

# The effect of surgery for symptomatic endometriosis: the other side of the story

P. Vercellini<sup>1,2,3,4</sup>, P.G. Crosignani<sup>1</sup>, A. Abbiati<sup>1,2,3</sup>, E. Somigliana<sup>2,3</sup>, P. Viganò<sup>2</sup>, and L. Fedele<sup>1,3</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, University of Milan, 20122 Milan, Italy <sup>2</sup>Center for Research in Obstetrics and Gynecology (C.R.O.G.), 20122 Milan, Italy <sup>3</sup>Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Istituto “Luigi Mangiagalli” 20122, Milan, Italy

<sup>4</sup>Correspondence address. Clinica Ostetrica e Ginecologica I, Istituto “Luigi Mangiagalli”, University of Milan, Via Commenda 12, 20122 Milan, Italy. Tel: +39-02-5503-2917; Fax: +39-02-5503-2331; E-mail: paolo.vercellini@unimi.it

## TABLE OF CONTENTS

- Introduction
- Methods
- Results
- Comment
- Conclusions

**BACKGROUND:** Surgery is often considered the best treatment option in women with symptomatic endometriosis. However, extent and duration of the therapeutic benefit are still poorly defined.

**METHODS:** The best available evidence on surgery for endometriosis-associated pain has been reviewed to estimate the effect size of interventions in the most frequently encountered clinical conditions.

**RESULTS:** Methodological drawbacks limit considerably the validity of observational, non-comparative studies on the effect of laparoscopy for stage I–IV disease. As indicated by the results of three RCTs, the absolute benefit increase of destruction of lesions compared with diagnostic only operation in terms of proportion of women reporting pain relief was between 30% and 40% after short follow-up periods. The effect size tended to decrease with time and the re-operation rate, based on long-term follow-up studies, was as high as 50%. In most case series on excisional surgery for rectovaginal endometriosis, substantial short-term pain relief was experienced by ~70–80% of the subjects who continued the study. However, at 1 year follow-up, ~50% of the women needed analgesics or hormonal treatments. Major complications were observed in 3–10% of the patients. Medium-term recurrence of lesions was observed in ~20% of the cases, and around 25% of the women underwent repetitive surgery.

**CONCLUSIONS:** Pain recurrence and re-operation rates after conservative surgery for symptomatic endometriosis are high and probably underestimated. Clinicians and patients should be aware that the expected benefit is operator-dependent.

**Key words:** endometriosis / chronic pelvic pain / surgery / laparoscopy

## Introduction

Endometriosis is by far the most frequent cause of pelvic pain in women of reproductive age (Vercellini, 1997). Symptomatic disease may cause prolonged suffering and disability, affecting negatively health-related quality of life (Gao *et al.*, 2006a; Bianconi

*et al.*, 2007). The economic and social costs of endometriosis impact unfavourably on national health systems, and a reduction in working ability has been reported (Gao *et al.*, 2006b; Simoens *et al.*, 2007).

Pain associated with endometriosis may be treated with surgery or drugs. For almost a century, the surgical treatment of endometriosis

has been based mainly on a straightforward oncologic principle, i.e. radical removal of lesions. This is still a mainstay of therapy in cases of bowel and ureteral stenosis or adnexal masses with doubtful characteristics. However, even when this is not the case, many surgeons maintain that it is preferable undergoing a minimally invasive intervention than years of medications with the associated untoward effects. Moreover, conservative surgery is the only alternative in women seeking conception, as drugs used for endometriosis interfere with ovulation.

Gynaecologists advocating medical treatments argue that, in the majority of patients, control of pain is simple and effective with oral contraceptives or progestins (Vercellini et al., 2003a, 2005). These hormones are safe, well tolerated, inexpensive and can be used for years, thus limiting the costs and morbidity of multiple surgical procedures (Vercellini et al., 2008a). According to this view, laparoscopy should be limited to non-responders as well as symptomatic women wishing to achieve a pregnancy spontaneously.

Because none of the above approaches is curative and both have advantages and disadvantages, the two positions co-exist and the debate continues (Vercellini et al., 2008a).

Medical therapy for endometriosis has been the subject of several RCTs. Pros and cons of this type of treatment are well known, and the impact on symptoms fairly clear (Telimaa et al., 1987a; Dlugi et al., 1990; Fedele et al., 1993; Vercellini et al., 1997, 2003a, 2008a; Bergqvist et al., 1998). On the other hand, only a few RCTs have been conducted on the effect of surgery for symptomatic disease, and particularly long-term outcomes are not completely defined (Jacobson et al., 2001).

Population-based data do not suggest that conservative surgery constitutes a durable remedy for severely symptomatic endometriosis patients. Weir et al. (2005) analysed the clinical records of 53 385 hospital admissions for the treatment of endometriosis in the province of Ontario, Canada, from 1994 to 2002. The records of 7993 patients with 15 years of age or older, with no prior hospital admission for endometriosis in the preceding 2 years, who underwent 'minor' or 'intermediate' conservative surgery for early disease, constituted the base for a 4 year longitudinal study. During the observation period, the likelihood of hospital re-admission for additional surgical treatment was 27% and that of having a hysterectomy was 12%. However, in spite of a substantial risk of re-operation, operative laparoscopy is increasingly performed for treating symptomatic endometriosis. On the basis of large epidemiologic databases, it has been estimated that ~1 in 400 North American women aged 15–45 years is hospitalized for surgical treatment of endometriosis each year (Weir et al., 2005).

In a clinical scenario that appears more lesion- than symptom-oriented, we deemed it of interest reviewing the best evidence available on the issue in order to define the benefit of surgery in the most frequently encountered clinical conditions and discuss the reliability of the results reported in light of the design of the relevant studies. This should assist the clinician in formulating a correct and balanced counselling to choose the medical decision that best matches the individual patient's needs.

Contrary to drug trials, technical skills and experience play an important role in surgery trials. Moreover, in the surgical field, publication bias appears decisive in selecting the type of information that will eventually reach the scientific community. Very few RCT on surgery for endometriosis have been published, and an extreme clinical heterogeneity characterizes the alternative available evidence.

In such conditions, the results of a formal systematic review may be less reliable than in usual circumstances, and pooling of results may be potentially misleading. Accordingly, we decided to use a traditional narrative synthesis of the studies conducted on women with peritoneal, ovarian and rectovaginal endometriosis.

## Methods

An electronic database search (PubMed, Medline, Embase) was performed with the objective of identifying all the RCTs published in English-language between 1990 and 2008 on the efficacy of conservative surgery for endometriosis-associated pelvic pain. Combinations of medical subject heading terms including endometriosis, pelvic pain, surgery and laparoscopy were used. References from retrieved papers were checked in order to identify additional reports. Owing to the paucity of RCTs on the effect of surgery for symptomatic endometriosis, we decided to include selected observational and retrospective studies based on informal appraisal of adequacy of description of setting, participants and surgical techniques; clarity of outcomes definition; study size; length and completeness of follow-up; and accuracy of results reporting. Articles reporting 'ad interim' results in advance of an available later full report were excluded. Studies on the effect of pelvic denervating procedures (presacral neurectomy and uterosacral ligament resection) were not included because systematic reviews are already available on this specific issue (Vercellini et al., 2000a; Proctor et al., 2005; Latthe et al., 2007). Two authors (A.A. and P.V.) independently performed an initial screening of the title and abstract of all articles to exclude irrelevant citations. The year of publication, type and design of study, treatment modality and main and secondary outcomes were recorded. The numbers of patients with pain at baseline and at the end of follow-up were obtained from individual studies. Correction or resolution of any discrepancies between reviewers was reached by consensus after discussion. Because the present review was not conceived as a formal systematic literature overview, a qualitative analysis of the selected studies was not planned and no attempt at data pooling was performed.

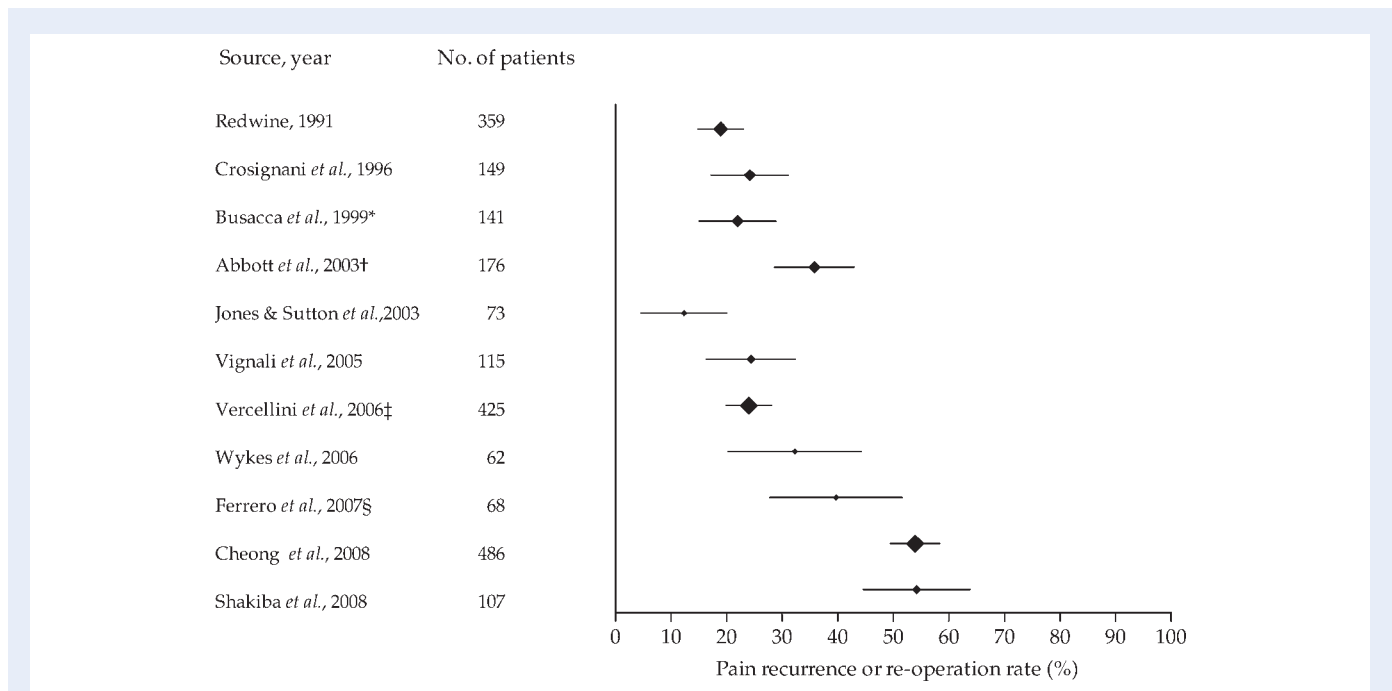
## Results

### Effect of surgery for stage I–IV disease: non-comparative studies

Data on several case series have been published reporting the purported efficacy of conservative surgery for stage I–IV endometriosis (The American Fertility Society, 1985) in terms of pain relief or need for re-operation (Redwine, 1991; Crosignani et al., 1996; Busacca et al., 1999; Garry et al., 2000; Abbott et al., 2003; Jones and Sutton, 2003; Vignali et al., 2005; Vercellini et al., 2006a; Wykes et al., 2006; Ferrero et al., 2007; Cheong et al., 2008; Shakiba et al., 2008; Fig. 1).

Redwine (1991) evaluated the long-term results of laparoscopic excision of stage I–IV endometriosis in a series of 359 women operated in a 10 year period. The cumulative rate of recurrent or persistent disease was 19% at 5 year follow-up. Of note, no adjuvant medical treatment was used.

Crosignani et al. (1996) determined the outcome of surgery for severe endometriosis performed at laparoscopy ( $n = 67$ ) or laparotomy ( $n = 149$ ). The 24 month cumulative probability of moderate or severe dysmenorrhoea recurrence was 20% in the former group and 25% in the latter, without statistically significant differences.



**Figure 1** Pain recurrence or re-operation rates reported after first-line conservative surgery for symptomatic endometriosis. Literature data, 1991–2008, observational and retrospective studies. Diamonds represent percentage point estimates and horizontal lines 95% confidence intervals. \*Cumulative dysmenorrhoea recurrence rate after surgery at laparotomy; †Cumulative re-operation rate; ‡Only subjects with moderate to severe dysmenorrhoea are considered; §Dyspareunia recurrence rate at intention-to-treat analysis.

A similar rate of pain recurrence (22%), 2 years after laparoscopic surgery for stage III–IV disease, was reported by Busacca *et al.* (1999) in a group of 141 patients.

Garry *et al.* (2000) introduced the evaluation of health-related quality of life after radical laparoscopic treatment of endometriosis. In 57 patients with severe pre-operative pain symptoms, a significant improvement in quality of life based on the EuroQOL and SF 12 questionnaires was observed 4 months after conservative surgery, with the exception of mental health scores. Substantial reductions in dysmenorrhoea, deep dyspareunia, dyschezia and pain were recorded using a visual analogue scale. Unfortunately, due to the very limited length of follow-up, it is not possible to assess the role of a placebo effect in determining the overall results.

Abbott *et al.* (2003) investigated the outcomes of laparoscopic excision of endometriosis up to 5 years after surgery in 176 women with severe pain symptoms. The median visual analogue scores decreased from 9 to 3 for dysmenorrhoea, from 8 to 3 for non-menstrual pelvic pain, from 7 to 0 for dyspareunia and from 7 to 2 for dyschezia. Quality of life, as measured by three different and validated instruments, improved significantly. Substantial ameliorations in sexual functioning as well as decrease in discomfort were also observed. Importantly, the 5 year cumulative probability of requiring further surgery was 36%.

Jones and Sutton (2003) studied pain variation and patient satisfaction 3–12 months following ablative laparoscopic surgery using CO<sub>2</sub> and KTP (potassium titanyl phosphate) lasers and bipolar coagulation in a series of 73 women with stage III–IV endometriosis. Significant reductions in dysmenorrhoea, dyspareunia, and non-menstrual pain

scores, as measured by a 10 cm visual analogue scale, were observed at 3 month evaluation. Pain relief did not vary significantly during the following 9 months. According to the authors, 88% of the subjects (64/73) were satisfied or very satisfied at final assessment. However, the choice of the cut-off points defining different satisfaction categories on a 10-point scale has not been validated.

Vignali *et al.* (2005) evaluated the risk of pain and disease recurrence after conservative surgery for endometriosis in a series of 115 women with deep lesions. After a minimum follow-up of 12 months, recurrence of pain was observed in 28 patients (24%) and recurrence of lesions in 15 (13%). Twelve subjects (10%) underwent repetitive surgery. Multivariate analysis demonstrated that only age was a significant predictor of pain recurrence, enhancing the risk in younger patients. Recurrence of lesions was predicted by obliteration of the Douglas pouch and re-operation was predicted by non-radical first-line surgery.

Wykes *et al.* (2006) evaluated, by means of postal questionnaires, 62 women with chronic pelvic pain who underwent laparoscopic excision of peritoneal endometriosis. After an average follow-up of 13 months, 67% of assessed subjects reported reduction of pain symptoms and 71% were satisfied with the results of treatment. However, 40% of women still reported regular use of analgesics and one-third noted deterioration in initial symptom relief within 12 months. One in six women required repeat surgical intervention for persistent symptoms. The impact of surgery on health-related quality of life was less clear and deterioration in subjective response over time was observed. Finally, the 70% response rate to postal questionnaires, the lack of a control group and the relatively short-term and varied

length of follow-up, probably resulted in over-estimation of the treatment effect.

Ferrero *et al.* (2007) examined the effect of laparoscopic excision of endometriosis on deep dyspareunia and quality of sex life in a group of 68 women with intensity of pain  $\geq 6$  on a 10 cm visual analogue scale. Only 52 subjects completed the 12 month follow-up. At intention-to-treat analysis, a decrease in the intensity of deep dyspareunia of  $\geq 4$  points at 12 month evaluation was achieved in 60% of the study population (41/68), in 61% (27/44) of the patients with endometriosis infiltrating the uterosacral ligaments, and in 58% (14/24) of those without such an involvement. Significant improvements in several aspects of sex life were observed at the end of follow-up in the former subjects.

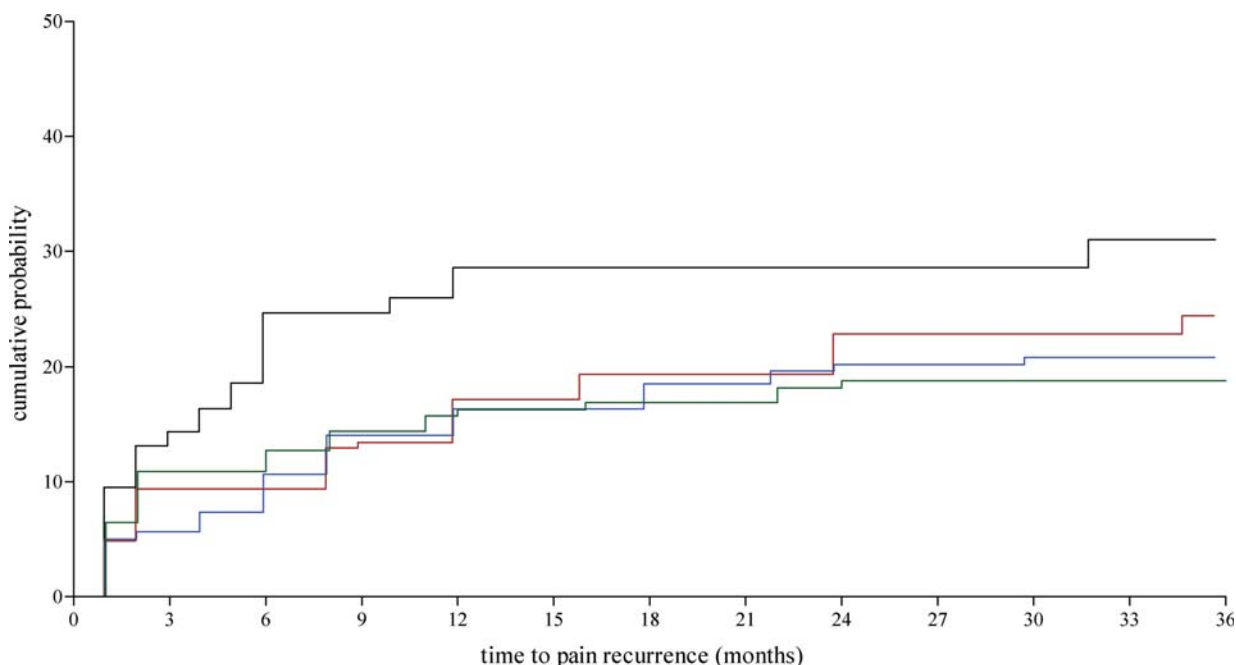
The results observed in a large surgical series of 729 consecutive women undergoing first-line laparoscopic surgery have been reported by our group (Vercellini *et al.*, 2006a). To evaluate variations in pelvic pain, only subjects with moderate or severe symptoms of over 6 month duration before surgery were considered. Pain symptoms were graded according to a 0–3-point multidimensional categorical rating scale and a 100 mm visual analogue.

A total of 425 subjects had moderate or severe dysmenorrhoea before surgery. The overall cumulative probability of dysmenorrhoea recurrence at 3 years from surgery was 24% (32% at stage I, 24% at stage II, 21% at stage III, 19% at stage IV; Fig. 2). At multivariate proportional hazards regression analysis, the only covariate significantly associated with recurrence of dysmenorrhoea was age at surgery. In particular, endometriosis stage was not associated with risk of recurrence of moderate or severe menstrual pain. Deep dyspareunia and

chronic pelvic pain were reported before surgery by, respectively, 110/729 (15%) and 167/729 (23%) patients, respectively. Recurrence of moderate or severe pain at intercourse was experienced by eight women (7%), and of chronic pelvic pain by 24 (14%). After surgery, *de novo* dysmenorrhoea occurred in only eight subjects, *de novo* deep dyspareunia in seven, and *de novo* non-menstrual pain in eight (Vercellini *et al.*, 2006a).

Cheong *et al.* (2008) examined the rate of re-operation in women with endometriosis over a 10 year period. A total of 486 patients underwent first-line laparoscopic surgery, 240 (49%) of whom because of pelvic pain and 246 for subfertility. After a mean follow-up of 5.4 years, 264 (54%) subjects underwent an average of another two surgical procedures (1 re-operation,  $n = 134$ ; 2,  $n = 67$ ;  $\geq 3$ ,  $n = 63$ ). Patients with pelvic pain were more likely to be re-operated compared with subfertile ones. The risk of repetitive surgery was increased in women  $< 30$  years of age and decreased in those who achieved a pregnancy.

Shakiba *et al.* (2008) recently reported the results of a long-term follow-up study (median, 7 years and 8 months) conducted on a series of 240 women who underwent conservative or definitive surgery for endometriosis associated with chronic pelvic pain. Overall, of the 107 patients in the conservative surgery group with ovarian preservation, 62 (58%) required further surgical intervention after their index operation. Women between the ages of 19 and 29 years had, respectively, a 1.75 times and 4.76 times higher risk of re-operation than women 30–39 years old and those older than 40. In the 19–29 years age group, the surgery-free percentages after 2, 5 and 7 years were only 63.9%, 33.3% and 27.8%, respectively.



**Figure 2** Cumulative 36 month probability of recurrence of moderate or severe dysmenorrhoea by disease stage in 425 symptomatic women who underwent conservative surgery for endometriosis (black line, stage I; red line, stage II; blue line, stage III; green line, stage IV). From Vercellini *et al.* (2006a), reproduced with permission of the publisher.

Corresponding figures in the 30–39 years and in the more than 40 years age groups were 88.0%, 58.0%, 43.8%, and 85.7%, 76.2%, 76.2%, respectively. Disease stage had no effect on 'surgery-free' time. The authors maintain that local excision of endometriosis is associated with good short-term outcomes, but high long-term re-operation rates.

The modality to treat peritoneal endometriosis appears inconsequential with regard to pain relief. Wright *et al.* (2005) conducted a randomized, double-blind trial comparing laparoscopic excision and ablation of peritoneal lesions in 24 patients with symptomatic endometriosis. After 6 month follow-up, about two-thirds of subjects in each study group reported substantial reduction of pain.

In contrast, the modality adopted to treat ovarian endometriomas seems to have a major impact on surgical outcomes (Chapron *et al.*, 2002; Vercellini *et al.*, 2003b). Hart *et al.* (2005) conducted a systematic literature review in order to determine the most effective technique of treating endometriotic cysts, either excision of the cyst pseudo-capsule or drainage and electro-coagulation of the pseudo-cyst wall, with regard to relief of pain, recurrence of the endometrioma, recurrence of symptoms and the subsequent spontaneous pregnancy rate. Laparoscopic excision of the pseudo-cyst wall was associated with a reduced rate of recurrence of the endometrioma [odds ratio (OR) 0.41, 95% confidence interval (CI) 0.18–0.93], reduced requirement for further surgery (OR 0.21, 95% CI 0.05–0.79), reduced recurrence rate of dysmenorrhoea (OR 0.15, 95% CI 0.06–0.38), dyspareunia (OR 0.08, 95% CI 0.01–0.51) and non-menstrual pelvic pain (OR 0.10, 95% CI 0.02–0.56). Excision was also associated with a subsequent increased rate of spontaneous pregnancy in women who had documented prior subfertility (OR 5.21, 95% CI 2.04–13.29). Consequently, excision of the endometrioma pseudo-capsule should be the favoured surgical approach (Chapron *et al.*, 2002; Vercellini *et al.*, 2003b). Moreover, only this modality allows histological examination. However, it has been reported that endometrioma excision may decrease ovarian reserve and lead to poorer IVF pregnancy outcomes (Catenacci and Falcone, 2008).

### Effect of surgery for stage I–IV disease: controlled studies

The results of three RCTs are available in order to evaluate properly the effect of surgery on endometriosis-associated pain (Sutton *et al.*, 1994, 1997; Kones *et al.*, 2001; Abbott *et al.*, 2004; Jarrell *et al.*, 2005, 2007).

Sutton *et al.* (1994) performed a double-blind study on 63 women with minimal to moderate endometriosis undergoing laparoscopy for pelvic pain symptoms. The subjects were allocated intra-operatively to laser destruction of endometriotic lesions plus uterosacral nerve ablation ( $n = 32$ ) or expectant management ( $n = 31$ ). At 6 month follow-up, 20 patients in the laser group were better (63%) compared with 7 (23%) in the expectant management group.

Three years later, Sutton *et al.* (1997) reported the results observed at 1 year follow-up. The authors maintain that symptom relief continued in 90% of those who initially responded. Nevertheless, based on an intention-to-treat analysis, this translates to a success rate of 56% (18/32) in the active management group versus 23% (7/31) in the

control group, with a pain recurrence rate of 44% after laser surgery. In other words, 1 year after laparoscopy, the absolute benefit increase of surgery was 33%.

A further, long-term report on the same population has been published in 2001 (Kones *et al.*, 2001). However, no additional information on the two separate study groups is obtainable as 24 patients in the expectant management arm eventually underwent laser laparoscopy, and their data were mixed with those originally allocated to the surgical arm. Unfortunately, 25 subjects of the resulting cohort of 56 patients have been lost to follow-up. After a mean period of 73 months since the procedure, 21 of the remaining 38 women (55%) experienced satisfactory symptom relief, whereas 17 (45%) described continued painful symptoms. Again, inclusion of drop-outs in the final analysis according to a conservative and probably more realistic approach would modify the optimistic view of the authors, because only 21 of the 56 (37%) women treated with laser laparoscopy have been actually demonstrated to experience a substantial symptomatic benefit.

A second, small, blinded RCT was conducted by Abbott *et al.* (2004) on 39 symptomatic women undergoing laparoscopy for minimal to severe endometriosis. Twenty of them were allocated to immediate excision of lesions, whereas in 19 no surgical procedure was performed. A second laparoscopy was scheduled after 6 months with the aim of excising all the visible lesions in both study groups. At 6 month follow-up 16 subjects (80%) in the surgery group reported symptomatic improvement compared with 6 (32%) in the expectant management group. The benefit increase of 48% is similar to the 40% observed by Sutton *et al.* (1994) after the same, short, follow-up period. A total of 33 women underwent a second laparoscopy, 15 in the surgery group and 18 in the expectant management group. After a further 6 month follow-up, 8 subjects in the surgery group (53%) and 15 in the expectant management group (83%) reported improvement in pain. This demonstrates that second-line surgery is less effective than that of first-line, as the proportions of non-responders were, respectively, 47% and 20%. In both groups, amelioration in health-related quality of life was demonstrated after excisional surgery.

The third-blind study on the efficacy of surgery for endometriosis was conducted by Jarrell *et al.* (2005) who allocated 29 women with severely symptomatic minimal to moderate endometriosis to laparoscopic excision ( $n = 15$ ) or observational laparoscopy ( $n = 14$ ). The subjects completed pain diaries at baseline and then at 3 month intervals for 1 year. Only seven women in the excisional surgery group and eight in the control group completed the entire follow-up period. No significant difference was observed in visual analogue scale pain score reduction (45% versus 33%, respectively). Similar proportional reductions were observed also in dropouts at their last evaluation (42% versus 35%, respectively).

Recently, Jarrell (2007) reported long-term follow-up data of the above study population in order to determine the predictors of subsequent surgery. The overall repeat surgical operation rate 12–14 years after the original trial was 52% in the excision group and 48% in the observational laparoscopy group. Only the reported measurement of pain prior to the initial trial was a significant covariate in the prediction of repeat surgery among all subjects. Age, stage of disease and excision of endometriosis were not associated with improvement in pain as measured by the time to repeat surgery.

## Effect of surgery for deep infiltrating disease

Endometriosis infiltrating the posterior vaginal and anterior rectal walls usually causes severe organic-type symptoms, such as deep dyspareunia and dyschezia, in addition to dysmenorrhoea (Vercellini et al., 1996, 2004, 2009; Vercellini, 1997). In this technically demanding condition, incomplete lesion resection generally does not achieve benefits, whereas radical interventions carry the risk of major complications, and ureteral and rectal injuries with associated sequelae are not exceptional (Koninckx et al., 1996; Fedele et al., 2004a; Ford et al., 2004).

The diagnosis of rectovaginal endometriosis is based on vaginal and rectal examinations, transvaginal and transrectal ultrasonography, pelvic magnetic resonance imaging and histological demonstration of endometriosis in biopsy of the posterior fornix. The pre-operative workup must also include kidney and urinary tract ultrasonography as well as rectosigmoidoscopy.

Since year 2000, the results of more than 30 case series have been published in English-language, peer-reviewed journals, with the aim of evaluating the effect of radical conservative surgery for rectovaginal endometriosis on pelvic pain symptoms, compared with only six articles identified in the period 1990–1999 (Reich et al., 1991; Candiani et al., 1992; Nezhat et al., 1992; Donnez et al., 1995, 1997; Koninckx et al., 1996; Possover et al., 2000, 2005; Anaf et al., 2001; Chapron et al., 2001; Redwine and Wright, 2001; Wright and Shafic, 2001; Duepreet et al., 2002; Fedele et al., 2004a; Ford et al., 2004; Thomassin et al., 2004; Volpi et al., 2004; Campagnacci et al., 2005; Chopin et al., 2005; Darai et al., 2005; Fleisch et al., 2005; Keckstein and Weisinger, 2005; Mohr et al., 2005; Angioni et al., 2006; Ayroza Ribeiro et al., 2006; Dubernard et al., 2006, 2008; Landi et al., 2006; Langebrenke et al., 2006; Lyons et al., 2006; Vercellini et al., 2006b; Brouwer and Woods, 2007; Kristensen and Kjer, 2007; Mereu et al., 2007; Seracchioli et al., 2007; Matsuzaki et al., 2008; Zanetti-Dallenbach et al., 2008; Supplementary Table S1).

With one exception (Vercellini et al., 2006b), all the available studies are observational or retrospective and non-comparative, most of them including a limited number of patients. The criteria used to define the presence and extent of deeply infiltrating endometriosis are not always clearly described and the surgical access is inconsistent (i.e. laparotomy alone, laparoscopy alone, a combination of laparotomy or laparoscopy and a vaginal approach). The proportion of women undergoing colorectal surgery is highly variable, as some groups advocate an aggressive strategy (Duepreet et al., 2002; Darai et al., 2005; Dubernard et al., 2006), whereas others discourage bowel resection whenever possible (Donnez et al., 1995, 1997; Vercellini et al., 2006b), and colorectal surgery has been performed differently, as some authors support simple nodulectomy (disk resection) (Reich et al., 1991; Candiani et al., 1992; Donnez et al., 1995, 1997; Anaf et al., 2001; Chapron et al., 2001; Angioni et al., 2006; Kristensen and Kjer, 2007) and others low anterior resection (Campagnacci et al., 2005; Fleisch et al., 2005; Brouwer and Woods, 2007). Moreover, in many reports, it is not stated if resection of the posterior vaginal fornix has been performed systematically. Rates of major intra- and post-operative complications vary widely, ranging from 0% to 13%. The follow-up period is very different but, in the vast majority of the considered studies, is unusually short (only a few months), and in general, dropouts are not included in the efficacy analysis. Finally, the

proportion of patients who used post-operative medical treatment is usually not reported. Such an extreme clinical heterogeneity virtually impedes data pooling as well as generalization of the observed results (Vercellini et al., 2009). Results reported in the considered studies are summarized in Supplementary Table S1.

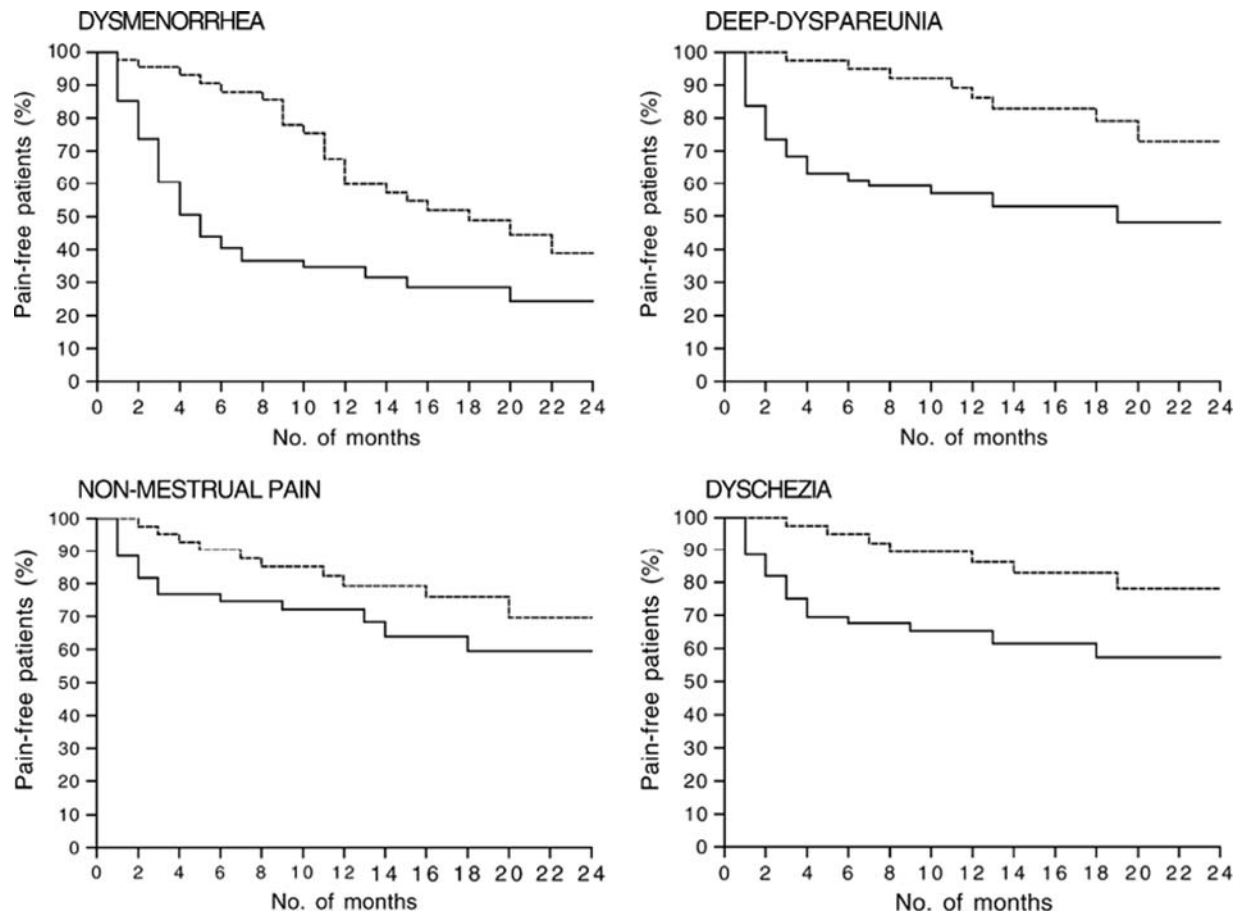
Controlled data have been reported in a single trial (Vercellini et al., 2006b). Women with infertility and pain symptoms were offered surgery at laparotomy or expectant management. The study was conducted according to an informed and shared medical decision-making approach. Therefore, the selected therapeutic option was not by random allocation but in accordance with patient's preference.

Of the 105 patients evaluated, 44 preferred surgical treatment and 61 chose expectant management. Seven patients underwent a low anterior rectal resection, ureterolysis was necessary in six subjects, and a segmental bladder resection for a full-thickness detrusor nodule in one. No severe intra-operative complication occurred. Post-operatively, a left utero-peritoneal fistula with urinary extravasation developed in a woman who underwent extensive ureterolysis because of dense fibrosis.

After a mean follow-up of >2 years, a statistically significant delay in time to moderate or severe pain experience in favour of the surgery group was observed. The benefit of surgery was particularly evident with regard to deep dyspareunia and dyschezia. Dysmenorrhoea was the most frequent type of pain reported. The 12 month cumulative proportion of subjects free from moderate or severe dysmenorrhoea was 59.8% in the surgery group compared with 34.6% in the expectant management group, while the corresponding figures at 24 months were, respectively, 38.9% and 24.5% ( $P = 0.001$ ). At the same time points, the cumulative proportions of women free from moderate or severe deep dyspareunia were, respectively, 86.2% and 72.9% in the surgery group compared with 57.1% and 48.2% in the expectant management group ( $P = 0.001$ ). The cumulative proportions of patients free from dyschezia at 12 and 24 months were, respectively, 86.3% and 78.1% in the surgery group versus 65.3% and 57.4% in the expectant management group ( $P = .008$ ) (Fig. 3).

The majority of severe complications of this type of surgery are specifically associated with inadvertent rectal perforation or incidental resection (Supplementary Table S1). The most frequently reported post-operative difficulty is urinary retention, probably due to damage to the parasympathetic plexus resulting in temporary bladder denervation. This problem is associated with, but it is not exclusive to, colorectal resection (Dubernard et al., 2008). Recently, nerve-sparing techniques have been suggested with substantial reductions in time to resumption of spontaneous voiding, residual urine volume and need for self-catheterization at discharge (Volpi et al., 2004; Possover et al., 2005; Landi et al., 2006).

The second most frequent complication is rectovaginal fistula formation, with a reported risk as high as 10% even in expert hands (Darai et al., 2005; Dubernard et al., 2006). To limit this psychologically devastating event, opening of the rectal lumen should be avoided whenever possible. If bowel involvement is known in advance, the decision to resect the rectum must be shared preoperatively with the patient after detailed information and should be based more on symptoms severity than on degree of infiltration. Many women prefer to live with residual dyschezia than to risk a fecaloid fistula or a derivative colostomy.



**Figure 3** Time to recurrence of symptoms during follow-up of 105 women with rectovaginal endometriosis who had conservative surgery at laparotomy (dashed line) or expectant management (straight line). From Vercellini *et al.* (2006b), reproduced with permission of the publisher.

Rectovaginal endometriosis is a benign condition with limited tendency to progress. In a series of 88 women who underwent watchful waiting for a mean period of 6 years, Fedele *et al.* (2004b) did not observe an increase in the volume of endometriotic plaques at transrectal ultrasonography in more than 90% of the subjects. This seems logical based on the intraperitoneal origin of the lesion. In fact, the inflammatory cascade triggered by retro-uterine endometriotic implants induces the formation of a fibrotic cast of the deepest portion of the Douglas pouch. In this condition, ectopic endometrial glands may undergo cystic changes with typical bluish nodule formation but, once buried in dense connective tissue, they cannot easily further infiltrate the surrounding structures (Vercellini, 1997; Vercellini *et al.*, 1996, 2000b).

## Comment

When considering the expected effect of surgery for endometriosis-associated pain, clinicians and patients should be aware that the outcome is operator-dependent. Taking this premise into adequate account, some conclusions can be drawn based on the best available evidence.

In general, major methodological drawbacks limit the validity of the data presented in observational, non-comparative studies on the effect

of surgery for stage I–IV disease. Indeed, several factors could influence the information reported, such as the criteria adopted for the diagnosis of symptoms or lesion recurrence, the duration of follow-up of a chronic disease with a high relapse rate and the exclusion of drop-outs, a subgroup with a potentially worse prognosis. Publication bias seems probable, as the estimate of recurrence rate derives mainly from retrospective trials which tend to over-represent optimistic results. Surgeons with suboptimal long-term outcomes may be less willing to submit their data or less likely to have them published. Therefore, the real incidence of pain symptoms relapse cannot be assessed dependably due to misdiagnosis and under-reporting.

Noticeably, the reported proportion of women who experienced pain recurrence or underwent re-operation raised progressively and consistently during the considered years (Fig. 1). This observation may be interpreted as a result of performance of the procedures by multiple instead of a single, excellent, surgeon, more accurate data management or, more simply, a longer follow-up period. Whatever the case, recent reports reasonably reflect 'real-world' conditions more reliably than the older ones. However, heterogeneity of the patient population (e.g. different endometriosis stages, presence of superficial versus deep lesions, primary versus recurrent disease) may influence greatly the above findings. Moreover, it cannot be excluded that a variation in the biological characteristics of

endometriosis with a more infiltrative behaviour, associated with a greater awareness of deep forms with consequent improvement in diagnostic capabilities, may increase spuriously the reported incidence of recurrence.

The results of the few formal, comparative studies on the effectiveness of laparoscopic surgery for symptomatic stage I–IV endometriosis (Sutton *et al.*, 1994; Abbott *et al.*, 2004; Jarrell *et al.*, 2005) allow more reliable estimates. The absolute benefit increase compared with observational laparoscopy in terms of proportion of women reporting pain relief appeared realistically between 30% and 40% after short follow-up periods. The effect size tended to decrease with time, and the approximate re-operation rate because of pain recurrence was as high as 50%. This estimate has been recently confirmed by long-term follow-up data indicating an overall probability of re-operation of 54–58% after 5–7 years since the index intervention (Cheong *et al.*, 2008; Shakiba *et al.*, 2008). This figure was as high as 72% in the 19–29 years age group. The above results should be interpreted considering that patients undergoing repetitive surgery are probably only a fraction of those experiencing symptoms recurrence.

The researchers who designed the above trials (Sutton *et al.*, 1994; Abbott *et al.*, 2004; Jarrell *et al.*, 2005) are to be commended for the enormous efforts necessary for the conduction of randomized, blinded, comparative studies including a diagnostic only arm. However, even these methodologically valuable investigations are not free from some shortcomings, such as limited sample size (Sutton *et al.*, 1994; Abbott *et al.*, 2004; Jarrell *et al.*, 2005), short follow-up period (Sutton *et al.*, 1994) and a substantial number of dropouts (Jarrell *et al.*, 2005). This partly limits the precision of the estimate of the treatment effect. In all future RCTs on the outcome of surgery for endometriosis-associated pain, long-term data should be provided to allow for dropouts and likely reduction of effect size with time (Ford *et al.*, 2004; Wykes *et al.*, 2006).

Owing to the same methodological drawbacks described for observational studies on stage I–IV endometriosis, only generic assumptions may be formulated on the effect of conservative surgery for rectovaginal lesions. Overall, major variations in several health-related quality of life indicators were reported, and substantial short-term pain relief was experienced by ~70–80% of the patients attending follow-up visits. Also in this condition, the percentage tended to decline with time, and at 1 year follow-up a considerable proportion of the women needed analgesics or hormonal treatments (Anaf *et al.*, 2001; Thomassin *et al.*, 2004; Fleisch *et al.*, 2005). Major complications were observed in 3–10% of the patients, including haemoperitoneum, rectovaginal fistula, anastomotic leakage/fistula, ureteral fistula/uropertoneum, bowel perforation, pelvic abscess, need for temporary loop ileostomy, post-operative bowel or ureteral anastomotic stenosis, neurogenic bladder dysfunction, constipation and peripheral sensory disturbance (Supplementary Table S1). Excision of the posterior vaginal fornix was associated with substantial pain reduction (particularly deep dyspareunia), but concomitant resection of vaginal and rectal walls increased the likelihood of fistula formation due to juxtaposition of sutures of bacteria-containing hollow viscera. Medium-term recurrence of lesions was observed in ~20% of the cases (Fedele *et al.*, 2004a; Brouwer and Woods, 2007; Kristensen and Kjer, 2007), and around 25% of the operated subjects eventually underwent repetitive conservative or definitive surgery because of pain relapse (Reich *et al.*, 1991; Nezhat *et al.*, 1992; Mohr *et al.*, 2005; Mereu *et al.*, 2007).

Rectal endometriosis can be dealt with using three different modalities: superficial-thickness excision (shaving), full-thickness discoid resection/anterior rectal wall excision and segmental colorectal resection (Vercellini *et al.*, 2009). Lesions less than 2 cm in size or less than one-third of the rectal circumference can be excised in a full-thickness manner either trans-abdominally or laparoscopically. For lesions requiring segmental resection of the rectum, the proximal healthy colon should be mobilized and the ureters identified. The lower the anastomosis, the higher the probability of post-operative leakage and rectovaginal fistula formation (Ret Davalos *et al.*, 2007). Accordingly, performance of low- or ultra-low anterior rectal resection, although sometimes inevitable, should be carefully weighed against the risk of complications (Donnez, 2008).

A balance between the expected benefit of a procedure and its related morbidity should always be defined when considering surgery for pain relief in women with endometriosis. Whereas destruction of peritoneal implants and enucleation of endometriotic cysts are generally uneventful, removal of rectovaginal plaques is associated with serious complications (Slack *et al.*, 2007). Furthermore, the results reported after the treatment of peritoneal and ovarian disease are reasonably generalizable, whereas those relative to treatment of deeply infiltrating lesions are strictly operator-dependent. Post-operative pain relief and complication rates are likely to vary considerably if surgeons are not specifically trained in particularly complex interventions. The decision to resect rectovaginal endometriosis should be undertaken in highly motivated women, after detailed and unbiased counselling, and considering that the tendency towards lesion progression is limited (Fedele *et al.*, 2004b). A cautious approach, especially in technically challenging conditions, should also limit the number of litigation cases, another important outcome variable.

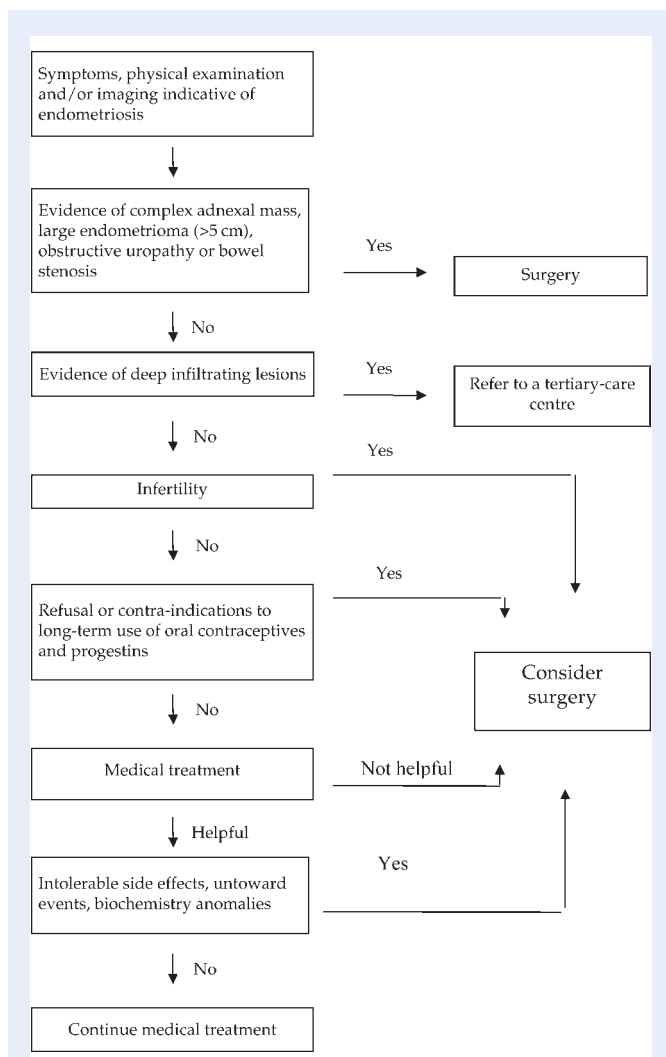
Excision of endometriotic lesions is a valid alternative in patients not responding to or not tolerating progestogens and estrogen-progestogen combinations. In particular, subjects suffering from severe deep dyspareunia and dyschezia should be considered good candidates, as removal of deep nodules is usually more effective than medical therapy in relieving organic-type pain. Finally, intolerable pain in women seeking a spontaneous conception constitutes a rational indication for conservative surgery. However, surgeons and patients should be aware that the effect of conservative surgery on endometriosis-associated pelvic pain is smaller than previously believed and that medium- as well as long-term symptoms recurrence is highly probable.

Exclusion from the present review of studies on pelvic denervation may have negatively biased our conclusions on the effect of conservative surgery. According to a Cochrane meta-analysis (Latthe *et al.*, 2007), the addition of uterosacral ligament ablation to laparoscopic treatment of endometriosis did not improve relief from secondary dysmenorrhoea (OR 0.77; 95% CI 0.43–1.39), whereas presacral neurectomy did (OR 3.14; 95% CI 1.59–6.21). However, the evidence for nerve interruption in the management not only of dysmenorrhoea but also of deep dyspareunia and non-menstrual pelvic pain is limited and further RCTs are needed. A further meta-analysis on the effectiveness of laparoscopic uterosacral ligament ablation is currently being performed by collecting individual patient data from the existing trials (Xiong *et al.*, 2007).

Figure 4 describes a proposed diagnostic and therapeutic progression for the management of chronic pelvic pain associated with



endometriosis in premenopausal women. This flow-chart should be considered taking into account that several variables may influence greatly the choice between laparoscopy, medical treatment or even IVF, or between conservative and definitive surgery (e.g. patient's age and preference, presence of other infertility factors, previous operations for the same condition) (Vercellini *et al.*, 2008b). Indeed, defining precisely the indications to conservative surgery for symptomatic endometriosis may reveal an awkward task. Because endometriosis is a benign disease, and since in a large number of cases there is no definitive best therapeutic solution, the choice between the available treatment alternatives should be shared with the patient. In our opinion, the caring gynaecologist must explain clearly the concrete probabilities of benefit and risks of complications of the various options, and verify that the woman has adequately understood what has been explained. At this phase, the final decision should not be imposed upon the patient, but taken together with her.



**Figure 4** Flow-chart describing a proposed diagnostic and therapeutic progression for the management of chronic pelvic pain associated with endometriosis in premenopausal women not previously operated for the same condition.

## Conclusions

It has been stated that ‘the definitive treatment of endometriosis is simple: surgical eradication’ and that ‘the success of surgical treatment is best assessed by determining how much disease, if any, remains after operative interventions’ (Redwine *et al.*, 2000). On the other hand, it has been considered that ‘increasingly, the focus has been on using research outcomes that matter to patients’ and that ‘patient oriented outcomes of relief of pain and pregnancy rate [...] are the outcomes considered to make a difference to the daily lives of women with endometriosis’ (Farquhar, 2000).

In the past two decades, it became progressively evident that the overall ‘amount’ of disease is not correlated neither with frequency and severity of symptoms nor with long-term prognosis in terms of conceptions and pain recurrences (Vercellini *et al.*, 2006a, 2007). Furthermore, effective pharmacological alternatives have been developed to deal with a chronic inflammatory disease, such as endometriosis, that needs drug modulation for years, and not only for a few months (Vercellini *et al.*, 2003a, 2008a, b). Accordingly, a more pragmatic approach to the treatment of symptomatic endometriosis gradually developed, focused more on the woman’s needs than on the extension of ectopic foci (Vercellini *et al.*, 2003a). In other words, the problems of patients with endometriosis are disease-related symptoms and not implants *per se*, and treatments should be centred on resolution of complaints, independently of a *a priori* excision of lesions.

When discussing any procedure, a woman should know the specific objectives of surgery, the evidence on which the alleged advantages are based, the frequency and severity of complications and, more importantly, she should be able to measure the purported benefits. A shared medical decision-making approach should be implemented in each centre caring for endometriosis patients (D’Hooghe and Hummelshoj, 2006). Endometriosis usually affects young and otherwise healthy women with high expectations in terms of well-being and health-related quality of life. In this population, intra- and post-operative complications are perceived and tolerated with difficulty, and invalidating pain recurrence is particularly frustrating. Consciousness of the real possibilities of surgery will enhance the patient’s collaboration, facilitating acceptance of what may be revealed as a reasonable compromise but might otherwise appear as a partial therapeutic failure.

## Author’s contribution

P. Vercellini contributed to the conception of the review, prepared the first draft and completed subsequent amendments. P.G.C. contributed to the conception of the review and subsequent amendments. E.S. contributed to the conception of the review and subsequent amendments. P. Viganò performed the literature search, selected the articles, and abstracted the data. A.A. performed the literature search, selected the articles, and abstracted the data. L.F. contributed to the conception of the review and subsequent amendments.

## Supplementary data

Supplementary data are available at <http://molehr.oxfordjournals.org/>.

## Funding

Supported in part by the University of Milan School of Medicine Research Grant FIRST no. 12-01-5068118-00067 and by the Center for Research in Obstetrics and Gynecology, Milano, Italy.

## References

- Abbott JA, Hawe J, Clayton RD, Garry R. The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2-5 year follow-up. *Hum Reprod* 2003;**18**:1922–1927.
- Abbott J, Hawe J, Hunter D, Holmes M, Finn P, Garry R. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril* 2004;**82**:878–884.
- Anaf V, Simon P, El Nakadi I, Simonart T, Noel J, Buxant F. Impact of surgical resection of rectovaginal pouch of Douglas endometriotic nodules on pelvic pain and some elements of patients' sex life. *J Am Assoc Gynecol Laparosc* 2001;**8**:55–60.
- Angioni S, Peiretti M, Zironi M, Palomba M, Mais V, Gomel V. Laparoscopic excision of posterior vaginal fornix in the treatment of patients with deep endometriosis without rectum involvement: surgical treatment and long-term follow-up. *Hum Reprod* 2006;**21**:1629–1634.
- Ayroza Ribeiro PA, Rodrigues FC, Kehdi IPA, Rossini L, Abdalla HS, Donadio N, Aoki T. Laparoscopic resection of intestinal endometriosis: a 5-year experience. *J Minim Invasive Gynecol* 2006;**13**:442–446.
- Bergqvist A, Bergh T, Hogstöm L, Mattsson S, Nordenskjöld F, Rasmussen C. Effects of triptorelin versus placebo on the symptoms of endometriosis. *Fertil Steril* 1998;**69**:702–708.
- Bianconi L, Hummelshoj L, Coccia ME, Viganò P, Vittori G, Veit J, Music R, Tomassini A, D'Hooghe T. Recognizing endometriosis as a social disease: the European Union-encouraged Italian Senate approach. *Fertil Steril* 2007;**88**:1285–1287.
- Brouwer R, Woods RJ. Rectal endometriosis: results of radical excision and review of published work. *ANZ J Surg* 2007;**77**:562–571.
- Busacca M, Bianchi S, Agnoli B, Candiani M, Calia C, De Marinis S, Vignali M. Follow-up of laparoscopic treatment of stage III-IV endometriosis. *J Am Assoc Gynecol Laparosc* 1999;**6**:55–58.
- Campagnacci R, Perretta S, Guerrieri M, Paganini AM, De Sanctis A, Ciavattini A, Lezoche E. Laparoscopic colorectal resection for endometriosis. *Surg Endosc* 2005;**19**:662–664.
- Candiani GB, Vercellini P, Fedele L, Roviato GC, Rebuffat C, Trespidi L. Conservative surgical treatment of rectovaginal septum endometriosis. *J Gynecol Surg* 1992;**8**:177–182.
- Catenacci M, Falcone T. The effect of endometriosis on in vitro fertilization outcome. *Minerva Ginecol* 2008;**60**:209–221.
- Chapron C, Jacob S, Dubuisson J, Vieira M, Liaras E, Fauconnier A. Laparoscopic assisted vaginal management of deep endometriosis infiltrating the rectovaginal septum. *Acta Obstet Gynecol Scand* 2001;**80**:349–354.
- Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriomas. *Hum Reprod Update* 2002;**8**:591–597.
- Cheong Y, Tay P, Luk F, Gan HC, Li TC, Cooke I. Laparoscopic surgery for endometriosis: how often do we need to re-operate? *J Obstet Gynaecol* 2008;**28**:82–85.
- Chopin N, Vieira M, Borghese B, Foulot H, Dousset B, Coste J, Mignon A, Fauconnier A, Chapron C. Operative management of deeply infiltrating endometriosis: results on pelvic pain symptoms according to a surgical classification. *J Minim Invasive Gynecol* 2005;**12**:106–112.
- Crosignani PG, Vercellini P, Biffignandi F, Costantini W, Cortesi I, Imperato E. Laparoscopy versus laparotomy in conservative surgical treatment for severe endometriosis. *Fertil Steril* 1996;**66**:706–711.
- Darai E, Thomassin I, Barranger E, Detchev R, Cortez A, Houry S, Bazot M. Feasibility and clinical outcome of laparoscopic colorectal resection for endometriosis. *Am J Obstet Gynecol* 2005;**192**:394–400.
- D'Hooghe T, Hummelshoj L. Multi-disciplinary centres/networks of excellence for endometriosis management and research: a proposal. *Hum Reprod* 2006;**21**:2743–2748.
- Glugj AM, Miller JD, Knittle J. Lupron depot (leuprolide acetate) for depot suspension in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study. *Fertil Steril* 1990;**54**:419–427.
- Donnez J. Is accreditation for surgery the next step? *World Endometriosis Society e-Journal* 2008;**10**:1–2.
- Donnez J, Nisolle M, Casanas-Roux F, Bassil S, Anaf V. Rectovaginal septum, endometriosis or adenomyosis: laparoscopic management in a series of 231 patients. *Hum Reprod* 1995;**10**:630–635.
- Donnez J, Nisolle M, Gillerot S, Smets I, Bassil S, Casanas-Roux F. Rectovaginal septum adenomyotic nodules: a series of 500 cases. *Br J Obstet Gynaecol* 1997;**104**:1014–1018.
- Dubernard G, Piketty M, Rouzier R, Houry S, Bazot M, Darai E. Quality of life after laparoscopic colorectal resection for endometriosis. *Hum Reprod* 2006;**21**:1243–1247.
- Dubernard G, Rouzier R, David-Montefiore E, Bazot M, Darai E. Use of SF-36 questionnaire to predict quality-of-life improvement after laparoscopic colorectal resection for endometriosis. *Hum Reprod* 2008;**23**:846–851.
- Duepree HJ, Senagore AJ, Delaney CP, Marcello PW, Brady KM, Falcone T. Laparoscopic resection of deep pelvic endometriosis with rectosigmoid involvement. *J Am Coll Surg* 2002;**195**:754–758.
- Farquhar CM. Endometriosis. *Br Med J* 2000;**320**:1449–1452.
- Fedele L, Bianche S, Bocciolone L, Di Nola G, Franchi D. Buserelin acetate in the treatment of pelvic pain associated with minimal and mild endometriosis: a controlled study. *Fertil Steril* 1993;**59**:516–521.
- Fedele L, Bianchi S, Zanconato G, Bettoni G, Gotsch F. Long term follow-up after conservative surgery for rectovaginal endometriosis. *Am J Obstet Gynecol* 2004a;**190**:1020–1024.
- Fedele L, Bianchi S, Zanconato G, Raffaelli R, Berlanda N. Is rectovaginal endometriosis a progressive disease? *Am J Obstet Gynecol* 2004b;**191**:1539–1542.
- Ferrero S, Abbamonte LH, Giordano M, Ragni N, Remorgida V. Deep dyspareunia and sex life after laparoscopic excision of endometriosis. *Hum Reprod* 2007;**22**:1142–1148.
- Fleisch MC, Xafis D, De Bruyne F, Hucke J, Bender HG, Dall P. Radical resection of invasive endometriosis with bowel or bladder involvement. Long-term results. *Eur J Obstet Gynecol Reprod Biol* 2005;**123**:224–229.
- Ford J, English J, Miles WA, Giannopoulos T. Pain, quality of life and complications following the radical resection of rectovaginal endometriosis. *BJOG* 2004;**111**:353–356.
- Gao X, Yeh YC, Outley J, Simon J, Botteman M, Spalding J. Health-related quality of life burden of women with endometriosis: a literature review. *Curr Med Res Opin* 2006a;**22**:1787–1797.
- Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL. Economic burden of endometriosis. *Fertil Steril* 2006b;**86**:1561–1572.
- Garry R, Clayton R, Hawe J. The effect of endometriosis and its radical laparoscopic excision on quality of life indicators. *BJOG* 2000;**107**:44–54.
- Hart RJ, Hickey M, Maouris P, Buckett W, Garry R. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev* 2005;**5**:CD004992.
- Jacobson TZ, Barlow DH, Garry R, Koninckx P. Laparoscopic surgery for pelvic pain associated with endometriosis. *Cochrane Database System Reviews* 2001;**4**:CD001300.

- Jarrell J, Mohindra R, Ross S, Taenzer P, Brant R. Laparoscopy and reported pain among patients with endometriosis. *J Obstet Gynaecol Can* 2005;**27**:477–485.
- Jarrell J, Brant R, Leung W, Taenzer P. Women's pain experience predicts future surgery for pain associated with endometriosis. *J Obstet Gynaecol Can* 2007;**29**:988–991.
- Jones KD, Sutton C. Patient satisfaction and changes in pain scores after ablative laparoscopic surgery for stage III-IV endometriosis and endometriotic cysts. *Fertil Steril* 2003;**79**:1086–1090.
- Keckstein J, Weisinger H. Deep endometriosis, including intestinal involvement—the interdisciplinary approach. *Minim Invasive Ther Allied Technol* 2005;**14**:160–166.
- Kones KD, Haines P, Sutton CJG. Long-term follow-up of a controlled trial of laser laparoscopy for pelvic pain. *JLS* 2001;**5**:111–115.
- Koninckx PR, Timmermans B, Meuleman C, Penninckx F. Complications of CO<sub>2</sub> laser endoscopic excision of deep endometriosis. *Hum Reprod* 1996;**10**:2263–2268.
- Kristensen J, Kjer KJ. Laparoscopic laser resection of rectovaginal pouch and rectovaginal septum endometriosis: the impact on pelvic pain and quality of life. *Acta Obstet Gynecol Scand* 2007;**86**:1467–1471.
- Landi S, Ceccaroni M, Perutelli A, Allodi C, Barbieri F, Fiaccavento A, Ruffo G, McVeigh E, Zanolla L, Minelli L. Laparoscopic nerve-sparing complete excision of deep endometriosis: is it feasible? *Hum Reprod* 2006;**21**:774–781.
- Langebrekke A, Istre O, Busund B, Johannessen HO, Qvigstad E. Endoscopic treatment of deep infiltrating endometriosis (DIE) involving the bladder and rectosigmoid colon. *Acta Obstet Gynecol Scand* 2006;**85**:712–715.
- Latthe PM, Proctor ML, Farquhar CM, Johnson NP, Kahn KS. Surgical interruption of pelvic nerve pathways in dysmenorrhoea: a systematic review of effectiveness. *Acta Obstet Gynecol Scand* 2007;**86**:4–15.
- Lyons SD, Chew SSB, Thomson AJM, Lenart M, Camaris C, Vancaillie T, Abbott JA. Clinical and quality-of-life outcomes after fertility-sparing laparoscopic surgery with bowel resection for severe endometriosis. *J Minim Invasive Gynecol* 2006;**13**:436–441.
- Matsuzaki S, Houille C, Botchorishvili R, Pouly JL, Mage G, Canis M. Excision of the posterior vaginal fornix is necessary to ensure complete resection of rectovaginal endometriotic nodules of more than 2 cm in size. *Fertil Steril* 2008 (Epub ahead of print).
- Mereu L, Ruffo G, Landi S, Barbieri F, Zaccoletti R, Fiaccavento A, Stepniewska A, Pontrelli G, Minelli L. Laparoscopic treatment of deep endometriosis with segmental colorectal resection: short-term morbidity. *J Minim Invasive Gynecol* 2007;**14**:463–469.
- Mohr C, Nezhat FR, Nezhat CH, Seidman DS, Nezhat CR. Fertility considerations in laparoscopic treatment of infiltrative bowel endometriosis. *JLS* 2005;**9**:16–24.
- Nezhat C, Nezhat F, Pennington E. Laparoscopic treatment of infiltrative rectosigmoid colon and rectovaginal septum endometriosis by the technique of videolaparoscopy and the CO<sub>2</sub> laser. *Br J Obstet Gynaecol* 1992;**99**:664–667.
- Possover M, Diebolder H, Plaul K, Schneider A. Laparoscopic assisted vaginal resection of rectovaginal endometriosis. *Obstet Gynecol* 2000;**96**:304–307.
- Possover M, Quakernack J, Chiantera V. The LANN technique to reduce postoperative functional morbidity in laparoscopic radical pelvic surgery. *J Am Coll Surg* 2005;**21**:913–917.
- Proctor ML, Latthe PM, Farquhar CM, Kahn KS, Johnson NP. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. *Cochrane Database Syst Rev* 2005;**4**:CD001896.
- Redwine DB. Conservative laparoscopic excision of endometriosis by sharp dissection: life table analysis of reoperation and persistent or recurrent disease. *Fertil Steril* 1991;**56**:628–634.
- Redwine D, Mann CH, Wright JT. Evidence on endometriosis. Elitism about randomised controlled trials is inappropriate. *Br Med J* 2000;**321**:1077–1078.
- Reich H, McGlynn F, Salvat J. Laparoscopic treatment of cul-de-sac obliteration secondary to retrocervical deep fibrotic endometriosis. *J Reprod Med* 1991;**36**:516–522.
- Redwine DB, Wright JT. Laparoscopic treatment of complete obliteration of the cul-de-sac associated with endometriosis: long-term follow-up of en bloc resection. *Fertil Steril* 2001;**76**:358–365.
- Ret Davalos ML, De Cicco Carlo, D'Hoore A, De Decker B, Koninckx PR. Outcome after rectum resection: a review for gynecologists. *J Minim Invasive Gynecol* 2007;**14**:33–38.
- Seracchioli R, Poggioli G, Pierangeli F, Manuzzi L, Gualerzi B, Savelli L, Remorgida V, Mabrouk M, Venturoli S. Surgical outcome and long-term follow-up after laparoscopic rectosigmoid resection in women with deep infiltrating endometriosis. *BJOG* 2007;**114**:889–895.
- Shakiba K, Bena JF, McGill KM, Minger J, Falcone T. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. *Obstet Gynecol* 2008;**111**:1285–1292.
- Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: cost estimates and methodological perspective. *Hum Reprod Update* 2007;**13**:395–404.
- Slack A, Child T, Lindsey I, Kennedy S, Cunningham C, Mortensen N, Koninckx P, McVeigh E. Urological and colorectal complications following surgery for rectovaginal endometriosis. *BJOG* 2007;**114**:1278–1282.
- Sutton CJG, Ewen SP, Whitelaw N, Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertil Steril* 1994;**62**:696–700.
- Sutton CJG, Pooley AS, Ewen SP, Haines P. Follow-up report on a randomized controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal to moderate endometriosis. *Fertil Steril* 1997;**68**:1070–1074.
- Telimaa S, Puolakka J, Rönnerberg L, Kauppila A. Placebo-controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis. *Gynecol Endocrinol* 1987a;**1**:13–23.
- The American Fertility Society. Revised American Fertility Society classification of endometriosis: 1985. *Fertil Steril* 1985;**43**:351–352.
- Thomassin I, Bazot M, Detchev R, Barranger E, Cortez A, Darai E. Symptoms before and after surgical removal of colorectal endometriosis that are assessed by magnetic resonance imaging and rectal endoscopic sonography. *Am J Obstet Gynecol* 2004;**190**:1264–1271.
- Vercellini P. Endometriosis: what a pain it is. *Semin Reprod Endocrinol* 1997;**15**:251–261.
- Vercellini P, Trespidi L, De Giorgi O, Cortesi I, Parazzini F, Crosignani PG. Endometriosis and pelvic pain: relation to disease stage and localization. *Fertil Steril* 1996;**65**:299–304.
- Vercellini P, Cortesi I, Crosignani PG. Progestins for symptomatic endometriosis: a critical analysis of the evidence. *Fertil Steril* 1997;**68**:393–401.
- Vercellini P, De Giorgi O, Pisacreta A, Pesole A, Vicentini S, Crosignani PG. Surgical management of endometriosis. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000a;**14**:501–523.
- Vercellini P, Aimi G, Panazza S, Vicentini S, Pisacreta A, Crosignani PG. Deep endometriosis conundrum: evidence in favor of a peritoneal origin. *Fertil Steril* 2000b;**73**:1043–1046.

- Vercellini P, Fedele L, Pietropaolo G, Frontino G, Somigliana E, Crosignani PG. Progestogens for endometriosis: forward to the past. *Hum Reprod Update* 2003a;**9**:387–396.
- Vercellini P, Chapron C, De Giorgi O, Consonni D, Frontino G, Crosignani PG. Coagulation or excision of ovarian endometriomas? *Am J Obstet Gynecol* 2003b;**188**:606–610.
- Vercellini P, Frontino G, Pietropaolo G, Gattei U, Daguati R, Crosignani PG. Deep endometriosis: definition, pathogenesis, and clinical management. *J Am Assoc Gynecol Laparosc* 2004;**11**:153–161.
- Vercellini P, Pietropaolo G, De Giorgi O, Pasin R, Chiodini A, Crosignani PG. Treatment of symptomatic rectovaginal endometriosis with an estrogen–progestogen combination versus low-dose norethindrone acetate. *Fertil Steril* 2005;**84**:1375–1387.
- Vercellini P, Fedele L, Aimi G, De Giorgi O, Consonni D, Crosignani PG. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. *Hum Reprod* 2006a;**21**:2679–2685.
- Vercellini P, Pietropaolo G, De Giorgi O, Daguati R, Pasin R, Crosignani PG. Reproductive performance in infertile women with rectovaginal endometriosis: is surgery worthwhile? *Am J Obstet Gynecol* 2006b;**195**:1303–1310.
- Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: a multivariate analysis of over 1000 patients. *Hum Reprod* 2007;**22**:266–271.
- Vercellini P, Somigliana E, Viganò P, Abbiati A, Daguati R, Crosignani PG. Endometriosis: current and future medical therapies. *Best Pract Res Clin Obstet Gynaecol* 2008a;**22**:275–306.
- Vercellini P, Somigliana E, Viganò P, Abbiati A, Barbara G, Crosignani PG. Surgery for endometriosis-associated infertility: a pragmatic approach. *Hum Reprod* 2008b (Epub ahead of print).
- Vercellini P, Aimi G, Amicarelli F, Abbiati A, Daguati R, Barbara G. Treatment of endometriosis associated with pain. In: Gomel V, Brill A (eds). *Reconstructive and Reproductive Surgery in Gynecology*. London, UK: Informa Healthcare, 2009 (in press).
- Vignali M, Bianchi S, Candiani M, Spadaccini G, Oggioni G, Busacca M. Surgical treatment of deep endometriosis and risk of recurrence. *J Minim Invasive Gynecol* 2005;**12**:508–513.
- Volpi E, Ferrero A, Sismondi P. Laparoscopic identification of pelvic nerves in patients with deep infiltrating endometriosis. *Surg Endosc* 2004;**18**:1109–1112.
- Weir E, Mustard C, Cohen M, Kung R. Endometriosis: what is the risk of hospital admission, readmission, and major surgical intervention? *J Minim Invasive Gynecol* 2005;**12**:486–493.
- Wykes CB, Clark TJ, Chakravati S, Mann CH, Gupta JK. Efficacy of laparoscopic excision of visually diagnosed peritoneal endometriosis in the treatment of chronic pelvic pain. *Eur J Obstet Gynecol Reprod Biol* 2006;**125**:129–133.
- Wright JT, Shafic A. Quality of life following radical excision of rectovaginal endometriosis associated with complete obliteration of the posterior cul-de-sac. *J Gynaecol Endosc* 2001;**10**:107–110.
- Wright J, Lotfallah H, Jones K, Lovell D. A randomized trial of excision versus ablation for mild endometriosis. *Fertil Steril* 2005;**83**:1830–1836.
- Xiong T, Daniels J, Middleton L, Champaneria R, Khan KS, Gray R, Johnson N, Lichten EM, Sutton C, Jones KD et al. Meta-analysis using individual patient data from randomised trials to assess the effectiveness of the laparoscopic uterosacral nerve ablation in the treatment of chronic pelvic pain: a proposed protocol. *BJOG* 2007;**114**:1580–1587.
- Zanetti-Dallenbach R, Bartley J, Müller C, Schneider A, Köhler C. Combined vaginal-laparoscopic-abdominal approach for the surgical treatment of rectovaginal endometriosis with bowel resection: a comparison of this new technique with various established approaches by laparoscopy and laparotomy. *Surg Endosc* 2008;**22**:995–1001.

Submitted on October 23, 2008; resubmitted on December 2, 2008; accepted on December 10, 2008