Chapter 3

Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial

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Objective: To evaluate postoperative long-term cyclic and continuous administration of combined oral contraceptive (OC) pills in preventing endometriosis-related pain recurrence.

Design: Prospective, randomized, controlled trial.

Setting: Tertiary care university hospital.

Patients: Three hundred eleven women who underwent laparoscopic excision for symptomatic ovarian endometrioma.

Interventions: Patients were randomly divided into three groups: nonuser group receiving no therapy, and cyclic user group and continuous user group receiving low-dose, monophasic OC pills for 24 months in either cyclic or continuous administration.

Main Outcome Measures: Presence and intensity of dysmenorrhea, dyspareunia, and chronic pelvic pain were assessed by a 10-point visual analogue scale (VAS) at 6, 12, 18, and 24 months postoperatively.

Results: A significant reduction in recurrence rate and VAS scores for dysmenorrhea was evident in the continuous users versus the other groups at 6 months and in cyclic users versus nonusers at 18 months postoperatively. No significant differences in recurrence rate and VAS scores for dyspareunia and chronic pelvic pain were demonstrated among the groups. The increase of VAS scores from 6–24 months during the study period for dysmenorrhea, dyspareunia, and chronic pelvic pain was significantly higher in nonusers than in the other groups.

Conclusions: Long-term postoperative use of OC pills can reduce the frequency and the severity of recurrent endometriosis-related dysmenorrhea.
INTRODUCTION

Endometriosis is a common cause of pelvic pain in women of reproductive age. The pain may occur during menstrual bleeding (dysmenorrhea), during sexual intercourse (dyspareunia), or not following any cyclic pattern (chronic pelvic pain) (1). If endometriosis involves the rectum or the bladder, symptoms as dyschezia or dysuria may, respectively, occur (2, 3). Women affected by symptomatic endometriosis often report a significant reduction in their quality of life (4). Furthermore, because this pathology affects primarily young women, it can impair social and professional functions. Therefore, relief of painful symptoms is one of the main goals of endometriosis treatment (5).

Some trials have shown that laparoscopic excisional surgery can significantly reduce painful symptoms and improve quality of life in 67%–80% of patients with endometriosis, probably by removing the deposits of ectopic endometrium (6). Conservative surgery is now considered the treatment of choice in ovarian endometriomas (7). At long-term follow-up, however, patients often report recurrence or worsening of associated pain. The recurrence of painful symptoms has been observed in 7%–30% of patients within 3 years after surgery, increasing to 40%–50% after 5 years (8).

Therefore, adjunctive postoperative hormonal therapy has been proposed to prolong the painful symptom-free interval or to provide a long-term reduction of pain.

In this context, oral contraceptive (OC) pills can offer an option in terms of safety and tolerability. The use of OC pills adjuvant prophylactic therapy in clinical practice is considerable, even without a high level evidence supporting their effectiveness (9, 10).

MATERIALS AND METHODS

A total of 311 patients, submitted to laparoscopic excision of symptomatic ovarian endometrioma in the Minimally Invasive Gynaecological Surgery Unit of S. Orsola University Hospital, Bologna, Italy, a tertiary referral center for treatment of endometriosis, from June 2002 to May 2006 were enrolled in the present study. The approval of the local ethics committee was obtained and all the patients gave informed consent to the trial protocol.

Nulliparous women between 20 and 40 years old, not attempting to conceive either at the time of study entry or for at least 2 years after surgery, were considered in the study. All the patients had ultrasonographic diagnosis of ovarian endometrioma and reported symptoms related to endometriosis, such as dysmenorrhea, dyspareunia, and chronic pelvic pain. Preoperatively, patients had been asked to grade the presence and the severity of pain by using a 10-point visual analogue scale (VAS), in which a score of 1–3 was considered mild pain, 4–7 moderate pain, 8–10 severe pain (11, 12). All the women recruited for the study presented with moderate or severe pain in at least one type of pain.
None of the patients had previously undergone any surgical treatment for endometriosis. None of them had been receiving hormonal treatment for endometriosis or for contraception for at least 6 months before surgery.

Patients having contraindications to OC therapy, or lack of the desire to postpone pregnancy for at least 2 years after surgery were excluded from the study. The presence of gastrointestinal or urologic diseases or the diagnosis of current pelvic inflammatory disease, which might cause painful pelvic symptoms not related to endometriosis, was regarded as exclusion criteria.

All patients underwent at least two transvaginal ultrasonographic (TVS) examinations: at 6–8 weeks before surgery and on the day before surgery. Laparoscopic excision of ovarian endometrioma was performed in all the patients as previously described (13) and lysis of adhesions was obtained when necessary. In all patients complete excision of visible endometriotic lesions was warranted. Endometriosis was intraoperatively staged according to the revised American Fertility Society (AFS) classification (14). Histopathological examination reports confirmed the endometriotic nature of the lesions in all cases. Patients in which deep infiltrating endometriosis was found during surgery were excluded from the study. Patients had been preoperatively counseled about the three different treatment options offered. It was explained that OC pill therapy could temporarily prevent or delay endometriosis-related pain appearance, or reduce its intensity when administered in short term (12, 15). The efficacy of a long-term OC pill therapy, however, had not been clearly demonstrated. Patients were also informed that no differences between cyclic and continuous administration, in terms of side effects and metabolic profile, have been demonstrated at present (16). Patients who considered unacceptable the absence of menstruation for at least 2 years, induced by continuous OC pill therapy, were excluded from the study. Women refusing the randomization to any of treatment groups were excluded from the study.

After surgery patients were randomly divided into three groups by the medical therapy protocol followed after surgery: the nonuser group received no medical treatment and the other two groups (cyclic users and continuous users) received low-dose monophasic combined OC (ethinyl E2, 0.020 mg and gestodene, 0.075 mg daily), which started on the day of discharge after surgery and lasted for 24 months. The cyclic user group received cyclic therapy (daily for 21 days followed by a 7-day pill-free interval), whereas the continuous user group received continuous therapy (no pill-free interval). Treatment allocation was performed in accordance with a computer-generated randomization sequence using numbered, opaque, sealed envelopes.

Patients who stopped OC pill therapy were excluded from the present study but were considered for a second phase of investigation, which aims to consider endometriosis-related pain management in OC pill users after discontinuation of the treatment.

Patients were followed for at least 24 months. All patients underwent clinical examination every 6 months to assess the presence and the severity of dysmenorrhea, dyspareunia, and chronic pelvic
pain. Patients were asked to report recurrence of painful symptoms in the interval between visits. When women reported symptoms between the postoperative visits, an additional visit was performed. Women were requested to grade the painful symptoms by using the 10-point VAS scale. Pain recurrence was defined as severity of pain graded R4 on the 10-point VAS scale. In the continuous user group, because patients could be symptomatic even when inhibition of menses was achieved, pain occurring during erratic bleeding episodes was considered as dysmenorrhea. Main variables assessed were: pain recurrence rate, cumulative pain-free survival, VAS scores, differences in VAS score from 6–24 months during the study period in the three study groups.

Statistical Analysis
The Kolmogorov Smirnov test was performed to test the hypotheses about normality. Using Kolmogorov Smirnov test to study the hypotheses about normality, continuous variables were not normally distributed so they were resumed by median (25th percentile – 75th percentile). The Wilcoxon test was performed to test the hypotheses about medians at different follow-up times. The Kruskal Wallis test was used to find differences among the three groups and the Mann-Whitney test with Bonferroni correction test was used as post hoc pairwise analysis. Kendall τ correlation test was performed to assess the diminution of pain recurrence rate among the groups starting with nonusers, to cyclic users, and to continuous users. Kaplan Maier survival analysis with Breslow test was performed to investigate the survival at first occurrence of VAS R4. For all tests \( P < .05 \) was considered significant.

Statistical analysis was carried out by means of the Statistical Package for the Social Sciences (SPSS) software version 14.0 (SPSS Inc., Chicago, IL).

RESULTS
Of the 311 patients considered for the study, the randomization process yielded 104 patients in the nonuser group, 103 patients in cyclic user group, and 104 patients in continuous user group. Sixty-three percent of the women who refused to be enrolled in the study did not accept the possibility of longterm amenorrhea. Seventeen patients of the nonusers (16.3 %) did not complete the study because 7 achieved a spontaneous pregnancy before 24 months of the control period and 10 started OC pill therapy because of dysmenorrhea. Eleven patients (10.6 %) among the cyclic users did not complete the treatment period: three for causes unrelated to endometriosis recurrence and eight for side effects attributable to OC therapy. Nine women (8.6%) among the continuous users did not complete the treatment period: three for causes unrelated to endometriosis recurrence and six for side effects attributable to OC therapy. Hence, 274 patients completed the study for the entire study period and were analyzed: 87 patients in the nonuser group, 92 patients in the cyclic user group, and 95 patients in the continuous user group (Fig. 1).
The three study groups were homogeneous with regard to mean age, mean body mass index (BMI), and endometriosis stage according to the revised AFS classification (14). At the end of the study every patient was controlled for at least 24 months after surgery. Baseline characteristics are summarized in Table 1.

<table>
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**Table 1**: Clinical features of the 274 patients who completed the study.

*Note: AFS: revised American Fertility Society classification; BMI: Body Mass Index; NS: Non significant.*
Recurrence Rate
Recurrence rates for the three types of pain in the three study groups for the entire study period are shown in Figure 2.

**Figure 2:** Recurrence rates for the three types of pain. (A) Dysmenorrhea recurrence rate: lower in continuous users for the entire study period ($P<.0005$); reduced in cyclic users versus nonusers at 18 and 24 months ($P=.01, P=.009$, respectively). (B) Dyspareunia recurrence rate: no significant difference among the study groups. (C) Chronic pelvic pain recurrence rate: no significant difference among the study groups.
The dysmenorrhea recurrence rate at 6, 12, 18, and 24 months postoperatively are shown in Figure 2A. For the entire study period the dysmenorrhea recurrence rate in continuous users was significantly lower than cyclic and nonusers ($P<.0005$). Between cyclic and nonusers, at 6 and 12 months postoperatively, no significant difference was detected, whereas at 18 and 24 months cyclic users showed a significant reduction in dysmenorrhea recurrence rate with respect to nonusers ($P=.01$, $P=.009$, respectively).

The values of dyspareunia recurrence rate and chronic pelvic pain recurrence rate at 6, 12, 18, and 24 months postoperatively in the three study groups are shown in Figure 2B and C, respectively. No significant differences were detected among the three groups for the entire study period for dyspareunia and chronic pelvic pain.

**Cumulative Pain-free Survival**

The Kaplan-Meier survival analysis demonstrated a significant difference among the three groups about the first occurrence of moderate-to-severe dysmenorrhea: the cumulative pain-free survival was significantly higher in continuous users versus cyclic users ($P<.0005$) and in cyclic users versus nonusers with an evident difference after 18 months postoperatively ($P=.01$) (Fig. 3).

![Figure 3: Cumulative pain-free survival in nonusers (..), cyclic users (_), and continuous users (---).](image)

The Kaplan-Meier survival analysis demonstrated no significant differences in terms of cumulative pain-free survival for dyspareunia and chronic pelvic pain among the three groups.
**VAS Score**

The VAS scores for the three types of pain in the three study groups for the entire study period are represented in Figure 4.

Analyzing the intergroup differences (comparing the same pain symptom scores among the three study groups), the VAS scores for dysmenorrhea reported by continuous users were significantly lower than the scores reported by cyclic and nonusers for the entire study period ($P<.0005$). At 12, 18, and 24 months postoperatively, cyclic users reported significantly lower VAS scores for dysmenorrhea than nonusers ($P=.017$, $P=.001$, $P<.0005$, respectively) (Fig. 4A).

The VAS scores for dyspareunia reported at 6, 12, and 24 months postoperatively did not significantly differ among continuous, cyclic, and nonusers, whereas at 18 months after the surgical intervention, continuous users showed a lower VAS score than nonusers ($P=.04$) (Fig. 4B).

The VAS scores for chronic pelvic pain did not significantly differ among the three groups for the entire study period (Fig. 4C).

At the evaluation of intra-groups VAS variations, evolution of VAS score from 6–24 months of the study period were compared among the three study groups for the three types of pain.

The difference in dysmenorrhea VAS score variation between 6 and 24 months postoperatively among the three treatment groups showed a significant worsening of pain intensity in the nonuser group ($P=.001$) (Fig. 4A).

The difference in dyspareunia VAS score variation between 6 and 24 months postoperatively among the three study groups showed a significant worsening of pain intensity in cyclic and nonuser groups compared to continuous users ($P=.042$ and $P<.0005$, respectively) (Fig. 4B).

With regard to chronic pelvic pain VAS score variation between 6 and 24 months after laparoscopic surgery, a significant worsening of pain intensity in the nonuser group was observed compared with continuous users ($P=.021$) (Fig. 4C).
Figure 4: The visual analogue scale (VAS) scores for the three types of pain at 6, 12, 18, and 24 months postoperatively. (A) Dysmenorrhea: VAS scores are lower in continuous users for the entire study period ($P < 0.0005$) and in cyclic users versus nonusers from 12 months postoperatively. Nonusers show a significant worsening in pain intensity from 6–24 months. (B) Dyspareunia: no significant difference in VAS scores among the three groups. Cyclic and nonusers versus continuous users show a worsening of pain intensity from 6–24 months. (C) Chronic pelvic pain: no significant difference in VAS scores among the three groups. Nonusers versus continuous users show a worsening of pain intensity from 6–24 months.
DISCUSSION

To the best of our knowledge our study is the only randomized controlled trial that evaluates the effects of long-term cyclic and continuous postoperative OC pill use on recurrent dysmenorrhea, dyspareunia, and chronic pelvic pain after laparoscopic excision of ovarian endometrioma.

The present study was performed in parallel with a trial regarding the efficacy of postoperative long-term continuous and cyclic OC pill therapy in reducing the risk of ovarian endometrioma recurrence (17). In this previous article, a significant difference in endometrioma recurrence rate was observed between untreated patients compared with women treated with OC pills. Furthermore, the mean diameter of endometriomas at the first observation and the increase of cyst dimensions were significantly reduced in women treated with OC pills, suggesting that therapy can reduce disease severity and restrain its progression. No significant differences were detected between cyclic and continuous OC pill administration.

In the present study, patients receiving long-term OC pill therapy, lasting 24 months, showed a significant reduction in frequency and severity of recurrent dysmenorrhea compared with surgery alone. Such findings were evident since the first visit, at 6 months, for the patients in continuous treatment, and after 18 months postoperatively in the women treated with the cyclic regimen.

Because dysmenorrhea seems related to recurrent microbleeding within the endometriotic implants and the associated inflammation (1), OC pills can be effective by inducing atrophy of the endometrial tissue (9), reducing cell proliferation, and increasing apoptosis in the endometrium (18). Furthermore, OCs, inducing ovarian inactivation, decrease prostaglandins production due to endogenous estrogens (E) and reduce the inflammatory status (5, 19).

It must be stressed that the capacity of continuous OC pills of providing early relief from dysmenorrhea could be mainly due to menses’ inhibition, and not to a real interference with pain mechanisms. The continuous administration of OC pills, however, may determine a homogenous hormonal milieu increasing the efficiency of therapy (20), whereas cyclic use of low-dose OC pills might not succeed in inducing a complete ovarian suppression, allowing the increase of endogenous E levels during the 7-day hormone-free interval (16).

Our data on the benefits of continuous treatment are in agreement with those of Sesti et al. (21) who observed, in a recent randomized controlled trial, a reduction in the VAS score for recurrent dysmenorrhea at 12 months of follow-up in women treated with postoperative continuous OC pills for 6 months. Similarly, Vercellini et al. (15) showed that 6-month continuous administration of OCs is effective in reducing recurrent dysmenorrhea after conservative surgery for endometriosis. In addition, the same investigators (20) observed, in a prospective self-controlled trial, that continuous administration can be successfully used in women undergoing conservative surgery for endometriosis and experiencing recurrent dysmenorrhea despite cyclic use of OC pills.
Continuous administration of OC pills seems, therefore, to be highly effective in reducing recurrent dysmenorrheal related to endometriosis. The main mechanism could be the induction of amenorrhea, a condition that could be unacceptable for some patients, mainly young women that need to prolong therapy for years. In our study, also cyclic administration of OCs has been demonstrated efficient in reducing dysmenorrhea, providing significant pain relief after at least 1 year of administration. Long-term therapy with cyclic OC pills could be an option for those women who do not tolerate the absence of menstruation.

In a randomized controlled trial, Muzii et al. (12) showed that a 6-month administration of cyclic OCs after surgery does not significantly influence endometriosis-related pain recurrence at 24 and 36 months of follow-up, although a positive effect of OC pills was reported at 12 months after surgery. The short duration of the treatment, however, could explain the results of this study, as it could be responsible for the lack of long-term effects. Furthermore, the study by Muzii et al. considered pelvic pain in general, whereas dysmenorrhea was not specifically evaluated.

From our data, no significant differences in terms of frequency and severity of dyspareunia and chronic pelvic pain were found among untreated patients, cyclic users, and continuous users. In our study, however, untreated patients showed a significant worsening in dyspareunia and chronic pelvic pain intensity from 6–24 months of the study period, compared with patients on continuous OC pill therapy, suggesting that OCs could play a role to restrain pain aggravation.

The more evident benefits achieved with OCs on dysmenorrheal in comparison with dyspareunia and chronic pelvic pain can be explained because dysmenorrhea can be related to endometrial bleeding, which can be decreased or suppressed by OC pills, whereas other types of pain are possibly due to different physiopathologic mechanisms. Furthermore, regarding dyspareunia, pain perception can be influenced by psychological factors depending on the woman’s personality, marital, and psychosexual issues. This consideration is supported by the study of Sesti et al. (21), which showed that placebo could be more effective than postoperative hormonal therapy in reducing dyspareunia.

A limitation of our study is that it was not double-blinded. Placebo was not administered and the patients in the control group were aware that they were not taking any hormonal therapy. Psychological factors could, therefore, have influenced pain perception in untreated women. Another potential limit of this trial is that we did not perform an intention-to-treat analysis. However, patients who dropped out after the randomization process were considered for a second phase of investigation, evaluating the effects of discontinuous OC pill therapy on endometriosis recurrence.

On the other hand, evaluation of pain intensity was performed by the patients themselves, using a validated, reliable, simple scale: the 10-point VAS scale (11). This should have avoided undue influences by the investigators. It may be supposed that preoperative social and clinical variations
of patients had no significant influence on the study results, as the exclusion of women who did not accept to be randomly assigned to one treatment group should have avoided selection bias.

In conclusion, long-term postoperative OC therapy seems to be reliable in reducing the frequency and severity of recurrent dysmenorrhea related to ovarian endometrioma. Because continuous and cyclic administrations induce appreciable improvement in dysmenorrhea relief, the choice of the regimen can be modulated according to the woman’s preference.
REFERENCES


