[Frontiers in Bioscience E1, 455-465, June 1, 2009]

Treatment of endometriosis-related pain: options and outcomes

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TABLE OF CONTENTS

1. ABSTRACT

Endometriosis-associated pain represents a challenge for both the patient and the health care provider since it is often difficult to design treatment strategies resulting in improvement of the symptoms. The association between endometriosis stage and severity of pelvic symptoms is limited. Surgery is generally considered the first line treatment in women affected, at least in those who have not been previously operated, but there are several situations in which medical treatments are useful. Given their good tolerability, minor metabolic effects and low cost, progestogens with or without the addition of estrogens, can be considered the drugs of choice and are currently the only safe and inexpensive alternative to surgery. Progestogens are effective in controlling pain symptoms in approximately three of four women with endometriosis. There is little or no difference in the effectiveness of GnRH agonist and add-back treatment in comparison with other medical treatments for endometriosis while the surgical interruption of pelvic nerve pathways entail some clinically relevant risks.

2. INTRODUCTION

Endometriosis-associated pain is a debilitating problem that can have a significant impact on the quality of life of the patients. It represents a challenge for both the patient and the health care provider since it is often difficult to design treatment strategies resulting in improvement of the symptoms. Variability in the prevalence of the symptoms reflects both the different forms of the disease in causing pain, and the differences in individual perception. Up to 70% of patients with chronic pelvic pain, as defined as pelvic pain in the same location for at least 6 months, may have endometriosis (1) and this entity can be extremely puzzling and often frustrating. The mechanisms that determine the onset, intensity, type of symptoms and relationships with the various aspects and sites of the lesions are still being studied. The aim of this paper is to give an update on our understanding of the endometriosis-related pain and on the different treatment options and outcomes that might assist practitioners about the appropriate health care for specific clinical circumstances.

3. NEUROBIOLOGY OF PAIN ASSOCIATED WITH ENDOMETRIOSIS

The structures that may give rise to pain in the pelvic region belongs to the urinary system, the reproductive system, the gastrointestinal system and the associated pelvic vasculature and lymphatic structures. The pelvis is innervated by a complex anatomical, neurobiological system with contribution from the somatic, sympathetic and parasympathetic nervous systems (2). This complexity might explain some of the challenges imposed in order to attain strategies for an early diagnosis and successful therapeutic approaches. Peritoneal inflammation, direct infiltration of the nerves, tissue damage, the release of chemical pain mediators, the formation of adhesions and scar retraction or the rupture of the endometrioma are all possible mechanisms responsible for the painful symptomatology.

3.1. Direct infiltration of the nerves

It has been demonstrated that there is a close histological relationship between deep endometriotic lesions and nerves by means of perineural and intraneural invasion and mechanical nerve injury and that patients with the highest pain scores display significantly more neural invasion by endometriosis than patients with lower pain scores (3). It is known that in presence of deep infiltrating endometriosis there is an important exacerbation of pain when pressure is exerted on deep nodular or indurated lesions at physical examination. This phenomenon of pain occurring when a nonpainful stimulus is applied is called hyperalgesia. Hyperalgesia is a major characteristic of "neuropathic pain," which corresponds to a pain sensation that is out of proportion with the intensity of nociceptors stimulation (4). Neuropathic pain is usually accompanied by a nerve injury and this phenomenon also occurs in deep infiltrating endometriosis where nerve invasion by endometriotic stromal cells is frequently observed (5).

3.2 Peritoneal inflammation, cell recruitment and release of pain mediators

Once the regurgitated endometrium has disrupted the peritoneal basal membrane, reached the submesothelial collagen matrix, and induced angiogenesis, it resumes its metabolic activity, generating an inflammatory condition. An inflammatory pelvic exudate is a common finding in women with endometriosis and is expressed as an increase in the volume of peritoneal fluid as well as in number of leucocytes, and an elevated concentration of proteases. Neurogenic inflammation forms part of the tissue response to injury. It seems to be an adaptive response, promoting rapid increases in tissue substrates, activating cells for local defence and enhancing fluid transport to isolate and dilute toxins. There is convincing evidence that inflammatory stimuli *per se* may cause pelvic pain regardless of the concomitant presence of nerve injury (5).

Mast cells are multifunctional immune cells that express high-affinity immunoglobulin E receptors and also release potent inflammatory mediators. They play an important role in the pathogenesis of chronic pain in many pathological conditions (6-9). These cells have been detected in peritoneal and ovarian endometriosis. An even more greater number has been found in deep infiltrating endometriosis in proximity of the nerves (10). Mast cells can release mediators that increase excitability of neurons, but in turn, neurotransmitters such as substance P or Nerve growth Factor (NGF) can trigger mast cell degranulation (11). NGF, which plays a key role in the occurrence of pain, hyperalgesia, and neuropathic pain, is strongly expressed in deep infiltrating endometriosis, and its specific receptor (Trk-A) is expressed in nerves lying within deep lesions or in the vicinity of deep endometriotic lesions (12). Activated mast cells release histamine that can sensitize nociceptors (13-14), and neuronal histamine receptors are upregulated or modulated by nerve injury (15-16). Moreover, activated mast cells contribute directly to neuropathic hyperalgesia by releasing mediators such as tryptase, tumor necrosis factor-alpha, prostaglandins, serotonin, and interleukin-1 (10). Activation of mast cells may also contribute indirectly to the development of neuropathic pain by the recruitment of leukocytes that release algesic mediators. Neutrophils and macrophages secrete molecules such as prostaglandin E_2, eicosanoids, and reactive oxygen intermediates, which can sensitize nociceptors and induce hyperalgesia (10).

4. CORRELATION OF PAIN WITH THE DIFFERENT FORMS OF THE DISEASE

Historically, it has been accepted that the stage of endometriosis based on the revised ASRM classification (17) does not correlate with the degree of pain. Conversely, some evidence supports the view that the histological aspect of the lesions may have a role. According to the study of Demco (18), red vascular lesions, followed by clear lesions, were the type of endometriosis lesions most commonly associated with pain. White scarred lesions were tender at their border but not centrally. Black lesions were least likely to be tender. The author concluded that "younger" lesions are more active and are more likely to result in pain. Of interest, some women did not note pain regardless of the type of lesion palpated and there was no relationship between the symptoms and the specific type of lesion. In line with these data, by analyzing 618 cases of laparoscopically diagnosed endometriosis, Fukaya et al (19) found that pain did not reflect the stage or severity of the disease in 40% of patients. Fedele et al (20) also did not find a consistent relationship between the severity of pain symptoms either for the stage or location of endometriosis. In this regard, our group recently reported data from a multivariate analysis of over 1000 patients (21). This large study documented an association between endometriosis stage and severity of pelvic symptoms but the extent of this association was extremely mild. The relevance of this finding is thus doubtful. The only clinically important observation emerging from this study is the association between posterior cul-de-sac lesions and pain at intercourse (21). Moreover, there is a general consensus that deeply infiltrating endometriosis is more likely to cause pain than superficial endometriosis (22).

Table 1. Main treatment options for endometriosis-related pain

Option	Comment
Pill (cyclic or continuous use)	Effective, safe, inexpensive, optimal side-effects prophyle, suitable for long-term use.
Progestagens	Effective, safe, inexpensive, suitable for long-term use but possible breakthrough bleeding and bone demineralization with 17-OH derivates.
Levonorgestrel-IUD	Effective, safe, inexpensive, suitable for long-term use but possible irregular bleeding, low compliance, unknown effects on deep dyspareunia and does not protect against endometriomas formation.
GnRH agonists + add-back therapy	Effective, safe, suitable for long-term use but expensive and complicated.
Conservative surgery	Effective, appropriate for symptomatic women seeking spontaneous conception, but surgical risks and elevated rate of recurrences.
Conservative surgery + medical treatment	Effective only if use is prolonged (> 6 months) and expensive and no benefit on reproductive performance.
Surgical interruption of pelvic nerve pathways	Presacral neurectomy effective only on hypogastric central pain but potential important side effects (neurologic bladder dysfunction, constipation, surgical risks such as haemorrhage). Laparoscopic uterosacral nerve ablation (LUNA) ineffective.

5. EFFECT OF ESTROGEN-PROGESTOGEN COMBINATION AND PROGESTOGENS IN WOMEN WITH SYMPTOMATIC ENDOMETRIOSIS

It is well established that hormonal drugs do not cure endometriosis but only induce temporary quiescence of active lesions. At restoration of ovulation and of physiologic levels of œstrogens, the endometrium, both eutopic and ectopic resumes its metabolic activity. As a consequence, medical therapy is symptomatic and pain relapse at treatment suspension is the rule (23). Surgery is thus generally considered the first line treatment in women affected, at least in those who have not been previously operated (24,25). However, there are several situations in which medical treatments are useful. Women who have already undergone several operations might prefer to avoid further surgery but need pain relief, and others may want only to postpone surgery because of study, work or family problems. Furthermore, drugs may be chosen as an alternative to surgery in the rare very difficult cases in which the risks of morbidity and complications outweigh the benefits of a radical operation. Accordingly, long-term pain relief is the main objective, and great care should be paid to the choice of drugs. Compounds to be administered only for some months due to poor tolerability, severe metabolic side effects or high cost do not greatly benefit women with symptomatic endometriosis. Progestogens alone or combined with œstrogens are generally well-tolerated, have a more limited metabolic impact than danazol or Gonadotropin Releasing Hormone (GnRH) agonists, are inexpensive and may be used on a long-term basis (23, 26, 27). The following paragraphs will better clarify these issues. The main characteristics of the different management strategies are summarized in Table 1.

5.1. Oral contraceptives

Only a limited number of studies have compared the effects of the oral contraceptives with those obtained during administration of other drugs. These studies have been extensively reviewed elsewhere (23, 28, 29) and tend to indicate that oestrogen-progestogen combinations should not be considered as second-line drugs for non-menstrual pelvic pain. When a long-term use is indicated, an OC may be prescribed without need of "preparation" with a GnRH agonist. OCs used cyclically are the only treatment for endometriosis that permits monthly uterine bleeding. Dysmenorrhoea is known as the most frequent and most severe complaint in women with this disease. The symptom may therefore not subside completely during administration of an OC. Recent studies have demonstrated that women with menstrual-related problems during cyclic use of an OC may benefit from a shift to continuous administration (30, 31). Although elimination of the 7-day interval is recommended by various experts, there are no specific data regarding women with endometriosis. Consequently, we prescribed a monophasic OC (desogestrel 0.15 mg and ethinyl oestradiol 0.02 mg) continuously to 50 patients with dysmenorrhoea recurring after conservative surgery for endometriosis, and not responding to the cyclic use of the same OC (32). During the 2-year study period, 38% of women reported amenorrhoea, 36% spotting and 26% breakthrough bleeding. The mean score of menstrual pain, evaluated according to a 100-mm visual analogue scale, showed a reduction from 75 ± 13 to 31 ± 17. Moderate or severe side effects were reported by 14% of the women. At final evaluation 26% of subjects were very satisfied, 54% satisfied, 2% uncertain, 16% unsatisfied and 2% very unsatisfied. When cyclic use of OCs does not resolve pain associated with monthly bleeding, continuous administration might constitute a simple, effective, safe and well-tolerated option for long-term treatment in women not wanting children.

5.2. Progestogens

Progestogens are gradually regaining popularity for the treatment of pain associated with endometriosis. Medroxyprogesterone acetate (MPA) use in the treatment of symptomatic endometriosis has been evaluated in two randomised controlled trials (33, 34). Evidence from these studies indicate that MPA is more efficacious than placebo but no less efficacious than GnRH agonists in reducing pain and in improving health-related quality of life, suggesting its use in women with symptomatic endometriosis. However, erratic bleeding episodes may be more frequent and prolonged with MPA compared with other progestogens. Furthermore, the optimal dosage of the drug still needs to be determined.

The depot formulation of MPA (DMPA) has been widely evaluated for contraceptive purposes and is currently being used by approximately 12 million women worldwide (35) Results from the first formal study on the use of DMPA in patients with endometriosis has been published in 1996 (36). The progestogen was compared to an association of a monophasic oral contraceptive with low-dose danazol (50 mg/day). After a 1-year treatment, a significant reduction in pain symptoms evaluated with a visual analogue and multidimensional scale has been observed in both groups. However, patients in the

combined OC/danazol group complained of a greater frequency and severity of dysmenorrhoea, which is a logical consequence of cyclic administration. The incidence of side effects was greater in DMPA users. More recently, two randomized multicenter studies confirmed the benefits of this approach. In both trials, patients were randomized to DMPA or GnRH agonists for 6 months and were followed-up for 12 months after suspension of treatment. Schlaff *et al.* enrolled 274 patients and demonstrated that both treatments were equivalently effective in terms of pain symptoms relief, but DMPA showed less bone mineral density loss, less hypoestrogenic side effects and more irregular bleeding (37). Conclusions from the second study recruiting 300 women were absolutely in line with these findings. Again, endometriosis-associated pain was equally reduced in both arms of the study but GnRH agonists determined a more significant reduction in bone mineral density (38). Overall, DMPA is an effective, safe, and extremely economic alternative for the treatment of symptomatic endometriosis. However, because of some of its characteristics, candidates for treatment need to be selected carefully. In fact, prolonged delay in resumption of ovulation is a contraindication to use of DMPA in women wanting children in the near future. Additionally, uterine breakthrough bleeding may be prolonged, repeated and troublesome to correct. More in general, treatment cannot be interrupted in the event of side effects, rendering clinical management complicated when these are severe or scarcely tolerable. Its indication of choice is residual symptomatic endometriosis following definitive surgery. In such circumstances, there are no problems regarding conception or irregular uterine bleeding, and use of DMPA allows a simple and well-tolerated suppression of persistent foci after non-radical operations with no need to opt for daily administration of drugs or further surgery.

Cyproterone acetate (CPA), a derivative of 17-hydroxyprogesterone with anti-androgenic and anti-gonadotropinic properties, has been first used in the treatment of endometriosis by Fedele *et al.* (39) at the dosage of 27 mg/day. The possibility to prescribe a lower dosage (12.5 mg/day) but administered continuously was recently investigated by our group (40) in a randomised study that compared its effects to those of an OC (desogestrel 0.15 mg and ethynilestradiol 0.02 mg) given continuously for 6 months. Ninety women were recruited with moderate to severe pelvic pain that recurred after conservative surgery for symptomatic endometriosis. The main outcome of the study was patients' degree of satisfaction, which was deemed important in order to be able to consider their point of view in the evaluation of drug efficacy, as well as the impact of side effects. At 6 months, dysmenorrhoea, deep dyspareunia and non-menstrual pelvic pain were considerably reduced. In addition, the health-related quality of life, psychological profile and sexual satisfaction improved significantly, with no major differences between groups. Metabolic and subjective side effects were limited. According to an intention-to-treat analysis, 33/45 (73%) women in the CPA group and 30/45 (67%) in the OC group were satisfied with the treatment received. Both schemes used have therefore been shown to be an effective, safe and inexpensive treatment for pain recurring after conservative surgery for endometriosis. CPA may be used when subjective and metabolic effects of œstrogens need to be avoided, or in women unwilling to use contraception because of cultural or religious objections. The continuous use of a low-dose monophasic OC is most probably the preferred option to prevent the effects of œstrogen deprivation in women for whom a long period of therapy is expected.

Norethisterone acetate (or norethindrone acetate, NETA) is a strong progestogen derivative of 19-nortestosterone. Its efficacy was studied by Muneyyirci-Delale and Karacan (41) in 52 women with symptomatic and laparoscopically confirmed endometriosis. Dysmenorrhoea regressed in 48/52 (92%) subjects and chronic pelvic pain in 25/28 (89%). At the end of treatment 49/52 (94%) women had few or no symptoms. Breakthrough bleeding was experienced by 30 (58%) patients, causing four (8%) to drop out. Overall, treatment was successful in 44/52 (84%) recruited subjects. NETA offers various advantages for the long-term treatment of endometriosis. In a recent randomized study of our group, we compared the effectiveness of a continuous treatment with daily ethynilestradiol 0.01 mg plus cyproterone acetate 3 mg to a regimen of NETA 2.5 mg/day in 90 women operated on for rectovaginal deep endometriosis who experienced recurrence of symptoms. At 12 months, dysmenorrhea, deep dyspareunia, nonmestrual pelvic pain, dyschezia and grade of satisfaction resulted similar in the two treatment groups (42). This progestogen allows good control of uterine bleeding as compared with other compounds, has a positive effect on calcium metabolism by producing greater increases in bone mineral density than alendronate, and at low dosages has no negative effects on the lipoprotein profile (43). This would represent a potential advantage of NETA over 17-OH derivates (e.g. MPA).

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

Data on the efficacy of other progestogens (dihydrogesterone, dienogest, lynestrenol, tibolone) in the treatment of symptomatic endometriosis are more scanty (23, 44, 45).

5.3. Levonorgestrel-releasing intrauterine device (IUD)

The possibility of aiming the therapeutic action of drugs at specific organs, thus reducing the general metabolic impact, is a subject of great interest. An intrauterine device (IUD) releasing 20 µg/day of levonorgestrel, a potent progestogen derived from 19-nortestosterone, may induce amenorrhoea in different ways compared to standard treatments and may relieve menstrual pain. In fact, the local administration of levonorgestrel has a profound effect on the endometrium, which becomes atrophic and inactive, although ovulation is generally not suppressed.

The interest surrounding the possibility to treat endometriosis with a levonorgestrel-releasing IUD has

rapidly grown over the last few years but scientific evidence is still scanty (46,47). This kind of IUD has been inserted in twenty parous women who had recurrent moderate or severe dysmenorrhoea after conservative surgery for endometriosis and did not want more children (48). Blood loss was measured with a semiquantitative method and was decreased during the 12 months of study, as did dysmenorrhoea which was evaluated according to visual analogue and verbal multidimensional scales. Of the 17 women who completed the study, four women were very satisfied with treatment, 11 were satisfied, two were uncertain, and three were dissatisfied. Lockat *et al.* confirmed this figure in a series of 34 women with endometriosis stage I-III (49). Of relevance, however, 32% of patients discontinued treatment within one year of treatment. Reasons to abandon were irregular and intolerable bleeding and persistent pain. Petta *et al.* recently randomized 82 women operated on for endometriosis to levonorgestrel-releasing IUD or GnRH agonist given for 6 months (50). The two treatment groups resulted equally effective in reducing pain symptoms and improving quality of life. No women discontinued treatment but duration of the study was too short to draw conclusions on this regard. The levonorgestrel-releasing IUD was used also in the treatment of persistent rectovaginal endometriosis in 11 patients undergoing non-radical conservative surgery (51). One year after insertion, dysmenorrhoea, which had been moderate or severe in all cases, and non-menstrual pelvic pain were absent. Of notable interest was the reduction of deep dyspareunia, from moderate or severe in eight cases prior to IUD insertion, to absent or mild in all subjects throughout treatment. Rectal tenesmus was also substantially alleviated. The results of this study are clinically important because they prove the efficacy of a progestogen in a type of lesion generally considered as non-responsive to medical therapy. Relief of deep dyspareunia and rectal tenesmus seems to be due not only to size reduction of the fibronodular rectovaginal plaques, but also to decrease of the intra- and perilesional inflammatory condition, and confirms the effect of treatment also on organic symptoms.

A potential drawback of levonorgestrel-releasing IUD in the long-term use is related to its inability to prevent ovulation. Indeed, recent evidence supports the notion that endometriomas may arise from ovulatory events and, as such, the formation of these cysts is strongly prevented by treatments inhibiting ovulation such as oral contraceptive (52).

6. LONG TERM GnRH AGONISTS AND ADD BACK THERAPY

Since endometriosis is an estrogen-dependent disease, there is an absolute consensus that the disease strongly benefits from an hypoestrogenic condition. Not surprisingly, GnRH agonists have been shown to work quite well in reducing all pain symptoms associated with endometriosis, including dysmenorrhea, dyspareunia and nonmenstrual pelvic pain (53). On the other hand, the use of these compounds cannot be extended longer than 6 months since their prolonged use expose women to the detrimental effects of hypoestrogenism such as in particular loss in bone mineral density (54-55). In order to extend duration of treatment over this limit, concomitant add-back therapy has been suggested. The rational would be to prevent bone loss and other symptoms of estrogen deficiency such as hot flushes and vaginal dryness while keeping endometriotic implants quiescent. The most appropriate add-back regimen has not been definitively ascertained but, based on available evidence, a low dose of continuous estrogen and interrupted progestogen should be first considered (53, 55-58). The possibility to extend the duration of treatment for several years has been recently emphasized (53,58).

Even if there is a consistent body of literature regarding the use GnRH agonist and add-back treatment in women with endometriosis, studies comparing this regimen to OCs or progestagens are scanty. This aspect is of crucial importance considering that GnRH agonist and add-back treatment is an expensive and complex treatment. Its use should be recommended only if studies support strong additional benefits over OCs or progestagens. According to a Cochrane review on this topic, there is little or no difference in the effectiveness of GnRH agonist and add-back treatment in comparison with other medical treatments for endometriosis (59). Zupi *et al* recently reported data from a three arms randomized study comparing GnRH alone (n=44), GnRH plus add-back (n=46) and OC (n=43) given for one year (60). At the end of treatment and six months after discontinuation, pain symptoms scores were higher in the OC group whereas no difference emerged between women randomized to GnRH who did and did not receive add-back therapy. The entity of these differences was however mild and of doubtful clinical relevance.

A minority of patients with pain recurrences cannot be satisfactory treated with progestagens or OCs. Second surgery and in some cases radical surgery are possible options but the vast majority of patients are comprehensibly not compliant with this approach. In these cases, the long-term use of GnRH agonists may be considered.

7. EFFECT OF THE SURGICAL TREATMENT ON SYMPTOMATIC ENDOMETRIOSIS

The goal of conservative surgery for endometriosis is to restore normal anatomy and alleviate pain. This is done by treating all lesions by either excision or ablation, lysing adhesions and, possibly, interrupting nerve pathways. In women in whom childbearing is desired, optimizing fertility is also a goal. There are several studies comparing operative laparoscopy to no treatment in women with chronic pelvic pain. Jarrell *et al* randomized 29 women to laparoscopy with a diagnostic biopsy followed by either no further intervention or complete surgical excision of their endometriosis (61). All women had pelvic pain, with most patients having stage II endometriosis and none having stage IV. A significant decrease in pain in both surgical and sham groups was found with no significant difference between these two

populations. One double-blinded randomized controlled trial (62) and two cohort studies (63,64) compared laser ablation plus uterine nerve ablation to diagnostic laparoscopy alone for relief of the pain associated with minimal to moderate endometriosis. Three months after surgery there were no significant differences in pain relief; 56% of the patients in the laser group experienced pain relief in comparison to 48% in the control group. At six months, however, there was a significant difference in pain relief in the operated group (62% vs 23%) that persisted at the one-year follow-up (62). A large cohort study evaluated the long-term follow-up of patients who received operative laparoscopic surgery (63,64). The mean follow-up time after surgery was 73 months. Painful symptoms recurred in 74% of patients, with a median time of recurrence of 19.7 months (range 5-60). At follow-up, satisfactory symptom relief was reported in only 55% of the patients. The remaining 45% of patients continued to experience pain; eight required hysterectomy (64). Abbott *et al* (65) prospectively randomized 39 women with histologically proven endometriosis to surgical excision or diagnostic laparoscopy followed by a second laparoscopy 6 months later. At least 50% of each group had stage III to IV endometriosis. Eighty percent of the surgically treated patients (16 out of 20) reported improvement of their pain compared with 32% (6 out of 19) of control subjects. Redwine (66) reported his results as sole surgeon in 359 patients treated by laparoscopic sharp excision of endometriosis. In **a** follow-up of up to 5 years, less than 20% of women had recurrent symptoms or disease. Taken together, these studies suggest that surgical treatment of endometriosis either by excision or ablation carries a substantial relief of symptoms for a significant percentage of women but about 40% of patients continue to experience symptoms after surgery. Therefore, for long-term symptomatic treatment in women not wanting children, the role of conservative surgery in the treatment of symptomatic endometriosis needs to be radically reconsidered. The guidelines provided by the American College of Obstetricians and Gynecologists (67) as well as by the Royal College of Obstetricians and Gynaecologists (70) suggest that, in the absence of adnexal masses, the administration of oestrogen-progestogen combinations can be undertaken without the need for preliminary laparoscopy. More recently, the Committee of the ASRM and the ESHRE Special Interest Group for Endometriosis and Endometrium guideline development gave similar indications (24,25).

Although there are no comparative studies, the literature addressing deep implants would suggest that excising nodular disease is still the treatment of choice. However, deeper infiltrating lesions may be extremely challenging to treat surgically. Surgeons should be thoroughly familiar with anatomy and advanced operative techniques. Even experienced surgeons have suggested that while an endoscopic approach may be effective for uterosacral ligament, bladder, and vaginal endometriosis, laparotomy still has a significant role for bowel lesions (69). Chopin *et al* (70) studied 132 patients with pelvic pain and histologically proven deeply-infiltrating endometriotic lesions. Removal of deeply infiltrating lesions resulted in a significant improvement in the patient's pain which persisted with a median follow-up of 3.3 years. Improvement was seen regardless of the number or location of the endometriosis including lesions in the uterosacral ligaments, vagina, bladder, and intestines. Chapron and Dubuisson (71) reported on 21 women who had all of their deeply infiltrating endometriosis excised including removal of affected uterosacral ligaments. There was an average follow-up of 20 months. Deep dyspareunia was effectively treated, with 94% of these patients showing relief. The symptoms of 84% of patients with dysmenorrhea improved, and 78% of women with chronic pelvic pain had a lessening of their symptoms.

Despite the demonstrated benefits of surgery in terms of improving pain symptoms, the elevated recurrence rate remains an important concern (72-77). A primary task in this area is to find out therapeutic strategies aimed to reduce this rate. In this context, a major point is the identification of specific risk factors. Unfortunately, available studies on this issue have led to conflicting results and firm conclusions cannot thus be drawn (72-77). No specific factor has been found to be consistently associated wither recurrences. Despite these controversies, there is a general consensus that an accurate and radical surgery represents an important point. Of relevance here, however, is that surgery for endometriosis is a complicated and possibly risky procedure (78,79).

8. MEDICAL TREATMENT AFTER CONSERVATIVE SURGERY

Due to the lack of evidence demonstrating necrosis and disappearance of residual foci following medical treatments after surgery for endometriosis, the urge to prescribe such treatments seems to be overzealous. These schemes, which have clearly been derived from oncological practice, have a clinical significance only if prolonged over an extended period of time in women not wanting children immediately. Again, progestogens and oestrogen-progestogen combinations constitute the only reasonable alternative for endometrial suppression of longer duration with respect to the conventional, arbitrary 6-month period. Evidence supporting a role for a brief post-operative pharmacologic treatment with GnRH analogues or danazol is not consistent (80-85).

In a randomised controlled study, Muzii *et al.* (86) demonstrated that the postoperative administration of low-dose cyclic OC for 6 months does not significantly affect the long-term recurrence rate of endometriosis after surgical treatment. However, OC determined a delay in recurrence as shown at life-table analysis.

Results of a randomised, controlled multicentre European trial on 142 patients showed that oral administration of dienogest for 4 months following conservative surgery for endometriosis is as effective as the GnRH triptorelin depot taken for the same period of time (87). The degree of pain symptoms reported was similar in the two groups, as was the proportion of satisfied subjects at the end of treatment (86% in the dienogest arm versus

80% in the triptorelin arm). Spotting was more frequent in the former group (62% versus 25%) and vasomotor symptomatology more frequent in the latter (10% versus 61%).

The use of GnRH agonists as surgical adjuncts has been studied by several investigators. Their use preoperatively has not been shown to be of value (53, 88-89). Similarly, 3 months of postoperative administration has failed to enhance treatment (88-90). However, 6 months of postoperative GnRH agonists may improve the duration of relief of pain symptoms but evidence is still scanty (53).

When dysmenorrhoea is the main symptom of a patient undergoing surgical treatment for endometriosis, the insertion of a slow-releasing levonorgestrel IUD at the end of the procedure may substantially reduce the frequency and severity of postoperative pain. We conducted a randomised study on 40 women with symptomatic endometriosis and scheduled for operative laparoscopy (91). Recurrent moderate or severe dysmenorrhoea was observed within a year of surgery in 2/20 (10%) women in the laparoscopy plus medicated IUD group and in 9/20 (45%) of those allocated to laparoscopy only. Hence, a medicated IUD needs to be inserted intraoperatively in three patients in order to avoid recurrence of dysmenorrhoea in one of them. One year after randomisation, 75% of subjects allocated to the medicated IUD versus 50% of those allocated to surgery only were satisfied with the treatment received.

9. SURGICAL INTERRUPTION OF PELVIC NERVE PATHWAYS

Both sympathetic and parasympathetic fibers are found in the anterior two thirds of the uterosacral ligaments, around the area of attachment of the cervix (92). Presacral neurectomy has been widely performed in order to ameliorate dysmenorrhea but a certain degree of failure has been attributed to incomplete denervation – namely, resection of the superior hypogastric plexus that spared the nervi erigentes. Therefore, it has been subsequently hypothesized that surgical interruption of both the sympathetic and parasympathetic pathways was fundamental to achieve satisfactory pain relief. A recent meta-analysis has been performed to assess the effectiveness of surgical interruption of pelvic nerve pathways in primary and secondary dysmenorrhea (93). In dysmenorrhea associated to endometriosis, along with laparoscopic surgical treatment of the disease, the addition of laparoscopic uterosacral nerve ablation did not improve the pain relief (OR 0.77; 95% CI 0.43-1.39), while presacral neurectomy did (OR 3.14; 95% CI 1.59-6.21). However, adverse events were much more common for presacral neurectomy than procedures without presacral neurectomy (OR 14.6; 95% CI 5.0-42.5). Since these procedures entail some clinically relevant risks, further information on their neuroanatomical rationale and efficacy should be obtained before accepting their routine performance in clinical practice.

10. CONCLUSIONS

Endometriosis is generally viewed as a disease requiring surgical treatment. Even if laparoscopy remains in most cases the first-line therapeutic option, medical therapy aimed to control pelvic pain associated with the disease is currently gaining consent. In this regard, it is noteworthy that the medical treatment plays a role in the overall therapeutic strategy of endometriosis symptoms only if it can be administered over a prolonged period of time. Given their good tolerability, minor metabolic effects and low cost, progestogens with or without the addition of estrogens, can be considered the drugs of choice and are currently the only safe and inexpensive alternative to surgery. Progestogens are effective in controlling pain symptoms in approximately three of four women with endometriosis. Their effect does not seem to be inferior to that obtained with other drugs usually used in treating the disease. However, their contraceptive effectiveness limits their use to women who do not wish to have children in the short term.

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Key Words: Endometriosis, Medical Therapy, Pelvic Pain, Review

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