestosterone, and has androgenic and anti-estrogenic effects on the endometrium.[45] An intrauterine device (system) releasing 20 μg/day of levonorgestrel (levonorgestrel-IUS) may induce amenorrhoea in different ways compared with standard treatments and may relieve menstrual pain.[46] In fact, the local administration of levonorgestrel has a profound effect on the endometrium, rendering it atrophic and inactive, although ovulation is generally not suppressed. The identification of safe and effective alternatives to prolong treatment is an essential component of current clinical research on symptomatic endometriosis, and there is intense interest in the possibility of targeting drug action towards specific organs, thus reducing the general metabolic impact. The levonorgestrel-IUS has been used in patients with peritoneal, superficial ovarian, rectovaginal and recurrent endometriotic lesions, and also as a post-operative measure.

1.3.1 Symptomatic Peritoneal and Superficial Ovarian Lesions

In a study involving 37 women of reproductive age who underwent laparoscopy for pelvic pain, Lockhat et al.[46] investigated the efficacy of the levonorgestrel-IUS in providing relief from symptoms associated with minimal to moderate endometriosis. Stage I to III endometriosis was diagnosed but not treated in 34 patients, and the levonorgestrel-IUS was inserted intra-operatively. The levonorgestrel-IUS was removed soon after surgery in five patients because of adverse effects or worsening of pain, and one other patient was withdrawn from the study because of protocol violation. After 6 months, dysmenorrhoea was significantly relieved in the remaining 28 women, and the proportion of patients experiencing moderate or severe menstrual pain fell from 96% to 50%. Twenty women reported dyspareunia at

the start of the study, of whom 13 felt this had improved after 6 months of therapy, two felt it had worsened, two reported no change and three were no longer sexually active. Non-cyclical pelvic pain was not significantly reduced. The number of days of pain experienced per month (mean ± standard deviation [SD]) was 15.0 ± 6.9 at baseline and 10.7 ± 8.7 after 6 months of treatment.

Monthly blood loss assessed by the semiquantitative pictorial blood loss assessment chart (PBAC) score[47] varied from 204 ± 196 at evaluation prior to insertion of the levonorgestrel-IUS to 90 ± 157 at 6 months post-insertion (a score of >100 is suggestive of menorrhagia). At the end of treatment, 14 patients were very satisfied, 5 satisfied, 8 uncertain and 2 dissatisfied. In an intent-to-treat analysis, with those who withdrew from the study before its completion included as treatment failures, 56% (19/34) of the patients recruited into the study were satisfied or very satisfied with their treatment. Six patients requested removal of the levonorgestrel-IUS device at the end of the study period.

Three-year follow-up data were also reported for those patients enrolled in the 6-month trial who requested continuation of therapy with the levonorgestrel-IUS.[48] The device was retained by 23/34 (67.6%) women at 12 months, 21 (61.8%) at 24 months and 19 (55.9%) at 36 months. There were a total of 15 discontinuations, five (33%) of which were for unacceptable irregular bleeding, most of these occurring within the first 6 months. Pelvic pain (20.6%) and weight gain (8.8%) were the second and third most common reasons, respectively, for requesting removal of the levonorgestrel-IUS. There were no expulsions of the device over the 3-year follow-up period.

The 10-cm VAS dysmenorrhoea score fell from a mean (±SD) of 7.7 ± 1.3 before insertion of the levonorgestrel-IUS to 2.7 ± 1.5 at 36 months. Moderate or severe dysmenorrhoea was experienced by 27 patients at pre-insertion, seven at 12 months, three at 18 months and only one at 24 months. The mean number of monthly days with pain decreased from 15.0 ± 6.9 at baseline to 6.0 ± 3.4 after 12 months of treatment. The greatest improvement in symptoms occurred during the first 12 months of therapy and there were no significant changes over the remaining 24 months.

Petta et al.[49] compared the efficacy of the levonorgestrel-IUS (n = 39) with leuprorelin depot 3.75 mg/28 days (n = 43) for control of endometriosis-related pain, in a 6-month randomized, controlled, multicentre trial. Pelvic pain was decreased substantially from the first month of treatment throughout the study period, with no significant differences between the two treatment groups. Bleeding scores were higher in users of the levonorgestrel-IUS than in GnRH analogue users. QOL improved to a similar extent in both treatment groups. In the opinion of the study authors,[49] the levonorgestrel-IUS could become the treatment of choice for symptomatic endometriosis, because it does not provoke hypoestrogenism and requires only one medical intervention for its introduction every 5 years.

1.3.2 Recurrent Endometriosis

Vercellini et al.[50] conducted a study involving 20 parous women who did not wish to conceive who had undergone conservative surgery for endometriosis during the previous 12 months, did not want to undergo further surgery and who presented with recurrent moderate-to-severe menstrual pain. After 1 year of treatment with the levonorgestrel-IUS, variations in the severity of dysmenorrhoea and patient satisfaction with therapy were assessed.

Two women withdrew from the study (one requested removal of the levonorgestrel-IUS because of weight gain and abdominal bloating; in the other, the device was expelled 3 months after insertion) and one was lost to follow-up. Among the remaining 17 women, after 12 months of treatment, the menstrual pattern was characterized by amenorrhoea in four (24%), hypomenorrhoea or spotting in eight (47%) and normal flows in five (29%). The PBAC scores (mean ± SD) at baseline and 12-month follow-up were 111 ± 36 and 27 ± 26, respectively. During the study period, the mean 100-mm VAS decreased from 76 ± 12 to 34 ± 23, and the mean 0–3 verbal rating scale score decreased from 2.5 ± 0.5 to 1.2 ± 0.5 points.

At the final evaluation, only five (29%) of the women were considered still symptomatic.

Adverse effects were reported by nine patients (bloating in seven, weight gain in five, headache in four, breast tension in three, and pelvic pain and decreased libido in one). At the 12-month follow-up, four women (20%) were very satisfied with treatment, eleven (55%) were satisfied, two (10%) were uncertain and three (15%) were dissatisfied.

1.3.3 Post-Operative Adjuvant Treatment

Vercellini et al.[51] performed a pilot study to investigate the frequency and severity of dysmenorrhoea recurrence at 1-year follow-up in women in whom a levonorgestrel-IUS was inserted immediately after laparoscopic surgery for endometriosis, compared with women treated with laparoscopic surgery alone. After the complete excision or coagulation of endometriotic lesions, 20 patients were randomized to receive the levonorgestrel-IUS and 20 to post-operative expectant management. Displacement of the levonorgestrel-IUS was observed in one woman 5 months after insertion. One patient from each group was lost to follow-up. At the 12-month evaluation, amenorrhoea was reported by 5 (28%) of the remaining 18 women in the levonorgestrel-IUS arm, hypomenorrhoea or spotting by 9 (50%), and normal flows by 4 (22%). Median (inter-quartile range) dysmenorrhoea VAS scores fell by 50 mm (35–65) and multidimensional categorical rating scale scores by 1 point (1–2) in the post-operative levonorgestrel-IUS group; the corresponding reductions in scores were 30 (25–40) and 1 (0–2) in the surgery only group ($p = 0.012$ and 0.021). In an intention-to-treat analysis, the recurrence of post-operative moderate or severe dysmenorrhoea was less frequent in the levonorgestrel-IUS group (2/20 subjects, 10%) than in the surgery-only group (9/20, 45%; $p = 0.03$; relative risk = 0.22; 95% CI 0.05, 0.90). Based on these numbers, a levonorgestrel-IUS would need to be inserted post-operatively in three patients to avoid the recurrence of moderate-to-severe dysmenorrhoea in one of them 1 year after surgery.

Dyspareunia and non-menstrual pain scores were also reduced to a greater extent with the post-operative use of levonorgestrel-IUS. Adverse effects were reported by eight of the 20 patients who were allocated to levonorgestrel-IUS insertion (bloating in six, weight gain in six, headache in three, seborrhoea and acne in two, breast tenderness in one, decreased libido in one and pelvic pain in one); however, these adverse effects were deemed tolerable and removal of the IUS was not necessary except in the case of a displaced device. At 12 months, 75% of women in the group that received surgery plus the levonorgestrel-IUS reported being satisfied or very satisfied after 1 year of treatment compared with 50% of those in the surgery-only group.

Insertion of the medicated device after conservative surgery for endometriosis may therefore constitute an innovative, effective, well tolerated and convenient adjuvant treatment for reducing the risk of recurrence of dysmenorrhoea.

1.3.4 Advantages and Drawbacks of the Levonorgestrol Intrauterine Device for Endometriosis

The use of a levonorgestrel-IUS in women with endometriosis confers several advantages over other conventional systemic therapies. These include the avoidance of the need for repeated administration, effective contraception and, possibly, fewer adverse effects, and may increase compliance during long-term treatment. Although it may be expensive at the outset, the cumulative final costs could be less than those of other medications. In several European countries and in the US, many insurances and governmental health authorities provide a reimbursement of the cost and, consequently, the levonorgestrel-IUS may prove a cost-effective treatment. In Brazil, the cost of the device is reported to be equivalent to one ampoule of GnRH agonist and this situation could be similar in other countries.[49]

Women should be informed that menstrual irregularities, including spotting, prolonged or continuous bleeding, and, rarely, menorrhagia, are to be expected during the first 3–4 months of use. After the first year of use, few women report

inter-menstrual bleeding and about 30% are amenorrheic. Figures on bleeding pattern reported in users of the levonorgestrel-IUS for contraception or menorrhagia are better than those observed in the usually limited number of subjects included in studies on endometriosis. This is relevant because dysmenorrhoea is the most frequent symptom in patients with endometriosis.

The intrauterine administration of levonorgestrel with a possible direct distribution to pelvic tissues would suggest a local concentration greater than that in plasma. This could translate into a superior effectiveness with limited adverse effects, also as a result of the absence of the hepatic first-pass effect following oral administration of the drug. The metabolic consequences of the levonorgestrel-IUS should be less pronounced than those of other contraceptive methods, based on the administered dose of drug. However, a general effect secondary to uterine absorption of levonorgestrel cannot be excluded, since most of the reported adverse effects are typical of progestins. In fact, Lockhat et al.[48] observed high levonorgestrel concentrations (in the order of 300–400 pg/mL) several months after levonorgestrel-IUS insertion, and this suggests that the progestin released by the IUS is rapidly absorbed by the subendometrial vascular network.

The expulsion rate of the device is over 5% and the risk of pelvic infection about 1.5%.[52] Accordingly, the recommended patient profile consists of women with no history of pelvic inflammatory disease. Nulliparity is not a contraindication; however, the use of intrauterine devices (IUDs) in women with smaller uteri may be associated hypothetically with increased uterine cramping. Although unproven, this theoretical disadvantage could be worrisome in patients with endometriosis-associated severe dysmenorrhoea.

Finally, there is only limited information available on the risk of endometrioma formation during extended therapy. In fact, it has been shown that development of endometriotic ovarian cysts is associated with ovulation.[53] The levonorgestrel-IUS generally does not inhibit ovulation other than for the first few months after insertion, and in theory, this may represent a specific drawback compared with other forms of progestin therapy.[54] In addition, comparative trials are required to confirm the effect on organic pain symptoms, including dyspareunia and dyschezia, and to verify whether the positive results observed are maintained during the entire 5-year period of efficacy. Doubts have been expressed recently with regard to the overall satisfaction and continuation rate in levonorgestrel-IUS users as a result of unscheduled bleeding, lower abdominal pain and progestogenic adverse effects.[55]

Given all these factors, the levonorgestrel-IUS may be considered as a long-term treatment option for women with symptomatic endometriosis; however, it should be suggested in specific circumstances after careful counselling.[55]

1.3.5 Progestin Treatment for Rectovaginal Endometriosis

It is erroneously assumed, in current medical practice, that medical treatments are not efficacious for rectovaginal endometriosis.[56-58] This viewpoint, based on a reportedly different receptor pattern from eutopic endometrium,[57] leads to the obvious conclusion that surgery is the only reasonable therapeutic option, and thus exposes women to potentially severe morbidity, particularly if procedures are performed by gynaecologists not specifically trained in this difficult and technically demanding field. This clinical approach should be challenged because, in these patients, good results can be achieved with safe, well tolerated and inexpensive drugs that can be used over prolonged periods of time.

To evaluate the effectiveness of the levonorgestrel-IUS for rectovaginal endometriosis, Fedele et al.[59] recruited 11 symptomatic women who previously underwent conservative surgery without excision of deep lesions, and assessed variations in their pain symptoms and in the size of plaques. At 1-year follow-up, nine women were oligomenorrhoeic and two experienced amenorrhoea; dysmenorrhoea, which had been moderate or severe in all patients, and nonmenstrual pelvic pain was absent. Of notable interest was the reduction of deep dyspareunia; this had been moderate or severe in eight patients prior to insertion of the IUD and was reduced to being absent or mild in all subjects throughout

the treatment period. Dyschezia was relieved in four of five women by the sixth month of treatment. There was a slight but significant reduction in rectovaginal lesions after 6 months of therapy, as shown by trans-rectal ultrasonography. The use of the levonorgestrel-IUS was associated with headache in four patients; breast tenderness in four; seborrhoea, oily hair or acne in three; and weight gain in four.

The mechanism of action of the levonorgestrel-IUS could be based on a receptor-mediated effect of levonorgestrel that can reach endometriotic foci through the circulation or through direct diffusion from the uterus. Another mechanism of action could be secondary oligoamenorrhoea and the consequent reduction in cyclic bleeding at ectopic endometrial sites. The relief of organic symptoms, such as deep dyspareunia and rectal tenesmus, is probably related not only to a reduction in the size of the fibronodular rectovaginal plaques but also to a decrease in the intra- and peri-lesional inflammatory condition.

A randomized controlled trial was conducted more recently[60] that involved 90 women with recurrent moderate or severe pelvic pain following unsuccessful conservative surgery for symptomatic rectovaginal endometriosis. The women were allocated to 12 months of continuous treatment with oral ethinylestradiol 0.01 mg/cyproterone 3 mg/day, or norethisterone acetate 2.5 mg/day. Seven patients in the ethinylestradiol/cyproterone arm of the study and five in the norethisterone acetate arm withdrew because of adverse effects (n = 5) or treatment inefficacy (n = 6) or were lost to follow-up (n = 1). At 12 months, scores were substantially reduced for dysmenorrhoea, deep dyspareunia, non-menstrual pelvic pain and dyschezia, without any major differences between the treatment groups. In particular, moderate-to-severe deep dyspareunia was reported at baseline by 12 women in the group receiving ethinylestradiol/cyproterone, and by 13 women in the norethisterone acetate group. The symptom was not relieved in two women in each group. Moderate-to-severe dyschezia was present before treatment in 10 and 15 patients, respectively, in the two treatment groups, and regressed under therapy in all patients.

Among the women who completed the study, 17/38 (45%) who received the ethinylestradiol/cyproterone combination achieved amenorrhoea compared with 29/40 (72%) women who received norethisterone acetate. In total, 21 women in the ethinylestradiol/cyproterone group and 11 in the norethisterone acetate group experienced erratic bleeding episodes (spotting in 14 and nine subjects, respectively; breakthrough bleeding in seven and two), and were advised to interrupt treatment for 1 week. Adverse effects were reported by 16/41 (39%) of the women who were allocated to ethinylestradiol/cyproterone, and by 21/42 (50%) of those taking norethisterone acetate. Among those patients who reported increases in bodyweight, the mean weight gain was 2.3 ± 1.0 kg (+4.1%) in seven women in the ethinylestradiol/cyproterone group, and 3.6 ± 2.3 kg (+6.7%) in 12 women in the norethisterone acetate group. Both regimens induced minor unfavourable variations in serum lipid profile.

The mean ± SD volume of rectovaginal plaques, measured on trans-rectal ultrasonography, was reduced from a baseline value of 3.1 ± 1.4 mL to 2.2 ± 1.0 mL at the end of treatment in the ethinylestradiol/cyproterone group; the corresponding decrease in the norethisterone acetate group was from 3.0 ± 1.3 mL to 1.9 ± 1.1 mL.

Based on an intention-to-treat analysis, 28/45 (62%) patients in the ethinylestradiol/cyproterone group and 33/45 (73%) in the norethisterone acetate group were satisfied with the treatment received.

In Italy, the monthly cost of treatment with norethisterone acetate 2.5 mg daily is approximately €1.5. Consequently, low-dose norethisterone acetate has been suggested by the authors as the treatment of choice for patients with recurrent or persistent deeply infiltrating lesions after the failure of conservative surgery who do not want to conceive. The ethinylestradiol/cyproterone combination was slightly less effective but well tolerated, and could be suggested for women with acne or hypertrichosis and for those who experience androgenic adverse effects with norethisterone acetate.

A study involving 12 women with rectovaginal endometriosis using a two-drug oral regimen including norethisterone acetate (2.5 mg/day) and

the aromatase inhibitor letrozole (2.5 mg/day) was reported by Remorgida and Abbamonte.[61] After 6 months of treatment, pain symptoms were significantly reduced, although promptly recurred on drug withdrawal. The magnitude of the effect appears substantially similar to that observed with the use of norethisterone acetate alone.[60] Consequently, the addition of letrozole does not seem to offer any additional benefit. Moreover, in pre-menopausal women, aromatase inhibitors stimulate the ovary and induce cyst formation.

In our opinion, if other studies confirm the efficacy of progestins in women with symptomatic rectovaginal endometriosis, patients' consent to surgery should no longer be sought based solely on the purported ineffectiveness of medical therapies.

1.4 Estrogen-Progestin Combinations as a Preventive Measure

A high rate of recurrence of post-operative endometrioma, ranging from 30%[62-64] to 40%,[65,66] has been reported in the past few years. Therefore, tertiary prevention is an additional important objective of medical treatment after surgery, especially in women desiring conception in the future.

The major reduction in risk of recurrence of endometrioma, demonstrated recently in post-operative users of OCs,[66] constitutes an important benefit of prolonged suppression of ovulation. In fact, a crude cyst-recurrence rate of 9% (9/102) in OC users and of 56% (26/46) in never users was observed. The adjusted odds ratio (OR) for OC use was 0.04 (95% CI 0.02, 0.13). The 36-month cumulative proportion of patients free from endometrioma recurrence was 94% in always users compared with 51% in never users (log-rank test, $\chi^2_1 = 36.2$; $p < 0.001$). The adjusted incidence rate ratio was 0.10 (95% CI 0.04, 0.24). The absolute risk reduction of endometrioma recurrence in always users compared with never users was 47% (95% CI 37%, 57%). This means that regular post-operative use of an estrogen-progestin combination prevented endometrioma recurrence in one of two patients (95% CI 0.2, 7) 3 years after surgery, with a relative risk reduction of 80%. However, the protective effect of the estrogen-progestin combination tended to disappear rapidly after discontinuation.[67]

There have been many reports of an increase in the risk of ovarian cancer in women with endometriosis in both hospital-based and population-based studies. Specifically, endometriosis has been associated with endometrioid and clear-cell epithelial histotypes.[68-71] This relationship has been interpreted in terms of shared risk factors, such as incessant ovulation, retrograde menstruation, chronic peritoneal inflammation, immune imbalance, and even an estrogen-rich and progesterone-deficient hormonal environment.[72]

In order to define the effect of several factors, including OC use, on the risk of developing ovarian cancer in women with endometriosis, Modugno et al.[72] pooled data from four population-based, case-control studies that recruited women from four regions of the US from 1993 through 2001. Cases represented women with ovarian cancer who participated in one of the four studies, and controls were women without ovarian cancer who served as controls in the original studies. Of the 2098 cases and 2953 controls included in the combined analysis, 177 cases (8.5%) and 184 controls (6.3%) reported a history of endometriosis. After adjustment for several potentially confounding factors, women with endometriosis were more likely to have ovarian cancer than women without a history of the disease (OR 1.32; 95% CI 1.06, 1.65). As expected, women with ovarian cancer were less likely to have used an OC, whereas women with endometriosis were more likely to have used an OC (79.2% vs 61.7% among controls and 65.9% vs 50.5% among cases). The use of OCs decreased the risk of ovarian cancer independently of a history of endometriosis; however, the decrease in risk was particularly evident in women with a history of the disease. In addition, a dose-response effect was observed with lifetime duration of OC use. The adjusted ORs for <10 years and >10 years of exposure to OCs compared with never users were 0.58 and 0.21, respectively, among women with endometriosis, and 0.70 and 0.47 among women without endometriosis.

Based on their findings, the authors[72] maintain that the prescription of OCs to women with endometriosis may have the added benefit of protection against ovarian cancer. The authors encourage long-term OC use, because this would counteract efficaciously the increase in risk of endometrioid and clear-cell epithelial ovarian cancer observed in patients with endometriosis. Such an efficacious preventive measure might save a number of lives, given the poor prognosis of these types of malignancy. Patients should be routinely informed that long-term OC use can counteract the increase in the risk of ovarian cancer associated with endometriosis, to allow them to decide on an individual basis.

1.5 Hormone Therapy in Women with a Past Medical History of Endometriosis

The question of initiating hormone therapy may arise in young patients after pelvic clearance or in women with a previous diagnosis of endometriosis who reach physiological menopause. The risk of recurrence of endometriosis during hormone therapy remains unknown. Of greater concern is the risk of malignant transformation of residual foci. Soliman and Hillard[73] recently reviewed published data on this topic, and concluded that the available evidence does not suggest withholding hormone therapy from patients with hypoestrogenic symptoms. These authors are in favour of continuous rather than cyclic therapy because symptoms of endometriosis are known to be stimulated by hormone fluctuations. In their opinion, the lowest effective dose should always be used, commencing hormone therapy shortly after definitive surgery or as soon as menopausal symptoms arise, without delays of unproven benefit.[73]

The avoidance of estrogen-only treatments and the use of combined preparations is strongly suggested.[73] In fact, there are many reports of malignancies arising in women with endometriosis associated with use of unopposed estrogen replacement.[74-76] Gücer et al.[77] reported that unopposed estrogen stimulation may lead to premalignant or malignant transformation of ectopic foci. Therefore, the addition of progestogens to estrogens should be considered in women with a previous diagnosis of endometriosis even if they have undergone hysterectomy with bilateral oophorectomy. In fact, eutopic and ectopic endometria share similar risk factors for malignant degeneration, and unopposed estrogens have been observed to increase the risk of developing cancer in endometriotic implants.[78]

The risk of post-menopausal malignant transformation of endometriosis is approximately 1%. When both ovaries have been removed, adenocarcinomas associated with unopposed estrogen treatment arise mainly in the upper vagina and rectosigmoid colon.[77,79] Based on the available evidence, this risk appears to be lower with combined hormone therapy than with estrogen-only therapy.[80] Accordingly, there appears to be a consensus on the need to use combined therapy in women with endometriosis even after pelvic clearance.[73,80,81]

Tibolone is a synthetic steroid with weak estrogenic, progestinic and androgenic activity. Tibolone has an inhibitory effect on the endometrium, as the progestinic-androgenic activity is prevalent. Tibolone is metabolized *in vitro* by endometrial Δ-4 isomerase/dehydrogenase to its Δ-4 metabolite, which is characterized by strong progestinic activity. This accounts for its endometrial tissue-specific progestinic effect as well as a positive effect on calcium metabolism.

Fedele et al.[82] compared treatment using transdermal estradiol (50 mg twice weekly ± cyclic medroxyprogesterone 10 mg/day) with tibolone (2.5 mg/day orally), administered for a minimum of 12 months to 21 women with residual pelvic endometriosis following bilateral oophorectomy with or without hysterectomy. Residual endometriosis was present in the bowel wall in four patients, in the rectovaginal septum in six and deep in the retroperitoneal pelvic space in six patients. All women were symptomatic prior to definitive surgery. Moderate-to-severe pain recurred in four of the patients in the transdermal estradiol treatment group compared with one patient in the tibolone group. These findings suggest that tibolone may be considered as a postmenopausal replacement therapy for women with pelvic endometriosis. In addition, tibolone may

be used as an add-back therapy in patients selected for prolonged treatment with a GnRH analogue.[83]

2. Gonadotropin-Releasing Hormone (GnRH) Agonists and Antagonists

GnRH is a decapeptide that is released in a pulsatile fashion into the capillaries of the hypophyseal-portal circulation. It binds selectively to highly specific receptors on anterior pituitary gonadotrophic cells and activates intracellular signalling pathways that are involved in the regulation of both the production and release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[84]

Over the last three decades, a large number of structural analogues of GnRH, including both agonists and antagonists, have been synthesized. The agonists have a greater affinity for the receptor than native GnRH and produce an immediate increase in secretion of LH and FSH ('flare-up'). This is consistently followed by an inhibition of secretion of gonadotropins and gonadal steroids, a typical example of the ligand-induced downregulation of the receptors. The ultimate effect of these analogues is to produce a hypoestrogenic condition that resembles postmenopause.[85] More recently, GnRH analogues that display antagonist activity have been developed, with the advantages of producing an immediate decrease in circulating levels of gonadotropins and gonadal steroids, their ease of reversibility and absence of the initial surge that occurs with agonists. The 'flare-up' phase, which generally represents an undesirable effect of the use of agonists, is thus avoided.[86]

2.1 GnRH Agonists for Pelvic Pain

Given the estrogen-dependent nature of endometriosis, there is a consensus that the disease benefits from the establishment of a hypoestrogenic condition. Therefore, not surprisingly, GnRH agonists have been demonstrated to be reasonably successful in reducing the pain symptoms associated with endometriosis, including dysmenorrhoea, dyspareunia and non-menstrual pelvic pain.[87,88] However, in a recent Cochrane meta-analysis,[89] little or no difference in efficacy was shown between GnRH agonists and other medical treatments for endometriosis (danazol, OCs, gestrinone). However, there are differences related to adverse effect profiles.[89,90] Therefore, it should be noted that the administration of GnRH agonists cannot be extended as a single treatment for >6 months, as prolonged exposure risks the appearance of detrimental effects of hypoestrogenism, such as a reduction in BMD.[91,92] Moreover, symptoms of estrogen deficiency, including hot flushes, emotional lability, insomnia, loss of libido and vaginal dryness typically occur during treatment.[88]

The initial enthusiasm that accompanied the introduction of GnRH agonists into clinical practice diminished when it emerged that these agents were not able to eradicate the disease. Indeed, GnRH agonists, like other available medical options, offer a suppressive but not a curative therapy and pain symptoms typically resume after treatment is discontinued. The cumulative recurrence rate for the fifth year after treatment has been reported as 53% in women with endometriosis and 73% in those with a higher stage of disease.[93] Overall, despite their well recognized effectiveness, GnRH agonists do not represent the first-line medical treatment to cure endometriosis-associated pelvic pain.

2.2 Add-Back Therapy

To improve the effectiveness of GnRH agonists, the duration of treatment would have to be extended beyond the limit of 6 months. Hence, the concomitant use of add-back hormone therapy has been suggested to prevent the loss of bone mass and other symptoms of estrogen deficiency while controlling endometriotic implants. This 'estrogen threshold hypothesis' was formulated by Barbieri[94] and states that there is a specific estrogen threshold below which endometriosis is not stimulated, but hot flushes and loss of bone mass are controlled. The most appropriate add-back regimen has not been definitively determined, but on the basis of available evidence a low-dose continuous estrogen in combination with a progestin should be considered first.[87,92,95-97]

The possibility of extending the duration of treatment for several years has been emphasized recently.[87,92] Even with a consistent body of literature on the use of GnRH agonists with add-back hormone therapy in women with endometriosis, there are few studies comparing this regimen to OCs or progestins.[90] This aspect is of crucial importance considering that a GnRH agonist with add-back therapy constitutes an expensive and complex form of treatment, and its use could only be recommended if studies support strong additional benefits over OCs or progestins. According to a Cochrane review, there is little or no difference in effectiveness between a GnRH agonist with add-back therapy and other medical treatments for endometriosis.[90] Zupi et al.[98] recently reported data from a three-arm randomized controlled trial, in which treatment with a GnRH agonist alone (n = 44) was compared with a GnRH agonist plus add-back therapy (n = 46) and an OC (n = 43) for 1 year. At the end of treatment and 6 months after its discontinuation, pain-symptom scores were higher in the OC group, whereas no difference emerged between women who received GnRH agonists with and without add-back therapy. Both groups treated with GnRH agonist recorded significant loss of BMD at the conclusion of 12 months of therapy and at the 6-month follow-up, compared with baseline values and with corresponding values in the OC-treated group. Moreover, there was a higher rate of hot flushes and emotional change in the group treated with the GnRH agonist alone than in the other two treatment groups. Currently, the long-term use of GnRH agonists with add-back therapy may be considered for women who are refractory to treatment with OCs or progestins.

2.3 GnRH Agonists as a Peri-Operative Treatment

The use of GnRH agonists as a neo-adjuvant or adjuvant surgical therapy in the management of endometriosis is an issue that has been debated. The rational for this approach, clearly derived from oncology practice, is to extirpate endometriotic foci that may have been missed at the time of surgery. It has also been postulated that there may be benefit in terms of a reduction in post-surgical adhesion formation.[99] However, evidence supporting a role for this approach is not consistent, and the use of GnRH agonists pre-operatively has not been investigated in randomized controlled trials.[100,101] Studies evaluating the effectiveness of a post-operative treatment course of 3–6 months have documented a significant but temporary treatment benefit,[102-107] and this conclusion has been supported by systematic reviews.[100,101] However, a longer administration period of post-operative GnRH agonists with add-back therapy may improve the duration of pain relief, although evidence remains scant.[87]

2.4 GnRH Agonists and *In Vitro* Fertilization

The benefits of prolonged therapy with a GnRH analogue prior to *in vitro* fertilization (IVF) in women with endometriosis were first hypothesized in the early 1990s.[108] Sallam et al.[109] have recently combined the results from the three available randomized controlled trials[110-112] in a Cochrane meta-analysis. According to their analysis, clinical pregnancy rates were remarkably higher in women who received long-term down-regulation with GnRH agonists than in those who did not, with a pooled OR of 4.3 (95% CI 2.0, 9.1).[109] However, this reported strong benefit should be viewed with caution, as some experimental flaws limit the validity of this conclusion, particularly the fact that the sample sizes were insufficient. The combined analysis included 88 cases and 77 controls. Moreover, the treatment modality in women allocated to the control group was debatable in two of the three studies. Finally, even if the inclusion criteria are not clearly stated, it seems that women with compromised ovarian reserve were generally excluded, and this is an important limitation since ovarian reserve is frequently impaired in women with endometriosis.[113]

2.5 GnRH Antagonists

In contrast to GnRH agonists, which have been available for more than two decades, GnRH

antagonists have only recently become available.[86] This delay has been because the early GnRH antagonists were shown to stimulate the release of histamine by mast cells, and it has taken a number of years to develop compounds without this undesirable adverse effect. Not surprisingly, GnRH antagonists have been aimed at the same indications currently accepted for agonists, with the additional advantage of avoiding the initial flare-up in gonadotropin secretion.[86] However, there remains a lack of clinical trials supporting this assumption.

There is an obvious rationale to support the effectiveness of GnRH antagonists in endometriosis and several authors have claimed a role for these agents in the management of the disease,[86,114-119] although clinical evidence is insufficient. Two small series support its effectiveness,[88,120] but no randomized controlled trial has been published to date. The only such trial that compared GnRH agonists and antagonists in women with endometriosis was designed to assess their effectiveness in protocols for ovarian hyper-stimulation for IVF.[121] Of note, the authors failed to document any differences in terms of pregnancy rate between the two protocols.

The lack of randomized controlled trials on this issue is not surprising. Indeed, based on their pharmacological properties, the benefits of GnRH antagonists on endometriosis-associated symptoms would be expected to be similar to those of the agonists. Hence, to promulgate their use in clinical practice, compliance with GnRH antagonists should be higher than that observed with GnRH agonists. However, this is unlikely for at least three reasons. Firstly, although the flare-up phase should be viewed as a drawback of the agonists since an initial worsening of symptoms can be expected, clinical evidence supporting this hypothesis is lacking. Most studies document no increase in pain after the first month of therapy.[88] Secondly, a remarkable advantage of the agonists over the antagonists is that they are available in depot formulations that can be administered subcutaneously once a month (3.75 mg) or once a trimester (11.25 mg). In contrast, currently available GnRH antagonist formulations require subcutaneous administrations at least once a week (3 mg). This is an important aspect, since adherence to treatment is a crucial prerequisite to allow efficacy. However, in this context, long-acting formulations and potent oral non-peptide antagonists may become available in the future.[88,122] Thirdly, the antagonists are more expensive. In conclusion, currently available GnRH antagonists cannot be expected to markedly overcome the previously mentioned limitations of therapy with the GnRH agonists.

3. Danazol and Gestrinone

Danazol and gestrinone are two medical treatments for endometriosis that have received much attention in the past. Although these two agents have different pharmacological origins, they share a similar adverse effect profile characterized by androgenic activity. Their use has been limited by the availability of alternatives that are equally effective and are better tolerated.

3.1 Danazol

Danazol is an oral androgenic agent that induces amenorrhoea through suppression of the hypothalamic-pituitary-ovarian axis, accompanied by increased serum androgen levels and low-serum estrogen levels.[123] The rationale behind this approach is to interfere with ovarian cyclic activity, thereby disrupting the pathogenic mechanisms that lead to the development of endometriosis-associated pain symptoms.

Danazol represented the gold standard of treatment in the 1980s. Multiple studies have demonstrated its efficacy in reducing endometriosis-associated pain symptoms,[6,124-126] and this was confirmed in a Cochrane meta-analysis.[127] However, similar to other suppressive agents, symptoms typically resume after treatment discontinuation. Moreover, although danazol is less expensive than GnRH analogues, its use is associated with remarkable androgenic/anabolic effects. The most common adverse effects include weight gain, fluid retention, breast atrophy, acne, oily skin, hot flushes and hirsutism.[123] This pharmacological profile negatively

affects compliance and a remarkable proportion of patients withdraw from long-term treatment with danazol. The hypoestrogenic adverse effects of GnRH analogues are better tolerated than the androgenic, anabolic effects of danazol.[126] Like other suppressive agents, post-surgical administration for 3 months has also been shown to be ineffective.[6,128]

Cobellis et al.[129] reported the results of a 6-month study of an intrauterine device loaded with danazol 300–400 mg involving 18 women with recurrent symptomatic endometriosis. Dysmenorrhoea, dyspareunia and chronic pelvic pain, assessed at baseline and monthly thereafter using a VAS for pain, showed a substantial decrease over the entire study period. Two women reported spotting. In one patient, the device was removed because of partial expulsion. According to the authors, this treatment modality provided local drug release with negligible systemic absorption and no systemic adverse effects.

Recently, Razzi et al.[130] reported a study in 21 patients with recurrent deeply infiltrating endometriosis who self-administered danazol 200 mg/day vaginally for 12 months. Dysmenorrhoea, dyspareunia and pelvic pain decreased significantly within 3 months and disappeared after 6 months of treatment, with a persistent effect during the entire study period. A relief of dyschezia and a reduction in rectovaginal nodules were also observed, and few local vaginal adverse effects were reported.

Danazol is now used less frequently compared with its use in the last two decades. Although antalgic activity is similar to GnRH agonists, adverse effects are usually less tolerable. In addition, the benefits over a 19-nor-derivative progestogen such as norethindrone are unclear.[60] New delivery systems (vaginal ring and intrauterine system) and new modality of use (self-administration of vaginal capsules) may renew the interest in this drug, but more information on safety is needed. In particular, danazol induces profound and unfavourable changes in serum lipoprotein cholesterol distribution when used orally, and data are needed in this regard on the effects of long-term intrauterine and vaginal use.

3.2 Gestrinone

Gestrinone is a 19-norsteroid derivative with a complex mode of action. Originally designed as a weekly OC, it blocks follicular development and estradiol production; it also binds to androgen receptors and it exhibits both agonist and antagonist effects upon binding to progesterone receptors.[131] Gestrinone has been shown to be effective for the treatment of endometriosis-associated pain, with relief of symptoms being similar to that with danazol or GnRH analogues.[132,133] However, its use is limited by its low tolerability with the primary adverse effects including a decrease in HDL cholesterol, increase in LDL cholesterol, weight gain, hirsutism, seborrhoea and acne.[131]

4. Future and Alternative Drugs

4.1 Aromatase Inhibitors

Aromatase is a cytochrome P450 (CYP) enzyme that catalyzes the conversion of androgens to estrogens, which is the rate limiting step in estrogen biosynthesis.[134] It is expressed in many human cell types including ovarian granulosa cells, placental syncytiotrophoblasts, adipose cells and skin fibroblasts. Estrogen action is classically believed to occur via an endocrine mechanism. Studies on aromatase expression in breast cancer have demonstrated that paracrine mechanisms play an important role in estrogen action in this tissue.[135] Estrogens also display an 'intracrine' effect; estrogens produced by aromatase activity in the cytoplasm of leiomyoma smooth muscle cells or in endometriotic stromal cells can exert their effects by readily binding to nuclear receptors within the same cell.[134] Endometriotic tissue and extra-ovarian endometriotic implants express high levels of aromatase,[136] and aromatase might therefore be involved in the pathogenic mechanism of endometriosis through promoting the survival and growth of disease lesions. Mechanisms involved in the regulation of aromatase activity in endometriotic tissue have also been investigated. The cyclic-AMP-inducible promoter II seems to be responsible for *in vivo*

aromatase expression in endometriotic tissue. The stimulatory transcription factor (SF-1), expressed specifically in endometriotic tissue but not in eutopic endometrium, binds to aromatase promoter II more avidly than the inhibitory factor COUP-TF (chicken ovalbumin upstream promoter transcription factor). Thus, SF-1 activates aromatase gene transcription in endometriosis overcoming the protective inhibition maintained normally by COUP-TF in the eutopic endometrium.[116] These observations represent the molecular basis for application of aromatase inhibitors to the treatment of endometriosis.[137]

There are selective aromatase inhibitors available currently that offer significant safety advantages over previous nonselective inhibitors.[138] These new agents fall into two categories: steroidal/irreversible inhibitors of estrogen synthesis (exemestane and formestane), which compete at the substrate binding site; and non-steroidal/reversible inhibitors (anastrozole and letrozole), which interfere with the CYP moiety of the enzyme.[135]

The effects of inhibitors have been studied when added to cultured fibroblasts derived from breast adipose tissue. Letrozole is particularly potent in fibroblast cultures, in which it is clearly the most effective of these agents.[139]

In post-menopausal women, letrozole administered orally in milligram amounts per day, inhibits peripheral tissue aromatase by 99%. In general, both classes of aromatase inhibitors reduce circulating estrogen to 1–10% of pretreatment levels in post-menopausal women or in pre-menopausal women whose ovaries have been rendered non-functional with other treatments.[139] In humans, the pre-menopausal ovary is generally considered to be resistant to blockade of estrogen production by aromatase inhibitors, because any lowering of plasma estrogen levels would cause reflexive increases in gonadotrophins,[140] which would then induce increased ovarian production of estrogens. No clinical studies have demonstrated complete ovarian blockade with aromatase inhibitors; consequently, as a potential therapy for endometriosis, these agents should be administered only to post-menopausal women to block estrogen formation in the skin and adipose tissue as well as in endometriotic tissue or combined with other treatments.

Two observational studies have evaluated the effect of aromatase inhibitors combined with a progestin[141] or with an OC[142] in pre-menopausal women with endometriosis resistant to surgical or medical treatment. Both studies showed beneficial effects of the treatments on the disease symptoms without major adverse effects. The only randomized controlled trial[143] available evaluated the clinical efficacy of using either the combination of an aromatase inhibitor and GnRH analogue or GnRH analogue alone for 6 months in a post-surgical setting in 80 patients with severe endometriosis. At 24-month follow-up, the combination of the aromatase inhibitor and GnRH analogue had reduced pain symptoms to a greater extent than the GnRH analogue alone, without deleterious effects on BMD or patient quality of life.

4.2 Immunomodulators and Anti-Inflammatory Drugs

Endometriosis may be considered an inflammatory disease because there is a substantial body of evidence for elevated levels of cytokines and growth factors in peritoneal fluid, alterations in B-cell activity and an increased incidence of autoantibodies in women with endometriosis.[144-147] Moreover, peritoneal macrophages are increased in absolute number, concentration and activity in women with the disease. Although it is unclear whether elevated cytokine levels or inflammation are causes or consequences of the disease, the secretion of these pro-inflammatory substances and associated immune cells into the peritoneal microenvironment may contribute to a cascade of events that are responsible for the establishment and/or further progression of endometriosis.

Two different types of immunomodulators have been suggested for use in the treatment of endometriosis: agents that are capable of enhancing the cytolytic arm of the immune response, and agents that are able to reduce the inflammatory component. Noticeably, these drugs may act at different levels of the pathogenic cascade that

leads to the development and/or progression of the disease.

4.2.1 Agents Enhancing Cell-Mediated Immunity

Various agents that exhibit immune-enhancing properties have been investigated in endometriosis; these include the cytokines interleukin-12 and interferon (IFN)-α-2b as well as two synthetic immunomodulators, the guanosine analogue loxoribine and the acetylcholine nicotinic receptor analogue levamisole. In general, these compounds are well characterized pleiotropic stimulators of the components of the immune system.

IFNα-2b is particularly effective in regulating immune responses against viral infections, as demonstrated by its increasing use in chronic hepatitis C. It acts via mechanisms that include the activation of natural killer (NK) cell-mediated lysis and CD8+ T-cell expansion and stimulation.[148] Loxoribine enhances NK-cell activity, stimulates the proliferation of B cells, stimulates macrophage-mediated cytotoxicity and augments antibody responses.[149] Levamisole is used as an antihelminthic drug and, among the four compounds, is probably the least effective immune enhancer; indeed, the short-term administration of levamisole in humans has been found not to alter serum cytokine levels and to only minimally affect T helper-1 cell immune function.[150,151] These agents have been shown to be effective in eradicating endometriosis in animal models;[152-155] however, negative results have been reported in humans.[148] Moreover, most of these agents have substantial adverse effects that limit their use.

4.2.2 Agents Reducing Inflammatory Components

Since it is well established that the clinical profile of endometriosis is typical of an inflammatory disease, anti-inflammatory or anticytokine drugs have been suggested as good candidates for use in treatment.[156] There is clinical evidence in support of the use of cyclo-oxygenase (COX) inhibitors to treat pain and dysmenorrhoea associated with endometriosis, but any role for these agents beyond pain management is completely unknown. COX expression has been shown to be increased in endometriotic lesions.[157,158] Interestingly, several reports in patients with cancer have shown that treatment with a COX-2 inhibitor can lead to a marked reduction in tumour growth.[159] On this basis, several research groups have evaluated these agents in animal models. Celecoxib, indomethacin, rofecoxib, ibuprofen and nimesulide have been tested in murine models of endometriosis with controversial effects.[160,161]

In Italy, one placebo-controlled trial has been performed that was specifically designed to evaluate the effectiveness of COX-2 inhibitors in endometriosis-associated pelvic pain following conservative surgery.[162] Treatment consisted of rofecoxib (25 mg/day) or placebo administered for 6 months. Both pelvic pain and dyspareunia showed significant improvements that persisted for 6 months after treatment. There was no recurrence in the rofecoxib group, whereas a 16% recurrence rate was observed in the placebo study arm, and there were no significant adverse effects reported with the use of rofecoxib.

Tumour necrosis factor (TNF)-α, secreted by macrophages, is known to be increased in peritoneal fluid from women with endometriosis, and it has therefore been suggested that counteracting TNFα could have a beneficial effect in the disease. TNFα is a pleiotropic cytokine that can have a variety of beneficial and deleterious effects, dependent on the quantity produced, its tissue localization and the local activity of TNF-binding proteins. Therapies that interfere with the action of TNFα, such as the chimeric anti-TNFα monoclonal antibody infliximab or the TNFα receptor-immunoglobulin fusion protein etanercept, have been recommended as possible new treatments for endometriosis. Recent studies have shown that etanercept effectively reduces the degree of spontaneously occurring active endometriosis in the baboon.[163]

The results of a randomized, placebo-controlled trial on the use of infliximab in 21 women with severe pain and rectovaginal endometriosis have recently been reported by Koninckx et al.[164] After 1 month of observation, three infusions of infliximab (5 mg/kg) or placebo were administered and surgery was performed 3 months later. Pain severity, assessed by a VAS, decreased

during treatment by 30% in both study groups, and no effect of infliximab was observed for any of the outcome measures. After surgery, pain scores decreased in both groups with no between-group differences. These preliminary clinical data therefore suggest that TNFα inhibitors do not affect the pain associated with endometriosis.

4.3 Anti-Angiogenic Therapies

One of the most important factors in the process of invasion of other tissues by endometrial cells is probably the vascularization of endometriotic implants.[165] The peritoneal environment is highly angiogenic, and increases have been demonstrated in the quantity and activity of angiogenic factors in peritoneal fluid from women with endometriosis.[165] Angiogenesis is under the control of a number of inducers (including fibroblast growth factor, hepatocyte growth factor, transforming growth factor-α and -β) and inhibitors (such as angiostatin, endostatin and thrombospondin).[166] Of particular importance, however, is the vascular endothelial growth factor (VEGF) family of glycoproteins, which are being seen as increasingly significant in processes involving either physiological or pathological angiogenesis.[167] The expression of VEGF by endometriotic implants provides a mechanism for the neovascularization that is commonly observed around these lesions. VEGF immunostaining has been observed in the epithelium of endometriotic implants, particularly in hemorrhagic red implants.[167]

Elevated levels of VEGF-A have also been demonstrated in peritoneal fluid from women with endometriosis; the highest levels were seen during the proliferative phase of the cycle, a time at which the peritoneum is exposed to the retrograde endometrium.[168] There is a positive correlation between the severity of endometriosis and the level of VEGF-A in peritoneal fluid. The cellular sources of VEGF in peritoneal fluid have not been precisely defined and, although there is evidence suggesting that it is produced by endometriotic lesions, activated peritoneal macrophages also have the ability to synthesize and secrete VEGF.[169] Anti-angiogenic drugs such as VEGF inhibitors and angiostatic agents (AGM1470 [TNP470], endostatin, sirolimus) have been shown to reduce the establishment, maintenance and progression of endometriotic lesions in different laboratory and animal models.[170]

4.4 Selective Progesterone Receptor Modulators

Progesterone receptors (PR) exist as two separate isoforms (A and B) that are expressed from a single gene through an alternative splicing mechanism. The two isoforms have similar steroid-hormone and DNA-binding activities but have distinct functions that are dependent on the cell type. Generally, PRB is a much stronger transcription activator than PRA. Under certain conditions, PRA is inactive as a transcription factor but can act as a ligand-dependent repressor of other steroid receptors, including PRB, estrogen receptors, androgen receptors, mineralcorticoid receptors and glucocorticoid receptors.[171] Both isoforms are highly expressed in response to estrogens in human endometrium before ovulation, but their expression is downregulated by progesterone during endometrial maturation. The precise effect of these two proteins on the endometrium probably depends on the PRA : PRB ratio;[171] in fact, selective ablation of PRA results in a gain of PRB-mediated proliferative activity in the endometrium.[171,172]

The recognized importance of the role of progesterone in reproduction led to the development of synthetic PR ligands. Selective progesterone receptor modulators (SPRMs) possess mixed agonist and antagonist properties and exist as three different types: type I SPRMs prevent or attenuate progesterone receptor binding to the progesterone response element; type II promote progesterone receptor binding to DNA response element, but their ability to alter gene expression is highly variable and may be site-specific; type III influence progesterone receptor binding to the progesterone response element and inhibit DNA transcription. So far, only type II SPRMs have been used in the treatment of endometriosis, and they can act differently, depending on dose, the presence or absence of progesterone and site of action.[173]

SPRMs have the potential to selectively suppress estrogen-dependent endometrial growth and to induce reversible amenorrhoea without systemic effects of estrogen deprivation.[172,174] Several reasons have been suggested for their anti-proliferative effects: they could be secondary to inhibition of estrogen receptor gene transcription by the PRA isoform, or they could be caused by atrophy of spiral arteries, by the blockade of progesterone-dependent growth factors, by the inhibition of angiogenesis, by cell cycle blockade or by modulation of apoptosis via growth factors.[171] In addition, SPRMs have the ability to suppress endometrial prostaglandin production in a tissue-specific manner, which provides a further rationale for the treatment of endometriosis-related pain.[172]

The potential of SPRMs has not yet been thoroughly investigated. One randomized placebo-controlled trial[175] has evaluated the safety and efficacy of the type II ligand asoprisnil in the treatment of endometriosis symptoms. Three doses of asoprisnil (5, 10 and 25 mg/day) were administered for 12 weeks to 130 women with a laparoscopic diagnosis of endometriosis and moderate-to-severe pain at baseline. Interestingly, all doses of asoprisnil reduced non-menstrual pelvic pain and dysmenorrhoea with mild and self-limited adverse effects.

5. General Comments and Recommendations

The management of endometriosis using OCs or progestins, administered via various routes, is generally safe, effective and well tolerated, and should constitute the first-line of medical treatment in symptomatic women who do not want to have children. This pharmacological option is relatively inexpensive and suitable for prolonged therapy, with the additional advantages of being available globally and yielding reproducible results. With appropriate training, general practitioners could prescribe and monitor treatments, thus limiting medical costs involved.

Approximately 25% of patients will still require intervention because of inadequate treatment response or intolerance to adverse effects, but the overall impact of surgery would be greatly limited, with a reduction in morbidity and possible long-term complications. In fact, the outcomes of surgery are highly operator-dependent, and optimal results can be assured only in tertiary-care and referral centres. Endometriosis could be controlled, although not cured, in a non-invasive manner for the majority of women not seeking pregnancy.

A number of drugs for endometriosis have been investigated in studies usually lasting for 6 months. However, the objectives of these short-term treatment periods are far from clear because women with endometriosis may benefit marginally from such a short time interval without pain. Furthermore, the major adverse effects caused by GnRH analogues, danazol and gestrinone, may impact substantially on the HR-QOL of patients, tipping the balance towards unfavourable final outcomes.

Finally, the cost of 6 months of therapy with a GnRH analogue in Italy is more than €1000, with gestrinone (5 mg/week) it is about €450, with danazol (400 mg/day) it is more than €300, with a monophasic low-dose OC taken continuously it is about €60, with the levonorgestrel-IUS it is €19 and with norethisterone acetate (2.5 mg/day) it is €9. In the official guidelines from major international gynaecology organizations, it is clearly stated that the various agents available for treatment of endometriosis, including OCs and progestins, show equivalent antalgic efficacy, and that these agents differ only in their adverse-effect profiles and costs.[3-5,176]

Endometriosis, as a diagnosis, is somewhat vague because, apart from implying the presence of ectopic endometrium, it does not define a specific clinical pattern. Very different conditions are grouped under the endometriosis label, from major anatomic complications such as bowel or ureteral stenosis, large and complex adnexal masses, to dysmenorrhoea associated with limited peritoneal implants occurring in much younger patients. Therefore, different treatment alternatives need to be considered based on individual patient characteristics and specific therapeutic objectives. The choice of therapy should not be influenced by a fear of not prescribing the latest

drug, by technical limitations, conflicts of interest or even established but unproven 'gold standards'. Surgery may be an inappropriate response to a patient's complaint if an OC is all that is required. In the absence of proven superior efficacy of a specific medical treatment, it is sensible to prescribe the minimum effective dose of a safer and better tolerated drug that offers a reasonable compromise between antalgic benefit, adverse effects and costs. These criteria are satisfied by progestins and OCs, which are currently the only safe and inexpensive alternative to surgery for patients with symptomatic endometriosis.

6. Conclusions

Because the available medical therapies for treatment of symptomatic endometriosis generally inhibit ovulation, these are indicated for women who do not wish to have children in the short term. Pharmacological treatment of endometriosis-associated pain is invariably symptomatic. Therefore, as the underlying disease is temporarily suppressed but not cured, prolonged treatment schedules, possibly extending for years, are necessary to be clinically meaningful. Progestins and OCs should be considered as first-line options; these have anti-inflammatory properties and are no less efficacious than other hormonal regimens. The alleviation of symptoms has not been found to differ between various OC formulations, and future studies should therefore focus primarily on tolerability and control of endometrial bleeding during continuous use. GnRH analogues, danazol and gestrinone should be regarded as second-line treatments or be limited to specific patients, such as those with contraindications to progestin use. New therapeutic agents are in development, and non-hormonal treatment options may become available in the future, although the safety, efficacy, tolerability and costs of any novel agents should be compared formally with those of OCs or progestins.

The therapeutic approach towards patients with endometriosis should be 'problem-oriented' and not 'lesion-oriented'; before suggesting surgical resection, one should be reasonably confident that this will substantially increase the chances of overcoming the main clinical problem compared with medical treatment.

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