

Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial

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Objective: To evaluate long-term cyclic and continuous administration of oral contraceptive pills (OCP) in preventing ovarian endometrioma recurrence after laparoscopic cystectomy.

Design: Prospective, randomized, controlled trial.

Setting: Tertiary care University Hospital.

Patient(s): Two hundred thirty-nine women who underwent laparoscopic excision of ovarian endometriomas.

Intervention(s): Patients were divided randomly into three groups: nonusers receiving no therapy and cyclic and continuous users receiving low-dose, monophasic OCP for 24 months in cyclic or continuous administration, respectively.

Main Outcome Measure(s): Endometrioma recurrence, size of recurrent endometrioma, and growth rate during at least 2 years follow-up evaluated by transvaginal ultrasonography.

Result(s): The crude recurrence rate within 24 months was significantly lower in cyclic (14.7%) and continuous users (8.2%) compared with nonusers (29%). The recurrence-free survival was significantly lower in nonusers compared with cyclic and continuous users. The mean recurrent endometrioma diameter at first observation was significantly lower in cyclic (2.17 ± 0.45 cm) and continuous users (1.71 ± 0.19 cm) compared with nonusers (2.73 ± 0.56 cm). The mean diameter increase every 6 months of follow-up was significantly reduced in cyclic users (0.31 ± 0.18 cm) and continuous users (0.25 ± 0.09 cm) versus nonusers (0.48 ± 0.3 cm). No significant differences between cyclic users and continuous users in terms of endometrioma recurrence were demonstrated.

Conclusion(s): Long-term cyclic and continuous postoperative use of OCP can effectively reduce and delay endometrioma recurrence. (Fertil Steril® 2010;93:52–6. ©2010 by American Society for Reproductive Medicine.)

Key Words: Endometrioma recurrence, cyclic, continuous oral contraceptives

Ovarian endometrioma is one of the most common endometriotic lesions, affecting approximately 55% of patients with endometriosis (1). There is general agreement that conservative surgery by laparoscopy is the treatment of choice for ovarian endometriotic cysts (2, 3), because medical treatment alone is inadequate (4). However, a frustrating aspect of laparoscopic excision is cyst recurrence after surgery, with a cumulative rate of endometrioma recurrence after 2 to 5 years of follow-up of 12% to 30% (5–7). Therefore, many authors recently have studied adjuvant therapeutic modalities that may reduce the rate of postoperative recurrence.

Hormones used in the medical therapy of endometriosis are not curative because it has been demonstrated that they are not cytoreductive (8). Therefore treatments need to be administered for years or until women desire a pregnancy. Among

hormones considered in postoperative adjuvant therapy, oral contraceptive pills (OCPs) can provide a better option in terms of safety, tolerability, and cost. However, data from clinical studies on this topic are still few and controversial (9).

The only published prospective randomized trial demonstrated that the postoperative cyclic use of OCPs does not significantly influence long-term recurrence rates, for either symptoms or endometrioma recurrence (10). However, in this trial, OCPs were administered for only 6 months after surgery. A recent retrospective study (6) analyzed risk factors that influence the recurrence of endometriomas after laparoscopic excision. The authors demonstrated that postoperative medical treatment did not significantly affect recurrence. Mean time of OCP use in this study was 9.5 months. In a recent cohort study about the postoperative risk of endometrioma recurrence, 94% of patients given OCPs for the entire follow-up period of 36 months were free from endometrioma recurrence in comparison with 51% in the untreated group (11).

The influence of OCPs in endometrioma recurrence has been investigated mainly by studying the effects of their cyclic administration (6, 10, 11). Continuous administration potentially can avoid reseeding of refluxed endometrial

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tissues because of monthly uterine bleeding (12). In this prospective randomized controlled trial we, therefore, sought to evaluate the efficacy of long-term cyclic and continuous administration of monophasic, combined low-dose OCPs on preventing ovarian endometrioma recurrence after laparoscopic cystectomy.

MATERIALS AND METHODS

A total of 239 patients scheduled for laparoscopic excision of ovarian endometriomas in the Minimally Invasive Gynaecological Surgery Unit of S. Orsola University Hospital, a tertiary referral center for treatment of endometriosis, were enrolled in the present study. All patients had ultrasonographic diagnosis of ovarian endometrioma of which the diameter was at least 4 cm. 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. None of the patients previously had undergone any surgical or recent medical treatment for endometriosis. None of them had been receiving OCs for at least 6 months before surgery. Patients having contraindications to OC therapy, unwillingness to tolerate the absence of menstruation, or lack of the desire to postpone pregnancy for at least 2 years after surgery were excluded from the study.

All patients included in the present study underwent at least two transvaginal ultrasonographic examinations: at 6 to 8 weeks before surgery and on the day before surgery. Laparoscopic excision of ovarian endometriomas was performed in all the patients by the classic stripping technique, as previously reported (2, 10, 13). No intraoperative complications occurred during surgery, and no abdominal conversion was needed.

Endometriosis was intraoperatively staged according to the revised American Fertility Society classification (14). Histopathologic examination reports confirmed the endometriotic nature of the cysts in all cases.

After surgery, patients were randomly divided into three groups differing in the medical therapy protocols to be followed: the nonusers group received no medical treatment, and the other two groups (cyclic users and continuous users) both 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 users group received cyclic therapy (daily for 21 days followed by a 7-day interval), and the continuous users group received continuous therapy (no pill-free interval). Treatment allocation was performed in accordance with a computer-generated randomization sequence with use of numbered, opaque, sealed envelopes.

Patients had been counseled before surgery about the three different treatment options offered. It was explained that

OCP therapy theoretically could prevent or delay endometrioma recurrence, although its efficacy was not already clearly demonstrated. Women refusing the randomization of treatment were excluded from the study from the beginning. A total of 239 subjects accepted to be randomly assigned to one of the three treatment group and were scheduled for the study. The study was performed with intention to treat.

At the end of the study, patients were followed up for at least 24 months. One month after surgery, clinical examination and transvaginal ultrasonographic scan were performed in all the patients to exclude subjects with persistent ovarian endometriomas. No endometriotic cysts were found in any patients, clearly confirming the complete excision of endometriomas.

Thereafter, all patients underwent clinical and transvaginal ultrasonographic examination every 6 months to assess the possible recurrence of ovarian endometrioma. Recurrence was defined as the presence of a cyst with a minimum diameter of 1.5 cm with a typical aspect detected by transvaginal ultrasonography (15). All the scans were performed by experienced operators, blinded to the study allocation. Main variables assessed were recurrence rate, recurrence-free survival, and size and rate of growth of recurrent cysts in the three study groups. Time of recurrence was expressed in months after surgery. Two months after the detection of a recurrent cyst, additional ultrasonographic examination was carried out to confirm the diagnosis.

Statistical Analysis

All continuous variables are expressed in terms of mean \pm SD of the mean; categorical variables are expressed as proportions or percentages. One-way analysis of variance (ANOVA) was performed to test hypotheses about the means of different treatments. When results of the Levene test for homogeneity of variances were significant ($P < .05$), the Kruskal-Wallis test was used to check ANOVA results; Scheffé test or Mann-Whitney test with Bonferroni correction was used as post hoc pairwise analysis of, respectively, one-way ANOVA or Kruskal-Wallis test. Pearson's χ^2 test, calculated by exact method, was performed to investigate the relationships between grouping variables.

Ordered differences among treatments were analyzed by Jonckheere-Terpstra test. Kendall tau correlation analysis was used to test relationship between ordinal variables. For all tests $P < .05$ was considered significant. Kaplan-Meier survival analysis with Breslow statistic was performed to study the local recurrence survival according to treatments. Statistical analysis was carried out by means of the Statistical Package for the Social Sciences software (version 14.1; SPSS Inc., Chicago, IL).

RESULTS

Of the 239 patients considered for the study, the randomization process yielded 79 patients in the nonusers group, 81

patients in the cyclic users group, and 79 patients in the continuous users group. Ten nonusers (12.6 %) did not complete the study because four of them achieved a spontaneous pregnancy before 24 months of the control period and six started to receive OCP therapy because of dysmenorrhea. Six patients (7.4 %) among the cyclic users did not complete the treatment period: two of them for causes unrelated to endometriosis recurrence and four for side effects attributable to OC therapy. Six women (7.6%) among the continuous users did not complete the treatment period: two of them for causes unrelated to endometriosis recurrence and four for side effects attributable to OC therapy. Hence 217 patients completed the study for the whole follow-up period and were thus analyzed: 69 patients in the nonusers group, 75 patients in the cyclic users group, and 73 patients in the continuous users group.

The three study groups were homogeneous with regard to mean age, mean body mass index, endometriosis stage, mean endometrioma diameter, and the proportion of patients with bilateral cysts for a total of 246 endometriomas excised. The length of follow-up periods was comparable in the different groups. At the end of the study every patient was controlled for at least 24 months after surgery (Table 1).

At follow-up, 37 endometrioma recurrences were detected in the three groups: the crude recurrence rate within 24 months was 29% (20/69) in nonusers, 14.7% (11/75) in cyclic users, and 8.2% (6/73) in continuous users (Pearson's χ^2 : $P=.003$).

Kaplan-Meyer survival analysis demonstrated a significant difference in recurrence-free survival between nonusers versus cyclic and continuous users, respectively (cyclic users: Breslow test $P=.012$; continuous users: Breslow test $P=.006$) for the whole follow-up. However, no significant differences were detected between cyclic and continuous users ($P=.21$) for the whole follow-up (Fig. 1).

The mean recurrent endometrioma diameter when it was first observed during follow-up was 2.73 ± 0.56 cm in nonusers, 2.17 ± 0.45 cm in cyclic users, and 1.71 ± 0.19 cm in continuous users. The Kruskal-Wallis test demonstrated a significant difference among the three groups of patients ($P<.0001$). The post hoc pairwise analysis showed that the mean diameter of endometriomas at the first observation was significantly smaller in cyclic and continuous users compared with nonusers (cyclic users: $P=.02$ and continuous users: $P=.003$). The Jonckheere-Terpstra test demonstrated the existence of a significant ($P<.0005$) positive trend among the three groups (Fig. 2).

The mean diameter increase every 6 months of follow-up was 0.48 ± 0.3 cm in nonusers, 0.31 ± 0.18 cm in cyclic users, and 0.25 ± 0.09 cm in continuous users. The Kruskal-Wallis test demonstrated a significant difference of the increase of cyst dimension among the three groups of patients ($P=.013$). The post hoc pairwise analysis showed a significant reduction in endometrioma growth in cyclic and continuous users compared with nonusers (cyclic users: $P=.05$, continuous users: $P=.048$). The Jonckheere-Terpstra test demonstrated the existence of a significant ($P=.003$) positive trend among the three groups (Fig. 3).

DISCUSSION

In our study we demonstrated the usefulness of long-term low-dose monophasic OCP, in both cyclic and continuous administration, in reduction and delay of endometrioma recurrence after laparoscopic cystectomy. The efficacy of postoperative OC treatment is supported by the hypothesis that ovarian inactivation and moderately low estrogen concentration may down-regulate cell proliferation and enhance programmed cell death (apoptosis) of the endometrium (16). Furthermore, some authors hypothesized that ovarian endometriomas could develop from ovarian follicles (17).

TABLE 1

Clinical features of the 217 patients who completed the study.

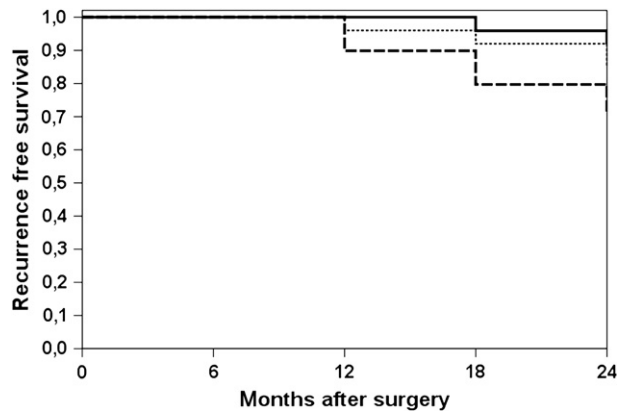
	Group A (nonusers)	Group B (cyclic users)	Group C (continuous users)
No. of patients	69	75	73
Age \pm SD (y)	30.1 ± 2.7	29.7 ± 2.8	28.6 ± 2.4
BMI \pm SD (kg/m ²)	20.7 ± 2.1	20.3 ± 2.5	21.2 ± 2.9
American Fertility Society stage			
III	30	37	32
IV	39	38	41
Mean diameter \pm SD (cm)	4.8 ± 1.2	4.9 ± 0.8	5.1 ± 1.1
Bilateral cysts	10/69	8/75	11/73
Associated implants	40	38	41
Associated adhesions	69/69	75/75	73/73
Follow-up (mo)	24	24	24

Note: P =not significant for all comparisons.

Seracchioli. OC preventing endometrioma recurrence. Fertil Steril 2010.

FIGURE 1

Recurrence-free survival in nonusers (— —), cyclic users (· · · ·), and continuous users (—).



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Therefore inhibiting ovulation could reduce the risk of endometriotic cyst development.

To the best of our knowledge, our study is the only randomized controlled trial that evaluates the effectiveness of long-term postoperative OCP treatment in preventing endometrioma recurrence. In another randomized controlled trial, Muzii et al. (10) analyzed the effect of postoperative OCP on endometrioma recurrence. However, in this trial, untreated patients were compared with women submitted to a 6-month course of cyclic OCs (10).

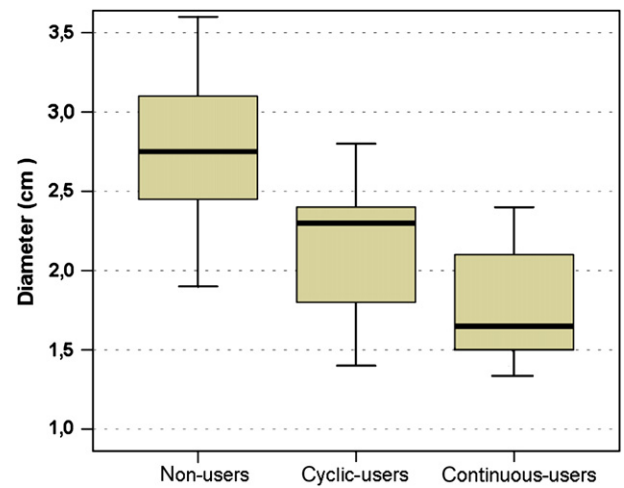
In our study, the exclusion of women who did not accept to be randomly assigned to one treatment group helped to avoid selection bias. Therefore, it may be supposed that preoperative social and clinical variations of patients had no significant influence on the study results. From our data, patients receiving long-term cyclic or continuous therapy showed a statistically significant endometrioma recurrence rate and a longer period free from recurrence as compared with patients who did not receive treatment.

Muzii et al. (10), in their study, affirmed that a 6-month administration of cyclic OCs after surgery does not significantly influence disease recurrence at 24 and 36 months of follow-up, although a positive effect of OCP, in terms of recurrence prevention, was reported at 12 months after surgery. The short duration of the treatment should be taken into account when considering the results of this study, because it could be responsible for the lack of long-term effects (10).

Furthermore Koga et al. (6) found in their retrospective study that a mean postoperative treatment of 9.5 months did not significantly influence recurrence, but the same authors suggested that a longer period of treatment might have an effect to prevent endometrioma recurrence. The length of the treatment, therefore, seems to be an important factor in the long-term efficacy of therapy.

FIGURE 2

Mean recurrent endometrioma diameter at first observation in the three groups of patients.

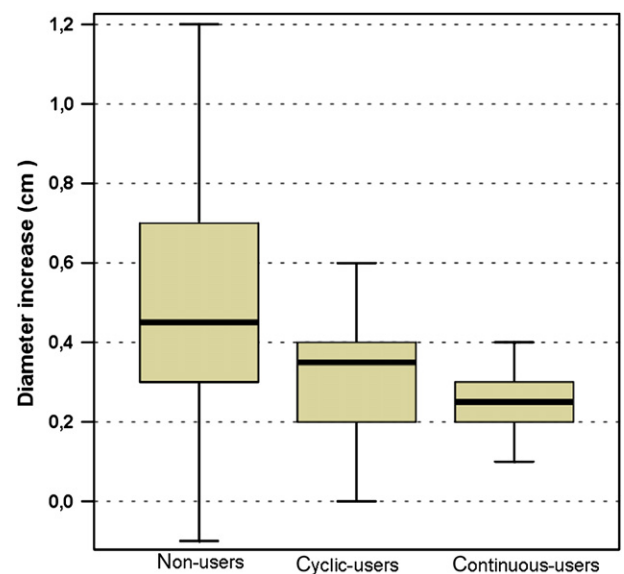


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In a recent cohort study of Vercellini et al. (11), long-term exposure to OCs after conservative surgery for ovarian endometriosis was associated with a major reduction in the risk of endometrioma recurrence, with a gradient effect observed with regard to duration of treatment. Our results are in agreement with these findings, because our patients, being treated

FIGURE 3

Mean diameter increase every 6 months of follow-up in the three groups of patients.



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for the whole 24-month follow-up, had successful outcomes, showing the efficacy of long-term therapy.

Our study showed that the mean diameter of recurrent cysts at first observation was significantly smaller in cyclic and continuous users, proving that OCP can even influence disease expression and reduce its severity. Furthermore, growth rate of endometriomas in 6 months was significantly reduced in the same patients, suggesting that OCP therapy could lessen the activity of the disease and restrain its progression. These findings can be supported by those of Vercellini et al. (18) who observed that there was no increase in diameter of recurrent endometriomas or appearance of new cysts during a 24-month follow-up in women given treatment with postoperative OCP.

One of the limitations of our study is that we focused on disease recurrence and severity in anatomic terms, without considering its correlation with symptoms. Further studies considering symptom recurrence with the postoperative use of OCP seem therefore necessary in clarifying their value.

Another potential limit is that in our study, detection of endometrioma recurrence was based on ultrasonographic examination. However, it has been demonstrated that transvaginal ultrasonography is a reliable instrument to make or exclude the diagnosis of ovarian endometriomas (19). Furthermore, all the scans were performed in a blind fashion by experienced sonographers in endometriosis diagnosis.

In our study, no statistically significant differences were found between cyclic and continuous users in terms of the number, size, and growth of recurrent endometriomas. However, there was a positive trend in patients receiving continuous therapy regarding size and growth of recurrent endometriomas. These findings can be supported by the theory that continuous use of OCs may determine a homogeneous hormonal milieu increasing the efficiency of therapy (18). Moreover, creation of a steady hormonal environment can suppress temporarily the ectopic implants and reduce the inflammatory status (9). Because of the limited number of cases of recurring endometrioma in cyclic and continuous users found in our study, further studies involving a considerably higher number of patients are necessary to evaluate whether continuous administration is significantly more efficient with respect to cyclic administration. In conclusion, the results of our study clearly demonstrate that long-term combined OCs, both cyclic and continuous administration, can effectively reduce and delay ovarian endometrioma recurrence.

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