Advances in the management of endometriosis: an update for clinicians

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Endometriosis is a chronic and recurrent disease characterized by the presence and proliferation of endometrial tissue outside the uterine cavity, which occurs in approximately 10% of women of reproductive age. In this estrogen-dependent disorder, lesions become inactive and gradually undergo regression during states of ovarian down-regulation, such as amenorrhoea or menopause. The impact of endometriosis includes impaired fertility potential, as well as symptoms of dysmenorrhoea, dyspareunia and chronic non-menstrual pain, all of which adversely affect quality of life. Management of endometriosis focuses on pain relief and includes medical and surgical treatment. Pharmacologic therapies currently in use include combination oral contraceptives (COCs), danazol, GnRH analogues and progestins. Although some agents show efficacy in relieving pain, all differ in their side effects, making it difficult to achieve a balance between efficacy and safety. Efficacy has been demonstrated with danazol or GnRH analogues; however, treatment is limited to 6 months because of significant metabolic side effects. Alternatives for longer-term management of symptoms include add-back therapy with GnRH analogues, COCs or progestins. Newer options for treatment of endometriosis include depot medroxyprogesterone acetate subcutaneous injection, as well as several agents under investigation that may prove to have therapeutic potential.

Key words: androgens/endometriosis/GnRH (AG/ANTAG)/progesterone/surgery

Introduction

Overview of endometriosis

Endometriosis is a chronic and recurrent disease characterized by the presence and proliferation of functional endometrial glands and stroma outside the uterine cavity (Child and Tan, 2001; Schweppe, 2001; Valle and Sciarra, 2003). It is estimated to occur in up to 10% of women of reproductive age (Eskenazi and Warner, 1997). Although endometriosis is seen primarily among women of reproductive age (Valle et al., 2003), this disease also can affect post-menopausal women (Valle et al., 2003) and adolescents—especially adolescents with uterine abnormalities (Valle et al., 2003). In particular, endometriosis is more common in women with Müllerian anomalies resulting in outflow obstruction (increasing retrograde menstrual flow) (Olive and Henderson, 1987), as well as in women with prolonged menstruation and shorter cycles (27 days or less) (Bérubé et al., 1998).

These observations are consistent with the widely accepted theory that retrograde menstruation is a key component in the development of endometriosis. The importance of retrograde menstruation is supported also by the distribution of endometriotic lesions in the abdominal cavity and the viability in tissue culture of endometrial cells shed during menstruation (Gazvani and Templeton, 2002). However, retrograde menstruation can be observed in up to 90% of women, suggesting the involvement of additional factors in the implantation and growth of endometriotic lesions in women who go on to develop the disease (Gazvani et al., 2002).

Susceptibility to endometriosis is thought to depend on the complex interaction of genetic, immunologic, hormonal and environmental factors. Endometriosis appears to be a multifactorial genetic disorder, in which allelic variants of many genes (including cancer susceptibility genes and genes coding for cytochrome P450 enzymes, nuclear receptors and immunologic mediators) can pre-dispose women to develop endometriosis, depending on environmental conditions (Wenzl et al., 2003). Critical steps postulated in the development of endometriotic lesions include attachment of endometrial cells (from retrograde menstruation) to the peritoneal surface, invasion of these cells into the mesothelium, followed by recruitment of inflammatory cells and angiogenesis around the beginning implant and endometrial cellular proliferation (Seli et al., 2003). Increasing evidence points to the role of immunologic factors and angiogenesis in the disease pathogenesis. Women with endometriosis appear to have altered function of
peritoneal macrophages, natural killer cells and lymphocytes, as well as changes in growth factors and inflammatory mediators in the peritoneal fluid (Gazvani et al., 2002). The growth of endometriotic lesions is also estrogen dependent, with lesions becoming inactive and gradually undergoing regression during states of ovarian down-regulation, such as amenorrhea or menopause (Bulun et al., 1999; Gurates and Bulun, 2003; Valle et al., 2003).

**Diagnosis**

Diagnosis of endometriosis can be difficult, given the non-specific nature of many of its symptoms, the common occurrence of pelvic pain in women without endometriosis and the considerable overlap with other conditions (e.g. pelvic inflammatory disease or irritable bowel syndrome) (Child et al., 2001; Kennedy et al., 2005). For this reason, a diagnosis can be confirmed only by a surgical procedure (generally laparoscopy) to excise and histologically evaluate disease implants (Rice, 2002). Due to the invasiveness of this procedure, however, some experts have recommended that empiric treatment of suspected endometriosis be initiated based on symptoms. The rationale for this approach includes the potential for endometriosis-associated pain to occur in the absence of visualized implants, the efficacy of some medical therapies and the demonstrated accuracy of clinical diagnosis when based on a thorough evaluation (Rice, 2002; Winkel, 2003).

A recent prospective study evaluated the positive predictive value of severe dysmenorrhea and pelvic examination findings in diagnosing endometriosis clinically (Cheewadhanaraks et al., 2004). In this study, 116 patients with severe dysmenorrhea, after excluding urinary and gastrointestinal disease, separately underwent pelvic examination and laparoscopy by different physicians. Results showed the prevalence of endometriosis in this study was 78.4%. The positive predictive value of severe dysmenorrhea with nodularity of the cul-de-sac and/or uterosacral ligament(s) was 94.0% (Cheewadhanaraks et al., 2004). The available evidence thus indicates the accuracy of a clinical diagnosis for endometriosis.

**Current options for the management of endometriosis**

The principal objective in treating endometriosis is symptom-relief management (Chwalisz et al., 2002). In addition to relieving pain, the goals of treatment for patients with endometriosis are to prevent or delay disease progression by reducing endometriotic implants through surgical treatment or medically induced atrophy of the implants (Rice, 2002; Valle et al., 2003). Because neither medical nor surgical treatments have been proven to improve fertility rates substantially in women with endometriosis in its early stages, the focus of treatment is on the relief of pain symptoms (Chwalisz et al., 2002; Shaw, 2003). Because of the chronic nature of this disease, long-term or repeated courses of medical therapy are required to control these symptoms (Schweppe, 2001).

In the past, endometriosis was treated primarily by surgery; and in fact, surgery—alone or in combination with medical therapy—remains a common treatment method for all stages of endometriosis (Viganò et al., 2003). In a 12 month trial (n = 39), more women reported improvement in symptoms after excisional surgery (80%) than after receiving placebo (32%) (Abbott et al., 2004). Nevertheless, surgery is an invasive therapeutic option that is far from ideal, because 20% of cases do not respond (Abbott et al., 2004), and the recurrence rate is high after surgery (Milingos et al., 2003). Although data directly comparing the results of surgical and medical treatment are scarce, the available evidence suggests that surgery does not provide any greater relief of pain symptoms than does medical therapy (Winkel, 2000). Although estimates vary, an independent, randomized, controlled clinical trial reported that 51% of women experienced a recurrence of symptoms sufficient to require additional medication for pain within 1 year of surgery (Hornstein et al., 1997). Other reports have indicated that 7–30% of patients experience recurrence of pain symptoms within 3 years of laparoscopic surgery, an estimate that increases to 40–50% at 5 years after surgery (Valle et al., 2003). Studies of laser surgical treatment also suggest increasing recurrence of symptoms with time (e.g. recurrence occurred in 23% of patients at 1 year and 31% of patients at 2 years in one study cohort of 106 patients) (Shaw, 2003). These rates are roughly comparable with those following medical therapy: a long-term follow-up study of GnRH.
analogue therapy reported recurrence rates of 28% at 2 years and 53% at 5 years after cessation of therapy (Waller and Shaw, 1993).

Surgical treatment for endometriosis requires considerable experience and expertise on the part of the surgeon, and therefore results are likely to be operator dependent (Winkel, 2000). In addition to differences in skill level and experience of surgeons, the wide variability in the appearance of endometriotic lesions can make them difficult to recognize. For example, subperitoneal, small or microscopic lesions may not be seen during laparoscopic procedures. Deep lesions (type III) can be particularly difficult to identify and are most likely to occur in patients with mild or minimal endometriosis. These and other factors may provide an explanation for why surgery does not improve pain in some patients. Because surgery frequently fails to remove all endometriotic lesions, many clinicians are now viewing medical therapy—alone or before or after surgery—as the most effective strategy for managing the pain symptoms of endometriosis (Winkel, 2000).

It has been understood for some time that endometriotic tissue is hormonally sensitive, and that symptoms of endometriosis usually improve during pregnancy or after menopause. Currently available medical therapies for endometriosis act by attempting to mimic periods during which a woman does not menstruate: menopause (GnRH analogues), amenorrhoea (chronic anovulation with danazol) or pregnancy [oral contraceptives (OCs) or progestins (Child et al., 2001)]. Unlike surgery, these methods of treatment are non-invasive and are not operator dependent. However, a disadvantage for women desiring pregnancy in the near term is that conception is generally not possible during medical therapy—indeed, many of these agents are also used as effective contraceptives. Therefore, before choosing therapy, health care providers should consider an individual woman’s family plans and fertility status (Child et al., 2001).

Medical treatment of endometriosis-associated pain is generally effective, with little difference in efficacy observed among the different types of agents used; however, the adverse-event profiles of the various drug regimens can differ markedly (Child et al., 2001). Therapies that have been used include non-steroidal anti-inflammatory agents (as first-line therapy for mild symptoms), androgenic agents (danazol), GnRH analogues, estrogen/progestin combined oral contraceptives (COCs) and progestins (Table I) (Rice, 2002).

### Androgenic agents

Danazol is an oral androgenic agent that induces amenorrhoea through suppression of the hypothalamic-pituitary-ovarian (HPO) axis, accompanied by increased serum androgen concentrations and low serum estrogen levels (Rotondi et al., 2002; Valle et al., 2003; Donnez et al., 2004; Crosignani et al., 2005; Schlaff et al., in press).

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**Table 1.** Agents for the pharmacologic management of endometriosis-associated pain (Overton et al., 1994; Gestrinone Italian Study Group, 1996; Vercellini et al., 1997; Rice, 2002; Valle et al., 2003; Donnez et al., 2004; Crosignani et al., 2005; Schlaff et al., in press)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Dosing frequency</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined oral contraceptives</td>
<td>30–35 μg ethinyl estradiol, plus progestin</td>
<td>Oral</td>
<td>Daily (cyclic or continuous)</td>
<td>Irregular bleeding, weight gain, bloating, breast tension and headache</td>
</tr>
<tr>
<td>Danazol</td>
<td>400–800 mg</td>
<td>Oral</td>
<td>Daily (duration limited to 6 months by side effects)</td>
<td>Androgenic/anabolic (weight gain, fluid retention, breast atrophy, acne, oily skin, hot flashes and hirsutism)</td>
</tr>
<tr>
<td>GnRH agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leuprolide</td>
<td>1 mg/day</td>
<td>SC injection</td>
<td>(Duration limited to 6 months due to BMD effects)</td>
<td>Hypoestrogenic (hot flashes, vaginal dryness, emotional lability, loss of libido and BMD decline)</td>
</tr>
<tr>
<td>Leuprolide depot</td>
<td>3.75 mg</td>
<td>IM injection</td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>Triptorelin depot</td>
<td>3 mg</td>
<td>IM injection</td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>Triptorelin</td>
<td>11.25 mg</td>
<td>IM injection</td>
<td>Every 3 months</td>
<td></td>
</tr>
<tr>
<td>Goserecin</td>
<td>3.6 mg</td>
<td>SC implant</td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>Busereclin</td>
<td>300–400 μg</td>
<td>Intranasal</td>
<td>Tid</td>
<td></td>
</tr>
<tr>
<td>Naferecin</td>
<td>200–400 μg</td>
<td>Intranasal</td>
<td>Bid</td>
<td></td>
</tr>
<tr>
<td>Progestins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>60 mg</td>
<td>Oral</td>
<td>12 days per cycle*</td>
<td></td>
</tr>
<tr>
<td>Gestrinone</td>
<td>2.5–5 mg</td>
<td>Oral</td>
<td>Daily/twice weekly</td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>40 mg</td>
<td>Oral</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>5 mg†</td>
<td>Oral</td>
<td>Daily</td>
<td>Irregular bleeding, weight gain, bloating and edema</td>
</tr>
<tr>
<td>MPA</td>
<td>30 mg</td>
<td>Oral</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>DMPA-IM 150‡</td>
<td>150 mg</td>
<td>IM injection</td>
<td>Every 3 months</td>
<td></td>
</tr>
<tr>
<td>DMPA-SC 104‡</td>
<td>104 mg</td>
<td>SC injection</td>
<td>Every 3 months</td>
<td></td>
</tr>
</tbody>
</table>

BMD, bone mineral density; DMPA, depot medroxyprogesterone acetate; IM, intramuscular; MPA, medroxyprogesterone acetate; SC, subcutaneous.

*During the luteal phase.
†Starting dose, with gradual dose escalation.
‡Also with transient BMD decline.
compared these agents with danazol (the gold standard of treat-
ment) in numerous randomized controlled clinical trials, most of which
reduced dyspareunia, pelvic pain, pelvic tenderness and induration
that treatment with either nafarelin acetate or danazol significantly
improved endometrial lesions and pain symptoms in 81 women with
endometriosis, with no significant differences between groups.
However, danazol was poorly tolerated, and 18.5% of patients
treated with this agent withdrew during the study due to adverse
events compared with 5.5% of patients receiving a GnRH
 analogue (P < 0.05) (Rotondi et al., 2002).

In fact, poor tolerability represents the major drawback of dana-
zol as a treatment for endometriosis: this agent has both andro-
genic and anabolic properties, leading to side effects, such as
weight gain, edema, myalgia, acne, oily skin and hirsutism
(Biberoglu and Behrman, 1981; Rotondi et al., 2002). These concerns
limit treatment duration to 6 months, and the use of this agent has been in decline in recent years (Valle et al., 2003). Danazol should not be used in women with liver disease or hyper-
lipidemia, and women receiving danazol therapy also must use
effective contraception during the entire course of treatment
(Valle et al., 2003).

GnRH

GnRH analogues are currently one of the most widely used medical
therapies for endometriosis (Valle et al., 2003). These agents induce medical menopause by down-regulating hypothalamic-
pituitary GnRH receptors, thus causing decreased gonadotropin
secretion, suppression of ovulation and reduced serum estrogen
levels (Child et al., 2001; Valle et al., 2003). Several GnRH ana-
logues used for the treatment of endometriosis include nafarelin,
buserelin, histrelin, goserelin, triptorelin and leuprolide (Fili
cori et al., 1993; Child et al., 2001). GnRH analogues have been studied
in numerous randomized controlled clinical trials, most of which
compared these agents with danazol (the gold standard of treat-
ment at the time). For example, a 6 month trial (n = 49) showed
that treatment with either nafarelin acetate or danazol significantly
reduced dyspareunia, pelvic pain, pelvic tenderness and induration
(Fraser et al., 1991). In a study that compared depot triptorelin
with danazol during 24 weeks of treatment, dysmenorrhea was
absent at the end of treatment in both groups, and dyspareunia and
pelvic pain had decreased by at least 50% (Cirkel et al., 1995).
These and other studies have revealed minimal or no difference in
efficacy between GnRH analogues and other medical therapies,
such as danazol, COCs or gestrinone (Child et al., 2001).

As expected, given their mechanism of action, GnRH analogues
are associated with significant hypoestrogenic side effects. Short-
term effects include menopausal symptoms, such as hot flashes,
vaginal dryness, loss of libido and emotional lability. Long-term
use is associated with substantial bone mineral density (BMD)
reduction (3.2% reduction in lumbar spine BMD after 6 months
and 6.3% after 12 months of continuous treatment), which limits
treatment with these agents to a maximum of 6 months’ duration
(Child et al., 2001; Valle et al., 2003).

Recent investigation has therefore focused on the use of ‘add-
back’ regimens to prevent or reduce the loss of BMD, which may
lengthen the duration of time that these agents can be administered
(Child et al., 2001). Such regimens include the addition of a pro-
gestin only, a progestin plus bisphosphonate or a progestin plus
estrogen (see Table II for examples that have been studied). Add-
back therapy is recommended by the United States Food and Drug
Administration if GnRH analogues are used longer than 6 months
(Lupron Depot [package insert], 2004), although add-back therapy
may be initiated earlier during GnRH analogue therapy. Several
regimens have shown success in reducing BMD loss. For example,
a 1 year, randomized, double-blind trial of 201 women
treated with leuprolide [3.75 mg intramuscular (IM) monthly]
reported preservation of BMD in add-back groups receiving pro-
gestin only (norethindrone acetate 5 mg daily) or progestin plus
conjugated equine estrogen (either 0.625 mg or 1.25 mg daily).
It should be noted, however, that a greater proportion of patients tak-
ing the higher dosage of estrogen withdrew from the study prematu-
rely, citing a lack of symptom improvement (Hornstein et al., 1998).
Due to the shortage of large-scale clinical trials to date, it is
not yet possible to define a single add-back therapy to recommend
for all women treated with GnRH agonists to relieve endometrio-
asis-associated pain (Child et al., 2001; Rice, 2002). A further caveat
regarding this therapy is the considerable expense of com-
bined GnRH analogue plus add-back therapy relative to other
endometriosis therapies, such as COCs or progestins (Child et al.,
2001).

COCs

COCs are used widely as initial therapy for women with chronic
pelvic pain whose suspected cause is endometriosis, as these
agents are generally well tolerated with less metabolic impact than
danazol or GnRH analogues (Rice, 2002; Vercellini et al., 2003a).
Use of COCs results in ovulation inhibition, decreased gonadotropin
levels, reduced menstrual flow and decidualization of endometriotic

<table>
<thead>
<tr>
<th>Table II. Add-back regimens investigated for use with GnRH receptor analogue therapy to minimize adverse effects</th>
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<tbody>
<tr>
<td>Regimen</td>
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<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Progestin only</td>
</tr>
<tr>
<td>MPA</td>
</tr>
<tr>
<td>Net</td>
</tr>
<tr>
<td>Net Ac</td>
</tr>
<tr>
<td>Tibolone</td>
</tr>
<tr>
<td>Progestin + bisphosphonate</td>
</tr>
<tr>
<td>Net + sodium etidronate</td>
</tr>
<tr>
<td>Progestin + estrogen</td>
</tr>
<tr>
<td>MPA + CEE</td>
</tr>
<tr>
<td>MPA + 17β-E2</td>
</tr>
<tr>
<td>Net + 17β-E2</td>
</tr>
<tr>
<td>Net Ac + CEE</td>
</tr>
</tbody>
</table>

17β-E2, 17β-estradiol; CEE, conjugated equine estrogen; MPA, medroxypro-
gesterone acetate; Net Ac, norethindrone acetate; Net, norethindrone.
Reprinted with permission from Rice (2002).
implants (Rice, 2002); COCs also have been shown to down-regulate cell proliferation and increase apoptosis in the eutopic endometrium of women with endometriosis (Meresman et al., 2002).

Although COCs have been used extensively in clinical practice for many years to relieve endometriosis pain, evidence for their efficacy has been largely observational (Rice, 2002; Vercellini et al., 2003a). One small, open-label, randomized clinical study comparing goserelin with a cyclic low-dose COC containing ethinyl estradiol and desogestrel found a greater reduction in dyspareunia in the GnRH-analogue group and similar relief of non-menstrual pain in both groups (Vercellini et al., 1993). A separate randomized clinical study compared treatment with a COC containing ethinyl estradiol and gestodene for 12 months with treatment with triptorelin for 4 months, followed by COC for 8 months in women who had undergone a laparoscopy or laparotomy (Parazzini et al., 2000). In this study, the treatment schedule of the GnRH analogue plus COC trended towards higher efficacy in relieving pelvic pain in women with endometriosis at 1 year. Another small, prospective, randomized trial compared post-operative administration of a cyclic low-dose COC containing ethinyl estradiol and gestodene for 6 months with no treatment. Results showed that post-operative administration of low-dose COCs did not significantly affect the long-term recurrence rate of endometriosis after surgical treatment (Muzii et al., 2000).

An issue to consider when using COCs for the management of endometriosis pain is their estrogen component, which may result in stimulation of the disease (Rice, 2002). In addition, because cyclic COC use permits monthly uterine bleeding, affected women continue to experience dysmenorrhea during the 7 day pill-free interval and potential reseeding of refluxed endometrial tissues. A 2 year, prospective, self-controlled clinical study of women with endometriosis-associated dysmenorrhea not responding to previous cyclic COC treatment found that continuous COC administration provided significant pain reduction from baseline ($P < 0.001$) (Vercellini et al., 2003b). A disadvantage of this treatment is that 18 packs per year are needed versus 12 packs per year that would be more expensive. In addition, women older than 35 years who smoke and use OCs containing estrogen may be at increased risk of myocardial infarction, stroke or venous thromboembolism (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1997).

**Progestins**

Progestins have been used as therapy for endometriosis worldwide for more than 40 years (Schweppe, 2001). The biological rationale for their use in treating endometriosis includes their suppression of the HPO axis, a process that induces anovulation and reduces serum estrogen levels (Luciano et al., 1988). Progestins also have direct effects on the endometrium, causing marked decidualization and atrophy of both the eutopic endometrium and endometriotic lesions (ESHRE Capri Workshop Group, 2001; Schweppe, 2001). In addition, progestins have been demonstrated to inhibit angiogenesis (Blei et al., 1993), required for maintenance of endometriotic implants and decrease markers of intraperitoneal inflammation (Haney and Weinberg, 1988). All these factors, along with the reduction or elimination of menstrual flow associated with progestin use (which can limit the pelvic contamination of retrograde menstruation), are likely to benefit patients undergoing this type of treatment (ESHRE Capri Workshop Group, 2001; Vercellini et al., 2003a).

Progestins are available in multiple forms, including pills, injections, subdermal implants, and intrauterine devices (Vercellini et al., 2003a), and a variety of these agents have been studied for the treatment of endometriosis. In a systematic review of progestin studies, pooled results of trials of oral or injectable progestins indicated that progestins reduced or eliminated pain symptoms in approximately 90% of women (with individual study results ranging from approximately 70–100% of women) (Vercellini et al., 1997). A recent 6 month, prospective, non-comparative observational study of the levonorgestrel intrauterine system also indicated that this progestin therapy significantly improved the severity and frequency of pain and menstrual symptoms in women with minimal to moderate endometriosis. The proportion of patients who reported moderate or severe dysmenorrhea declined from 96% before therapy to 50% at 6 months ($P < 0.001$). However, in this study non-cyclical pelvic pain was not significantly reduced during 6 months of treatment (Lockhat et al., 2004).

In addition, small placebo-controlled trials of progestins have reported significant relief of endometriosis-associated pain (Telimaa et al., 1987a,b; Overton et al., 1994). In a prospective, double-blind study of 59 patients with mild-moderate endometriosis, women were randomized to treatment with high-dose (100 mg daily) oral MPA, danazol or placebo for 6 months. The effect of treatment with either danazol or oral MPA produced significant reductions in pelvic ($P = 0.001$), lower back ($P = 0.002$) and defecation pain ($P = 0.007$) compared with placebo, with no significant differences between the two treatments (Telimaa et al., 1987a). In another prospective, double-blind trial, 62 women with mild-moderate endometriosis were randomized to luteal-phase dydrogesterone (40 or 60 mg) or placebo for 6 months. In this study, pain scores were significantly decreased at month 6 compared with month 1 in the 60 mg dydrogesterone group ($P = 0.044$) but not in the 40 mg dydrogesterone or placebo groups (Overton et al., 1994).

In more recent randomized comparative trials of progestins in the treatment of endometriosis, both depot MPA (DMPA, 150 mg/3 months by IM injection) and dienogest demonstrated pain reduction comparable with that achieved with other standard medical therapies: DMPA in comparison with danazol plus COCs (Vercellini et al., 1996) and dienogest in comparison with a GnRH analogue (Cossun et al., 2002). In fact, in the study of DMPA, after 1 year of treatment, dysmenorrhea was significantly worse in the danazol + COCs group than in the DMPA group (Vercellini et al., 1996). However, in a 6 month randomized trial comparing another progestin, oral lynestrenol, with a GnRH analogue in women with severe endometriosis, the GnRH analogue produced greater improvements in dysmenorrhea, chronic pelvic pain and dyspareunia (Regidor et al., 2001).

Progestins also appear to offer benefits in treating patients after surgery for endometriosis, reducing the probability of pain recurrence and lengthening the symptom-free period relative to postsurgical expectant management (Vercellini et al., 2003a). Because medical treatment for endometriosis symptoms (with or without surgery) is generally needed for longer periods of time due to the chronic and recurrent nature of the disease (Vercellini et al., 2003a), progestins may be an appropriate alternative for the medical management of endometriosis, given that these agents are relatively
well tolerated, have a more limited metabolic impact than other agents and also are inexpensive (ESHRE Capri Workshop Group, 2001; Vercellini et al., 2003a).

**DMPA-SC 104**

DMPA-SC 104, a lower-dose, 104 mg/0.65 ml formulation of DMPA specifically developed for subcutaneous injection, is administered once every 3 months (Jain et al., 2004a). The safety, tolerability and contraceptive efficacy of DMPA-SC 104 was demonstrated in clinical trials (Jain et al., 2004b).

In light of the history of MPA use worldwide in the management of endometriosis, DMPA-SC 104 has been evaluated recently for the treatment of endometriosis-associated pain in two large, 18 month, multinational, randomized, evaluator-blinded comparative trials (Crosignani et al., 2005; Schlaff et al., in press). In these trials, 574 women with laparoscopically diagnosed endometriosis were randomized to 6 months of treatment with DMPA-SC 104 or leuprolide, followed by 12 months of post-treatment evaluation. Both trials demonstrated that DMPA-SC 104 and leuprolide were statistically equivalent in the reduction of at least four of five endometriosis symptoms after 6 months of treatment, as well as after 12 months of post-treatment follow-up (observed case analysis). The two treatments also improved patient quality of life, as measured by the Endometriosis Health Profile (EHP-30) and Short Form-36 (SF-36) scales (Crosignani et al., 2005; Schlaff et al., in press).

In both trials, treatment with DMPA-SC 104 resulted in significantly \( P < 0.001 \) less decline in lumbar spine and total hip BMD after 6 months than treatment with leuprolide (Crosignani et al., 2005; Schlaff et al., in press). After 12 months of post-treatment follow-up, BMD levels had recovered to near-baseline levels in the DMPA-SC 104 groups of both trials while the leuprolide groups continued to show significant declines from baseline. Hypoestrogenic symptoms, as measured by the Kupperman Index, were reported more frequently in the leuprolide group than in the DMPA-SC 104 group, whereas treatment with DMPA-SC 104 was associated with more bleeding or spotting than treatment with leuprolide (Crosignani et al., 2005; Schlaff et al., in press). Median weight gain in both trials was not significantly different between groups (less than 1 kg increase after 6 months of treatment in both studies), and the incidence of adverse events was similar between groups (Crosignani et al., 2005; Schlaff et al., in press).

The reduced impact of DMPA-SC 104 versus leuprolide on BMD, and the degree of BMD recovery seen in DMPA-SC 104 subjects following cessation of therapy, was a particularly important finding of these clinical trials, given the need for extended periods of medical therapy to control symptoms of endometriosis. Data on DMPA-IM 150, which has been used as a contraceptive in women worldwide for more than 30 years, also have shown transient declines in BMD with current use (Cundy et al., 1998; Gbolade et al., 1998; Paiva et al., 1998; Tang et al., 2000; Berenson et al., 2001; Perrotti et al., 2001; Scholes et al., 2002, 2004); however, no significant difference has been observed between the BMD of post-menopausal former users of DMPA-IM 150 and that of non-users (Orr-Walker et al., 1998). Combined with the clinical data that demonstrate efficacy similar to that of leuprolide, these data highlight DMPA-SC 104 as a useful new option for the treatment of endometriosis-associated pain.

**Impact of endometriosis and its treatment on quality of life**

Because of the chronic nature of endometriosis, recurrences of symptoms are common over the long term (Valle et al., 2003). For this reason, medical therapies that can be administered for only a few months due to safety concerns or poor tolerability are not ideal for women with symptomatic endometriosis (Vercellini et al., 2003a). In addition, repeated surgical procedures for recurring pain increases morbidity, as well as physician and patient frustration (Vercellini et al., 2000). Thus, chronic pain symptoms and the effects of poorly tolerated, ongoing, or repeated treatment courses can contribute to poor quality of life for women with endometriosis, disrupting job performance, social relationships, or sexual functioning (ESHRE Capri Workshop Group, 2001; Marques et al., 2004).

Data regarding the effect of specific treatments on patient quality of life are limited. Laparoscopic excision of endometriosis was shown to be more effective than placebo in reducing pain and improving quality of life in a 12 month, randomized study \((n = 39)\) (Abbott et al., 2004). Whereas, the stimulatory phase of GnRH agonist therapy was associated with a clinically significant \( P < 0.001 \) increase in pain and a decrease in quality of life compared with placebo in a 4 week trial \((n = 120)\) (Miller, 2000), a separate study \((n = 133)\) showed that patients treated with GnRH agonist plus add-back therapy experienced fewer adverse effects and better quality of life than patients treated with a GnRH agonist alone (Zupi et al., 2004). In a study of 48 women with verified endometriosis, treatment with either oral MPA or nafarelin significantly improved quality-of-life factors including levels of anxiety-depression and sleep disturbance (Bergqvist and Theorell, 2001). Finally, the previously mentioned clinical trials assessing the efficacy of DMPA-SC 104 in the treatment of endometriosis-associated pain also assessed patient quality of life, using the EHP-30 and SF-36 scales (Crosignani et al., 2005; Schlaff et al., in press). In these trials, users of DMPA-SC 104 and leuprolide experienced improvements over time in all quality-of-life domains measured, with the greatest effects seen in the pain, control and powerlessness and emotional well-being dimensions (Crosignani et al., 2005; Schlaff et al., in press).

**Issues in the long-term management of endometriosis**

A major challenge in managing endometriosis is the chronic or recurrent symptoms that require long-term or repeated courses of medication (Schweppe, 2001). Treatment with GnRH analogues, such as leuprolide, is limited to only 6 months, because these agents induce a hypoestrogenic state (artificial menopause) that substantially decreases BMD (Rice, 2002; Lupron Depot [package insert], 2004). Although the addition of add-back therapy is an option, regimens are both complicated and costly, and no single add-back therapy has yet been recommended for all women treated with GnRH agonists (Child et al., 2001; Rice, 2002).

Daily oral COCs can be safely used for the long-term, although the high frequency of dosing may be inconvenient for some women. As a treatment for endometriosis pain, COCs are often used daily and continuously (without a pill-free interval) for 6–9 months (Valle et al., 2003). It has been estimated that approximately 20–50% of women who use COCs for contraceptive purposes miss at least one pill per cycle, with 10–20% missing two or
more pills per cycle (Rosenberg et al., 1995; Rosenberg and Waugh, 1999).

Progestins may be an appropriate alternative for longer-term management of endometriosis-associated pain due to their safety, tolerability and cost (ESHRE Capri Workshop Group, 2001; Vercellini et al., 2003a). In addition, progestins are available in multiple delivery forms, consistent with the trend in recent years towards the development of newer non-daily hormonal delivery systems. One example is DMPA-SC 104: as discussed previously, recent trials demonstrated that DMPA-SC 104 or leuproline effectively relieved endometriosis pain symptoms and similarly improved patient quality of life during 6 months of treatment. As newer delivery methods provide more convenient routes of administration, they may be used more effectively in women with endometriosis.

**Newer non-daily hormonal delivery systems**

Many delivery systems with extended dosing intervals have become available recently for the administration of progestins or combined estrogens/progestins, which may have applications in the treatment of endometriosis. Newer options include a transdermal patch, an intravaginal ring, and most recently, the addition of an SC injectable. The transdermal system developed for contraceptive purposes is a 20 cm² patch applied to the skin of the buttocks, abdomen, upper outer arm or upper torso (excluding the breast). Each patch is worn for 7 consecutive days (replaced weekly), delivering an average daily dose of 150 μg norelgestromin (the active metabolite of norgestimate) and 20 μg ethinyl estradiol into the systemic circulation (Abrams et al., 2002; Henzl and Loomba, 2003). The advantages of transdermal hormone delivery include the avoidance of first-pass hepatic metabolism, a reduced frequency of dosing and administration that is non-invasive and user controlled (Henzl et al., 2003). In clinical trials, the percentage of cycles with perfect dosing was significantly higher for the contraceptive patch than for COCs (88.2 versus 77.7%, P < 0.001) (Audet et al., 2001; Archer et al., 2004). However, the patch was found to have reduced efficacy as a contraceptive in women whose body weight is ≥90 kg (Ziemann et al., 2002). The impact of body weight on efficacy in the management of endometriosis is unknown, as the patch has not been studied in this context.

Intravaginal delivery of contraceptive levels of estrogen and progestin is available as a flexible, soft, transparent ring that releases daily doses of 120 μg etonogestrel and 15 μg ethinyl estradiol over a period of 3 weeks (replaced monthly) (Timmer and Mulders, 2000). Similar to the transdermal patch, advantages of intravaginal delivery include avoidance of first-pass hepatic metabolism and minimally invasive administration that is performed by the woman herself (Timmer et al., 2000; Roumen et al., 2001). In addition, the vaginal ring is more private than a patch, which is visible on the skin. In contraceptive clinical studies, the longer dosing interval resulted in correct and consistent use during 90.8% of cycles (Roumen et al., 2001), and >95% of women reported that they found it easy to use (Novák et al., 2003). Similar to the patch, the vaginal ring has not been studied specifically for efficacy in the treatment of endometriosis. Limitations of this delivery method include the possibility that the ring may be inadvertently expelled (NuvaRing [prescribing information], 2003) or that the device may interfere with intercourse (15% of women and 29% of partners indicated in clinical studies that they felt the ring during intercourse occasionally, frequently, or always) (Novák et al., 2003).

Subcutaneous injection (recently available through the progestin-only DMPA-SC 104) shares the advantage of other non-daily methods in avoiding first-pass hepatic metabolism.

A 3 month injection is also highly convenient (requiring action only four times per year) and offers a high degree of privacy (Nelson, 2002). Because SC absorption is slower than IM absorption, a lower dose of DMPA delivered by SC injection achieves effective serum MPA concentrations over the entire 91 day dosing interval (Jain et al., 2004a). These same data also indicate that this method is not immediately reversible, in contrast to pills, patches or rings, which can be discontinued at any time. In contraceptive clinical trials, DMPA-SC 104 demonstrated high efficacy that was not affected by body weight (Jain et al., 2004b). As discussed earlier in this article, DMPA-SC 104 also has been studied in clinical trials of women with endometriosis-associated pain (unlike the patch or ring hormonal delivery systems) and has been found to be as effective as leuproline in relieving pain symptoms.

**New treatment possibilities for the management of endometriosis: investigational agents**

Because of the systemic hypoestrogenic symptoms associated with currently available hormonal therapies that block ovarian function, new approaches to the medical therapy of endometriosis that have the potential to target the estrogen-dependent growth of endometrial lesions more selectively are under investigation (Figure 1) (Chwalisz et al., 2002; Viganò et al., 2003). These include aromatase inhibitors, selective estrogen receptor modulators (SERMs) and selective progesterone receptor modulators (SPRMs).

**Aromatase inhibitors**

Aromatase P450 is the key enzyme for estrogen biosynthesis, catalyzing the conversion of androstenedione and testosterone to estrone and estradiol. Although the normal endometrium contains no detectable levels of aromatase activity, this enzyme is induced to very high levels in endometriotic tissue by the inflammatory mediator prostaglandin estradiol (E₂) to increase local estrogen production in the disease implants. Aromatase inhibitors target this enzyme to decrease local estrogen synthesis and thus to inhibit the growth of endometriotic implants (Bulun et al., 2004). However, this treatment also would reduce ovarian estrogen production and may therefore require estrogen add-back therapy to protect bones (Chwalisz et al., 2002).

In the first published report of the use of an aromatase inhibitor (anastrozole) for the treatment of endometriosis, a 57 year old woman with severe recurrent endometriosis experienced complete relief of pain after 2 months of treatment. Despite the addition of calcium and alendronate (inhibitor of bone resorption), however, lumbar spine BMD decreased by 6.2% after 9 months of treatment (Takayama et al., 1998). A recent, small pilot study of 10 reproductive-aged women with treatment-resistant endometriosis investigated the effects of the aromatase inhibitor letrozole (2.5 mg/day), administered with the progestin norethindrone acetate (2.5 mg/day),...
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Calcium and vitamin D for 6 months. This treatment significantly reduced pelvic pain scores in 9 of 10 patients and achieved marked reduction of laparoscopically visible lesions in all 10 women, with no significant change in BMD (Ailawadi et al., 2004). Although promising, these results require confirmation in randomized clinical trials.

Anti-estrogens

Non-steroidal anti-estrogens that bind to estrogen receptors (ERs) and can act as either estrogen agonists or antagonists, depending on the target tissue, are known as SERMs. For use in the treatment of endometriosis, SERMs are being sought that have estrogen antagonist activity on the endometrium but agonist activity on bone and circulating lipoproteins (Riggs and Hartmann, 2003; Viganò et al., 2003). One such newly developed agent is TZE-5323, which is thought to exert its anti-estrogenic effects by inhibiting binding of E2 to ERα and ERβ, as well as suppressing E2–ERα transcriptional activation (Saito et al., 2003). In a rat model of endometriosis, TZE-5323 dose dependently reduced the volume of endometriosis implants without affecting serum estradiol concentrations or decreasing BMD in the intact rats (Saito et al., 2003). Its effects in human clinical studies are not yet known.

Progesterone receptor modulators

The SPRMs bind to progesterone receptors and, similar to the SERMs, can act as either agonists or antagonists of progestogenic activity, depending on the target tissue, dose and presence or absence of progesterone (Olive, 2002). These agents have the potential to suppress endometrial proliferation selectively in the presence of an estrogenic environment, allowing the treatment of endometriotic implants without the side effects of systemic estrogen deprivation (Chwalisz et al., 2002; Olive, 2002). Several SPRMs have been developed and are currently under investigation, including J867, J956, J912 and J1042. Preliminary studies with J867 have been promising, although clinical trials are still needed to assess the role of these agents in the treatment of endometriosis (Chwalisz et al., 2002; Olive, 2002).

Conclusions

Endometriosis is a chronic and recurrent disease that can cause pain symptoms, such as dysmenorrhoea, dyspareunia, or non-menstrual pelvic pain, and can impair fertility and significantly impair quality of life. Although surgical procedures to remove endometriotic implants are effective in relieving endometriosis-associated pain, recurrence rates are high and many women require repeated medical therapy to control symptoms. Many pharmacologic treatment options are currently available to inhibit the growth and activity of endometriotic implants, including COCs, danazol (an androgenic agent), GnRH analogues, and progestins. Because substantial metabolic side effects minimize the use of danazol or GnRH analogues to 6 months’ duration, progestins (oral or injectable) alone or combined with estrogen are often an alternative treatment option for the long-term management of endometriosis pain in women not currently desiring pregnancy.

Recently, the development of newer non-daily hormonal delivery options (transdermal, intravaginal, and SC injectable) has potentially increased the convenience and consistent use of estrogens/progestins over the long term for many women. Of these
newer delivery systems, DMPA-SC 104—a progestin-only SC injection—has been shown in randomized clinical trials to reduce endometriosis pain effectively, with significantly less impact on BMD compared with a GnRH analogue (with higher rates of irregular bleeding and slower return to ovulation following discontinuation). Other new treatments for endometriosis currently under investigation include aromatase inhibitors, SERMs and SPMRs. These agents are promising by virtue of their ability to target endometriotic implants more specifically rather than systemically reduce estrogen levels, but they are in early stages of development and have not yet been assessed fully in clinical studies. The goal of future research should be to define the optimal role of the different medical options in the treatment of endometriosis-associated pain.

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