The efficacy of medical and surgical treatment of endometriosis-associated infertility: arguments in favour of a medico-surgical approach

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This review discusses the efficacy of a combined, medical (GnRH agonist) and surgical, therapy in endometriosis-associated infertility. Because of the limited information currently available on the activity of lesions in minimal and mild endometriosis, any absolute statement is inappropriate at this time, although some arguments exist in favour of treating endometriosis at laparoscopy. In moderate and severe endometriosis, this review provides arguments in favour of a medico-surgical approach and discusses the possibility of combining medical and surgical therapy.

Key words: endometriosis/GnRH-agonist/laparoscopy/surgery

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Introduction

Endometriosis is one of the most frequently encountered benign diseases in gynaecology. It is the cause of pelvic pain (dysmenorrhea, dyspareunia) and infertility in more than 35% of women of reproductive age (Nisolle and Donnez, 1997). Complete resolution of endometriosis is not yet possible, but therapy has essentially three main objectives: (i) to reduce pain; (ii) to increase the possibility of pregnancy; and (iii) to delay recurrence for as long as possible.

The aim of this review is to discuss whether the combination of laparoscopic surgery by laser, coagulation or excision and adjuvant medical therapy with GnRH agonists is the most appropriate treatment for endometriosis.

Is medical therapy alone efficacious?

Medical therapy alone is relatively ineffective because: (i) a cumulative recurrence rate of 53.4% was observed 5 years after cessation of therapy (Waller and Shaw, 1993); (ii) a mean interval of only 5.2 months before pain recurred was described after cessation of therapy (Miller et al., 1998); (iii) histology provided evidence for persistence of endometriotic implants after GnRH agonist administration (Donnez et al., 1989); (iv) histology provided evidence for residual activity (high mitotic index and Ki 67) in hormone-independent residual foci with low steroid levels (Nisolle-Pochet et al., 1988); (v) ectopic endometrium (like normal endometrium) is able to proliferate under the influence of estrogens, even after a long time without estrogens (Nisolle et al., 1997); (vi) the adhesion score proved to be unchanged after GnRH agonist treatment (Donnez et al., 1989, 1990, 1994); and (vii) recurrence rates were high after discontinuation of endocrine treatment, such as oral contraception, progesterone, danazol and GnRH agonist (Minjarez and Schlaff, 2000).

The results of endometriosis therapy with GnRH agonist alone are even more disappointing. Following laparoscopic diagnosis of endometriosis in 130 patients, GnRH agonist treatment was administered for 6 months (Waller and Shaw, 1993), whereupon most of the women underwent second-look laparoscopy. The cumulative recurrence rate for the fifth year after cessation of treatment was 53.4% (36.9% for minimal disease, 74% for severe disease). The authors concluded that patients treated with GnRH agonist alone stand a greater chance of suffering a recurrence, particularly if the disease is more severe. A second trial (Miller et al., 1998) confirmed the poor results of purely medical therapy. Data from 327 patients treated for 6 months with either danazol (n=128) or GnRH...
agonist \((n=199)\) were analysed retrospectively. The mean interval before pain recurred was 6.1 months in the danazol group and 5.2 months in the GnRH agonist group. The time to recurrence of pain varied with the stage of endometriosis, but was disappointing in both treatment groups.

In our patient group it was clearly demonstrated that relatively hormone-independent endometriotic lesions persisted after GnRH agonist treatment (Donnez et al., 1989; Nisolle et al., 1997).

Evidence-based medicine: questions without answers

The question must be asked whether ‘evidence-based medicine’ (EBM) is really needed to prove that ovarian chocolate cysts must be removed. Do we really need prospective randomized double-blind, placebo-controlled studies to confirm that a histologically proven endometrial cyst disappears after surgical excision, but not after ‘placebo surgery’? Do we really need prospective, randomized studies to analyse the pros and cons of endometrioma surgery versus medical therapy? Do we really need placebo-controlled studies to demonstrate that endometrioma surgery improves pregnancy rates more significantly than placebo surgery? Do we really need prospective, randomized studies to prove that in the rectovaginal space a nodule of \(\geq 3\) cm in size must be removed?

Are such investigations really necessary, since it is known that in rectovaginal nodules there is a close histological relationship between nerves and endometriotic foci and fibrotic components of the nodules (Anaf et al., 2000)? It is also known that lateral extension of rectovaginal nodules can provoke silent kidney damage in 10% of cases (Donnez et al., 1997; M.Nisolle and J.Donnez, unpublished results). Is it not too easy to say: ‘no EBM, no proof’—and then to claim the contrary?

Evidence-based medicine is surely useful in determining guidelines, but it is not without some degree of surprise that we read some of the ‘Capri consensus’ conclusions (ESHRE Capri Workshop Group, 2000). It rather appeared that only a principle had guided the arguers: ‘If not proved by EBM-study, it does not exist’, but our response is this: ‘If some participants in a panel suggest the contrary of the view of experts with wide experience, we should ask them to prove their claims by conducting prospective randomized controlled studies’. We are often we should ask them to prove their claims by conducting prospective randomized double-blind studies in surgery and to define a type of placebo surgery.

Minimal and mild endometriosis-associated infertility

The first concept to bear in mind is that peritoneal, ovarian and rectovaginal endometriotic lesions must be considered as three different entities (Donnez et al., 1997; Nisolle et al., 1997). The second is to differentiate patients with minimal or mild endometriosis from those with moderate or severe endometriosis. The third is to differentiate patients with endometriosis-associated pelvic pain from those with endometriosis-associated infertility.

The only way to confirm absolutely the existence of peritoneal endometriosis is by laparoscopic operation. Any peritoneal lesions visualized at this time should then be rapidly treated by laser, coagulation or excision surgery. It is difficult to find objective data on preoperative GnRH agonist treatment for peritoneal endometriosis, although in one prospective study (Wheeler et al., 1992) it was reported that there was an almost 50% reduction in the endometriosis score at the end of 6 months’ therapy with leuprolide acetate.

In infertile women presenting with minimal or mild endometriosis (AFS classification), laparoscopic ‘destruction’ was found to be the first line of therapy (Marcoux et al., 1997), but a recently published Italian study (Gruppo Italiano per lo Studio dell’Endometriosis, 1999) showed exactly the opposite. This is an example of two EBM (degree 1) studies on the same subject reaching two completely different conclusions.

In the first of the studies (Marcoux et al., 1997), 341 infertile women (aged 20–39 years) with minimal or mild endometriosis were randomized into two groups and underwent either laparoscopic resection or ablation of the endometriotic lesions \((n=172)\) or only diagnostic laparoscopy \((n=169)\). The duration of follow-up after surgery was 36 weeks. In the first group, 50 patients became pregnant and their pregnancies continued for 20 weeks or longer, as compared with 29 pregnancies in the diagnostic laparoscopy group. This gives cumulative probabilities of 30.7 and 17.7% respectively. The authors concluded that laparoscopic resection or ablation of minimal and mild endometriosis enhances fecundity in infertile women. The most frequently cited bias is that patients were aware of the randomization. Another possible bias might be that mapping between red, black and white lesions was not considered in the group selection.

In contrast, the results of the Italian study (Gruppo Italiano per lo studio dell’Endometriosis, 1999) do not support the hypothesis that ablation of endometriotic lesions markedly improves fertility rates. However, bias also existed in this study: first, the series was small (54 versus 47 patients); second, seven centres participated in the study, giving a mean of 14 patients per centre; third, histological confirmation of diagnosis of endometriosis was not requested; and fourth, the percentage of active red lesions or non-active black or fibrotic lesions was unknown.

Criticism is easy, but which study should be believed if both trials were supposedly randomized and controlled?

In a third study (Fu-Hsing Chang et al., 1997), 176 women whose infertility was associated with minimal or mild endometriosis were randomized into four groups. The women underwent operative laparoscopy with \(\text{CO}_2\) laser vaporization and/or resection (group I, \(n=49\)), operative laparoscopy with electrocoagulation (group II, \(n=45\)), only diagnostic laparoscopy (group III, \(n=43\)), and danazol \((800\ \text{mg/day})\) for 3 months after diagnostic laparoscopy (group IV, \(n=39\)). After 36 months’
follow-up there were no significant differences in pregnancy rates between the different groups (88.3% in group I, 70.2% in group II, 66.2% in group III and 64.1% in group IV). The authors also concluded that advanced laparoscopic surgery with CO₂ laser may be more efficacious than other modalities in treating infertile women with minimal to mild endometriosis in terms of pregnancy rates. The difference between 88 and 64% was not statistically significant, but is it ethical to tell a patient that an 88% chance of pregnancy after laparoscopic endometriosis destruction is similar to a 54% chance after expectant management? How can one explain a non-significant 22% difference in the pregnancy rate in this study? Is it due to the small number of cases? Is it due to the test used for statistical analysis?

Thus, we can conclude that because of the limited information currently available on the activity of lesions described in studies on mild or minimal endometriosis, any absolute statement on endometriosis and infertility is probably inappropriate at this time. Nevertheless, it seems that there are more arguments in favour of treating minimal and mild endometriosis at laparoscopy, if laparoscopy is decided upon.

The conclusion of a meta-analysis (Hughes et al., 1993; Adamson and Pasta, 1994) was that either no treatment at all, or only surgery, was superior to medical treatment for minimal and mild endometriosis associated with infertility. Here too, criticism and questions abounded and bias existed. The ‘medical therapy’ groups were compounded (i.e. with different agents such as danazol, oral contraceptives and GnRH agonists). Nor was it clear what role was played by the treatment-time to pregnancy interval. Many questions were raised by A.DeCherney and M.Diamond in the discussion following publication of the article by Adamson and Pasta (1994) in the American Journal of Obstetrics and Gynecology. Some of the questions posed by DeCherney and Diamond were relevant, but did not receive an entirely satisfactory response!

**Moderate and severe endometriosis-associated infertility**

Consensus can be more easily established in the management of moderate and severe endometriosis. Indeed, most such patients present with ovarian endometriosis and/or periadinexal adhesions. Medical therapy alone is not effective in reducing endometriotic cysts and adhesions (Donnez et al., 1994). One of the first approaches in the treatment of endometriosis-associated infertility is combined therapy with surgery and GnRH agonists, but do we have arguments to support this approach?

In an initial study (Donnez et al., 1987), 50 patients with moderate and severe endometriosis were treated with hormonal therapy followed by microsurgery. Intrauterine pregnancy rates of 60% for moderate and 47% for severe endometriosis were obtained. In a second study (Donnez, 1987), 70 infertile women with endometriosis were treated by CO₂ laser laparoscopy. After a follow-up of 18 months, post-operative pregnancy rates of 52 and 42% were observed in patients with moderate and severe endometriosis respectively. In another prospective trial (Donnez et al., 1990), 126 patients with laparoscopically confirmed ovarian endometriosis showed, after hormonal therapy followed by surgical treatment of endometriotic cysts, a pregnancy rate which differed according to the disease stage. Women with moderate endometriosis conceived in 53% of cases, but in the severe endometriosis group only 45% conceived. In a third study (Donnez et al., 1996), 814 women who presented with ovarian endometriomas received combined treatment with GnRH agonist and laparoscopic surgery. A cumulative pregnancy rate of 51% was observed, with the majority of pregnancies occurring within 12 months of surgery (Figure 1).

A prospective randomized study clearly showed that drainage of endometriomas was ineffective if not associated with GnRH agonist treatment (Donnez et al., 1994). The positive effect that GnRH agonist exerts in reducing the size of ovarian endometriomas prior to surgery has been demonstrated (Rana et al., 1996). Drainage alone of chocolate cysts is ineffective, and only subsequent GnRH agonist administration can reduce endometrioma size, peri-ovarian inflammation and glandular mitotic activity (Donnez et al., 1994). Another clear benefit is that an absence of corpus luteum and/or follicles facilitates the ovarian surgery. The persistence of active endometriotic tissue after GnRH agonist therapy has been demonstrated however (Nisolle-Pochet et al., 1988; Donnez et al., 1989), and it is therefore

**Figure 1.** Pregnancy rate during the first year after surgery. Published with permission from J. Donnez et al. (1996) Large ovarian endometriomas. Hum. Reprod., 11, 641–646.
proposed that the residual endometriosis be surgically removed after the medical therapy.

In a recent prospective, multicentre clinical trial (Audebert et al., 1998), it was shown that in the case of combined medicosurgical treatment for stage III–IV endometriosis, preoperative medical therapy with GnRH agonist gives a greater improvement in the AFS score than does post-operative medical therapy. Patients (n=53) were allocated to two groups. Both groups received 6 months of nafareline therapy, the first group before conservative surgery, and the second group after surgery. Although the AFS scores were significantly better when nafareline was given before surgery, the authors confirmed that no conclusion could be drawn if preoperative treatment facilitated surgery. Hence, the clinical impression that GnRH agonist simplifies surgery persists, but further studies are necessary to confirm this.

A subsequent randomized prospective, placebo-controlled multicentre clinical trial confirmed the benefits of combined therapy (Hornstein et al., 1997). A total of 109 patients was treated for 6 months after laparoscopic surgery with either GnRH agonist or a placebo. The median time to initiation of alternative treatment was >24 months in the nafareline group, compared with 11.7 months in the placebo group. Some 31% of nafareline-treated patients required alternative therapy, compared with 57% in the placebo group. The authors concluded that adjuvant GnRH agonist therapy (nafareline) after laparoscopic surgery for endometriosis significantly delayed the return of endometriosis symptoms requiring further treatment.

In a recent review (Johnson, 1998), it was concluded that all symptomatic endometriotic diseases should be treated early and aggressively. After conservative surgical resection of all apparent endometriosis, the author strongly advocated medical treatment with GnRH agonist. In addition, the hypothesis that combined GnRH agonist and operative treatment for endometriosis offers the best therapy currently available was confirmed by an analysis of data from 198 patients (Schindler et al., 1998).

Is a purely surgical approach more effective than medical therapy?

Two prospective randomized studies illustrated the benefits of surgical treatment in infertile women suffering from moderate to severe endometriosis. In the first study (Yung-Kuei Soong et al., 1997), a group of 309 infertile women with stage III–IV endometriosis underwent different treatments, including operative laparoscopy with CO2 laser (group I, n=88), operative laparoscopy with electrocoagulation and sharp adhesiolysis (group II, n=85) and laparotomy with electrocoagulation (group III, n=92). The pregnancy rates observed after 36 months in groups I, II and III were 41.2, 33.8 and 32.3% respectively. These data confirmed that women with advanced stages of endometriosis can be treated efficiently by operative laparoscopy.

In a later study (Busacca et al., 1999), 141 women with stage III–IV endometriosis were followed-up for a minimum of 6 months after conservative operative laparoscopy. Of the 57 patients with infertility of more than 12 months’ duration, 25 (44%) became pregnant. The 24-month cumulative pregnancy rate was 37.5%, and 23 of 45 women (51%) with stage III endometriosis conceived, compared with two of 12 (16.7%) with stage IV. This difference was significant. The authors concluded that operative laparoscopy seems to be an effective treatment for stage III endometriosis, but in our opinion a larger series with a longer follow-up is required to clarify its role in managing stage IV disease or indeed to determine the possible need for preoperative GnRH agonist therapy.

Other authors also obtained good pregnancy rates in studies after operative treatment of endometriosis. In a retrospective study where ovarian endometriomas were treated by laser laparoscopy, data from 165 patients were analysed (Sutton et al., 1997). Thirty of 66 (45%) infertile women conceived, with most pregnancies being obtained in the 12 months following surgery. A similar rate of conception (41%) was obtained in another study (M. Canis, personal communication).

Is a consensus possible?

The average pregnancy rates after laparoscopic surgery reported in the literature, are thus approximately 42 and 50% after combined medical-laparoscopic surgical treatment.

In the case of ovarian endometriosis-associated infertility, GnRH agonist therapy combined with operative laparoscopy may be proposed. If conception does not occur within a fixed time period (10–12 months), then IVF is proposed as a second option. At present, results with IVF are better than those with reoperation. Indeed, in a group of infertile women with stage III or IV endometriosis who failed to conceive after a first operation, the cumulative pregnancy rate was significantly higher after two IVF cycles than after reoperation (69.9 versus 24.4%) (Pagidas et al., 1996). This treatment approach was also confirmed in a review (Pouly et al., 1996).

In case of endometriomas larger than 15 cm in diameter, a first laparoscopy to drain the cyst is suggested, followed by 8 weeks of treatment with GnRH agonist, before performing an echo-guided transvaginal puncture. GnRH agonist therapy is then continued for a further 8 weeks followed by second-look laparoscopy. The use of preoperative GnRH agonist provokes a reduction in ovarian endometrioma size, vascularization and inflammatory reaction. These changes allow and facilitate a subsequent laparoscopic procedure, which can then be more conservative (laser vaporization versus excision).

It is clear that laparoscopic surgical therapy requires considerable experience and expertise on the part of the surgeon, and the results are also likely to be operator-dependent (Donnez et al., 1987). In case of moderate or severe endometriosis due to the presence of an ovarian endometrioma, ‘perioperative’ GnRH agonist has proved helpful by reducing the size and inflammation of ovarian lesions (Donnez, 1987; Donnez et al., 1987, 1994).

The question of pain relief

Data have been reported which illustrate that results are unsatisfactory, following purely surgical therapy of endometriosis (Wheeler and Malinak, 1983). A total of 420 patients was followed-up, and cumulative 3- and 5-year recurrence rates of 13.5 and 40.3% respectively were obtained. The severity of the disease was not predictive of recurrence. Bearing this in mind, the better results achieved after GnRH agonist administration and surgery look promising.
A placebo-controlled, post-operative medical treatment of 60 patients over 6 months was reported whereby medically treated patients had significantly less pelvic pain and smaller peritoneal implants at second-look laparoscopy (Telima et al., 1987). Thus, post-operative medical treatment causing hypoestrogenism and amenorrhea might delay the recurrence of endometriotic symptoms (Miller et al., 1998). Post-operative GnRH agonist therapy was also shown to be beneficial, as patients treated with nafarelin after laparoscopic surgery suffered less pain and enjoyed longer pain-free intervals than control subjects (Hornstein et al., 1997).

Although laparoscopy is commonly used for the diagnosis and treatment of women with endometriosis and pelvic pain, it was suggested in a recent review (Winkel, 2000) that surgical therapy offers no better results in terms of pain relief than medical therapy using a GnRH agonist (Minjarez and Schlaff, 2000). Long-acting agonist treatment with addback therapy is another option that might be considered among the armamentarium of therapy for patients with extensive and severe endometriosis.

In conclusion, the question of pain relief does not appear to have been clearly answered!

**Conclusion**

Following this review of the literature, it can be concluded that:

(i) A consensus will probably never be reached on minimal and mild endometriosis. Why? Because studies on this subject have never prospectively evaluated the activity of the disease. No mapping of red vascularized lesions has ever been reported. Nevertheless, because the Canadian study (Marcoux et al., 1997) reported a large number of cases, we strongly support the view that visible endometriosis must be removed at the time of surgery and, from an ethical point of view, it would be difficult for us to advocate diagnostic laparoscopy and expectant management.

(ii) In cases of moderate and severe endometriosis-associated infertility, the use of GnRH agonist before laparoscopic surgery for large endometriomas may be supported by arguments from the literature. In the experts’ opinion, GnRH agonist treatment facilitates laparoscopic surgery for moderate and severe endometriosis.

(iii) The use of a combined GnRH agonist-surgical approach is rather more questionable in endometriosis-associated pelvic pain. In cases of moderate and severe endometriosis-associated infertility, the combined approach (operative laparoscopy with GnRH agonist) must be considered as ‘first-line’ treatment. The mean pregnancy rate of 50% reported in the literature following surgery provides scientific proof that operative treatment should first be undertaken to give patients the best chance of conceiving naturally. IVF is indicated only as a second line of treatment. In our department, after two IVF cycles, a pregnancy rate of approximately 61% was obtained. Today, it seems possible—by a combination of surgery and IVF—to offer the chance of pregnancy to a majority of women with endometriosis-associated infertility.

**Efficacy of treatment of endometriosis-associated infertility**


**References**


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