Chapter 4

Combined Oral Contraceptive Therapy in Women with Posterior Deep Infiltrating Endometriosis

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ABSTRACT

**Study Objective:** To estimate the effect of combined oral contraceptives (COCs) in women with deep infiltrating endometriosis (DIE).

**Design:** Retrospective study (Canadian Task Force classification II-2).

**Setting:** Tertiary care university hospital.

**Patients:** One hundred six women with uncomplicated posterior deep infiltrating endometriosis scheduled to undergo laparoscopic surgery between November 2004 and November 2009.

**Interventions:** During the waiting-list time, between surgical scheduling and laparoscopic intervention (preoperative period), 75 patients received cyclic COCs (users), and 31 received no hormone therapy (COC nonusers).

Measurements and Main Results: Patients had undergone 2 clinical examinations, at surgical scheduling and immediately before surgery. Presence and intensity of dysmenorrhea, dyspareunia, chronic pelvic pain, and dyschezia were evaluated using a 10-point visual analog scale (VAS) (primary outcome). In both examinations, patients underwent transvaginal ultrasonography to evaluate localization and mean diameter of endometriotic nodules. Quality of life was evaluated using the Short Form-36 (SF-36) score. Mean (SD) nodule diameter at the beginning and end of the preoperative period in COC users was, respectively, 24.81 (15.13) mm and 26.66 (15.5) mm (p = .09), and in the nonuser group was, respectively, 23.09 (11.11) mm and 30.89 (19.1) mm (p = .007). In COC users, VAS scores for dysmenorrhea, dyspareunia, chronic pelvic pain, and dyschezia did not vary significantly during the preoperative period (p = .90, p = .55, p = .15, and p = .17, respectively). In nonusers, VAS scores for dysmenorrhea and dyspareunia were significantly higher at the second examination than at the first examination (p=.002 and p=.005, respectively), whereas scores for chronic pelvic pain and dyschezia did not vary during the preoperative period (p = .88 and p = .16, respectively). The Short Form-36 total score did not vary significantly during the preoperative period in either the COC user group (p = .82) or the nonusers group (p = .76).

**Conclusions:** Combined oral contraceptive therapy can have a role in restraining the progression of dysmenorrhea and dyspareunia and the growth of deep endometriotic nodules.
INTRODUCTION

Deep infiltrating endometriosis (DIE) is usually characterized by severe pain. Endometriosis-associated pain may occur during menstruation (dysmenorrhea) or sexual intercourse (dyspareunia) or not demonstrate any cyclic pattern (chronic pelvic pain) [1]. If deep endometriosis involves the rectum, dyschezia may occur [2, 3]. Women with symptomatic endometriosis often report a significant reduction in their quality of life. Furthermore, because DIE affects young women primarily, it can possibly impair social and professional functioning [4]. Although it is generally accepted that DIE is a chronic and aggressive disease, its natural history is not completely understood. Moreover, in the current literature, there is no agreement as to whether endometriosis is a progressive disease [5, 6].

The treatment of choice for symptomatic DIE is laparoscopic surgery because endometriotic lesions can be completely excised and the pelvic anatomy can be restored [7, 8]. Furthermore, laparoscopic excisional surgery can significantly reduce pain and improve quality of life in 67% to 80% of patients with endometriosis [9].

In the last years, it has been observed that DIE responds to hormone treatment because estrogen and progesterone receptors are normally expressed in deeply infiltrating lesions [10]. Among hormones, combined oral contraceptives (COCs) are considered a good pharmacologic choice because they are safe, well tolerated, and relatively inexpensive and can be administered for long periods [11]. All of these data prompted us to retrospectively evaluate whether oral contraceptive therapy administered preoperatively can interfere in potential progression of DIE insofar as worsening of symptoms and growth of nodules.

PATIENTS AND METHODS

Patients with posterior DIE who were scheduled to undergo laparoscopic surgery between November 2004 and November 2009 at our tertiary referral center for treatment of endometriosis were considered for inclusion in the present retrospective study. Patients were evaluated between the surgical scheduling and the laparoscopic intervention (preoperative period) because in tertiary referral centers, women with uncomplicated DIE can be wait-listed for surgery for months.

Women aged 20 to 40 years with an ultrasonographic diagnosis of uncomplicated DIE were included in the study. All patients reported symptoms related to posterior DIE including dysmenorrhea, dyspareunia, chronic pelvic pain, and dyschezia. Patients with complicated DIE including bowel stenosis, obstructive uropathy, or severe symptoms required urgent surgical intervention and were, therefore, not included in the study. The presence of gastrointestinal or urologic disease or a diagnosis of current pelvic inflammatory disease that might have caused painful pelvic symptoms not related to endometriosis were considered exclusion criteria. None of the patients included in the
study had previously undergone any surgical treatment of endometriosis. None had received hormone therapy for at least 6 months before scheduling the surgical intervention.

After approval by the local ethics committee, data were collected from computerized medical records. All patients were routinely asked to give informed consent to anonymously use their clinical data for medical research. For every patient, data collected included age, weight, height, body mass index, and use of oral contraceptives to treat endometriosis during the preoperative period. Women included in the study were retrospectively divided into 2 groups: nonusers, who had not received any hormone treatment, and users, who had received COCs during the entire preoperative period. At our center, all patients with symptomatic noncomplicated DIE who are scheduled to undergo nonurgent surgery are offered COC therapy. Nonusers are patients who do not agree or who have contraindications to hormone therapy. All users received cyclic administration of COC therapy: active pills containing 3 mg drospirenone and 20 mcg ethinylestradiol for 21 days and no hormone therapy for 7 days.

At our center, all patients with DIE and scheduled for surgery routinely undergo at least 2 clinical examinations, the first at surgical scheduling and the second immediately before the intervention. In both examinations, patients included in the study underwent transvaginal ultrasonography performed by ultrasonographers (G.V., G.M.) with extensive experience in the diagnosis of endometriosis. Presence, localization, and diameter of deep endometriotic nodules were reported in computerized clinical records. Mean nodule diameter was obtained by measuring the diameter in 3 dimensions and calculating the average. Furthermore, patients had been asked to grade the presence and severity of pain using a 10-point visual analog scale (VAS), in which a score of 1 to 3 was considered mild pain; 4 to 7, moderate pain; and 8 to 10, severe pain [12]. All of the women included in the study had a VAS score of 4 or greater for at least 1 type of pain (dysmenorrhea, dyspareunia, chronic pelvic pain, or dyschezia).

At both examinations, the women completed the Short Form-36 questionnaire (SF-36, Italian version, release 1.6), a validated multipurpose health survey for evaluation of quality of life [13]. Total SF-36 score was considered for evaluation of changes in quality of life in patients with DIE in both study groups. The primary variables assessed were changes in VAS scores, diameter of endometriotic nodules, and SF-36 total score during the preoperative period in the COC user and nonuser groups.

Statistical Analysis

In the literature, treatment success at the 3-month follow up after medical therapy was defined as 25% reduction in the VAS score [14]. With change in VAS score as a primary outcome measure, we retrospectively assumed that a 25% reduction in VAS pain scores between the first and second examinations in COC users was clinically significant. The study was designed to have 80% power
to detect a difference of 25% in VAS scores with 2-sided α levels of 0.05. A sample of 24 patients was calculated for each group (total of 48 participants) to achieve this power. Because this was a retrospective study, all eligible patients who fulfilled the inclusion criteria were enrolled.

All continuous data are given as mean (SD). At univariable analysis, 1-way analysis of variance with the Scheffé post hoc pairwise test was performed to assess differences in the means of different groups. When the Levene test for homogeneity of variances was significant (p < .05), the Mann-Whitney test (2 independent groups) or the Kruskal-Wallis test (≥ 3 independent groups) was used. Differences in mean values at various follow-up times were assessed using the paired t-test. The χ² test, calculated using the exact method for small samples (nondicotomic variables) or the Fisher exact test (dicotomic variables) was performed to investigate the relationships between grouping variables.

Statistical analysis was performed using commercially available software (SPSS version 14.1; SPSS, Inc., Chicago, IL). For all tests, p < .05 was considered significant.

RESULTS

Of 241 patients considered for the study, 135 were excluded: 102 because they received hormone therapy before surgical scheduling, and 33 because of previous surgery to treat endometriosis. Thus, 106 patients were included in the study. Of these, 75 patients were included in the COC user group, and 31 in the nonuser group. The 2 study groups were homogeneous insofar as mean age body mass index (Table 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study group</th>
<th></th>
<th></th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COC Users</td>
<td>COC nonusers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 75)</td>
<td>(n = 31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>34.35 (5.09)</td>
<td>33.41 (5.38)</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>21.98 (3.35)</td>
<td>21.39 (3.44)</td>
<td>.56</td>
<td></td>
</tr>
</tbody>
</table>

Tabel 1: Clinical features in 106 Study patients

COC = combined oral contraceptives

Data are given as mean (SD)

The mean (SD) duration of the preoperative period, from surgical scheduling to laparoscopic intervention, was 5.8 (3.7) months (median, 5.5 months; 25th–75th percentile, 3.06–7.41). None of the patients included in the study declined the surgical intervention. Histopathologic reports confirmed DIE in all cases.
## Pain

Mean VAS scores for the 4 types of pain considered at the first and second clinical examinations are given in Table 2.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>VAS score</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First examination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>Second examination</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>COC Users</td>
<td>6.81 (3.38)</td>
</tr>
<tr>
<td></td>
<td>Nonusers</td>
<td>6.09 (3.35)</td>
</tr>
<tr>
<td>Chronic pelvic pain</td>
<td>COC Users</td>
<td>2.24 (3.41)</td>
</tr>
<tr>
<td></td>
<td>Nonusers</td>
<td>3.72 (3.31)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>COC Users</td>
<td>4.04 (3.53)</td>
</tr>
<tr>
<td></td>
<td>Nonusers</td>
<td>4.47 (3.14)</td>
</tr>
<tr>
<td>Dyschezia</td>
<td>COC Users</td>
<td>4.57 (3.87)</td>
</tr>
<tr>
<td></td>
<td>Nonusers</td>
<td>2.44 (3.81)</td>
</tr>
</tbody>
</table>

Boldface indicates significant values

CI = confidence interval; COC = combined oral contraceptives; VAS = Visual Analog Scale

**Tabel 2**: VAS scores for pain at first and second examination

In COC users, mean VAS scores for dysmenorrhea, dyspareunia, chronic pelvic pain, and dyschezia did not vary significantly from the first to the second examination. In nonusers, mean VAS scores for dysmenorrhea and dyspareunia were higher at the second examination (p = .002 and p = .005, respectively), and VAS scores of dyschezia and chronic pelvic pain did not vary significantly during the preoperative period (Table 2). Comparison of mean VAS scores for the 2 groups demonstrated that during the preoperative period, dysmenorrhea and dyspareunia scores were higher in nonusers (p = .02 and p = .005, respectively), with worsening of pain intensity (Table 3).
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>VAS score</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>------------------------------</td>
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<td>---------</td>
</tr>
<tr>
<td><strong>Dysmenorrhea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COC Users</td>
<td>0.06 (4,021)</td>
<td>0.79- 0.9</td>
</tr>
<tr>
<td>Nonusers</td>
<td>-1.91 (3,145)</td>
<td>-3.04 - 0.77</td>
</tr>
<tr>
<td><strong>Chronic pelvic pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COC Users</td>
<td>-0.64 (4,195)</td>
<td>-1.52 - 0.24</td>
</tr>
<tr>
<td>Nonusers</td>
<td>0.09 (3,541)</td>
<td>-1.18 - 1.37</td>
</tr>
<tr>
<td><strong>Dyspareunia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COC Users</td>
<td>-0.20 (3,167)</td>
<td>-0.87 - 0.46</td>
</tr>
<tr>
<td>Nonusers</td>
<td>-1.69 (3,136)</td>
<td>-2.82 - 0.56</td>
</tr>
<tr>
<td><strong>Dyschezia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COC Users</td>
<td>-0.60 (4,075)</td>
<td>-1.45 - 0.26</td>
</tr>
<tr>
<td>Nonusers</td>
<td>-1.13 (4,449)</td>
<td>-2.73 - 0.48</td>
</tr>
</tbody>
</table>

**Table 3:** Changes in VAS score during preoperative period

Boldface indicates significant values

CI = confidence interval; COC = combined oral contraceptives; VAS = Visual Analog Scale

*Defined as the mean difference between first and second examination VAS score

**Nodule Diameter**

In COC users, mean (SD) nodule diameter at the first and second examinations was, respectively, 24.81 (15.13) mm and 26.66 (15.5) mm (p = .09), and in nonusers was, respectively, 23.09 (11.11) mm and 30.89 (19.1) mm (p = .007) (Fig. 1). In the preoperative period, mean nodule diameter increased by 1.8 (10.3) mm in COC users and 7.8 (15.1) mm in nonusers (p = .02).

**Figure 1:** Mean nodule diameter at first and second examinations in combined oral contraceptive (COC) users and nonusers.
Quality of Life
In COC users, the mean (SD) SF-36 total score at the first and second examinations was, respectively, 48 (15) and 50 (21) (p = .82), and in nonusers was, respectively, 52 (17) and 50 (22) (p = .76). Using the Mann-Whitney test, we detected that the median variation in total SF-36 scores between the first and second examinations did not vary significantly between the 2 groups.

DISCUSSION
Data from the present study demonstrate that COC therapy can have a role in restraining the progression of dysmenorrheal and dyspareunia and in preventing endometriotic nodule growth in women with uncomplicated posterior DIE. Analysis of the data demonstrated that patients who did not receive COC therapy exhibited a significant increase in endometriotic nodule dimensions and significant worsening of dysmenorrhea and dyspareunia during the time considered. It seems, therefore, that from the clinical point of view, untreated DIE tends to progress over time. These results seem to be in contrast with those of Fedele et al [5], who affirmed that untreated rectovaginal endometriosis progresses in a low percentage of cases. It must be stressed, however, that none of the women included in that study had symptoms at first diagnosis of endometriosis. This lack of endometriosis-related symptoms could reflect a low inflammatory status and the presence of an inactive form of endometriosis. The literature, however, reports few data about the natural history of endometriosis.

In the present study, significant variations in nodule dimensions and symptom intensity were not observed in COC users, which demonstrates a potential restraining effect of oral contraceptive therapy on the hypothesized progression of DIE. Several mechanisms of action could explain the effect of COC on DIE. Oral contraceptive agents, through ovarian inactivation, decrease prostaglandin production due to endogenous estrogens and reduce the inflammatory status [11, 15]. In addition, oral contraceptives can induce atrophy of the endometriotic implants [16], downregulate cell proliferation, and increase apoptosis in endometrial tissue [17]. Therefore, COC therapy might prevent implant growth and reduce endometriosis-related pain because pain seems to be correlated with cyclic microbleeding within the endometriotic lesions [1].

Other authors, however, have affirmed that preoperative hormone therapy could be a risk factor for endometriosis recurrence because it may cause changes in the structure of endometriotic lesions, rendering their detection during surgery difficult [18–20]. However, it is generally accepted that in the treatment of DIE, surgical outcomes are highly operator-dependent and that optimal results can be assured in a tertiary care and referral center [21]. To assess whether, compared with nonusers, patients who receive preoperative COC therapy demonstrate a higher rate of recurrence of endometriosis after surgery is, therefore, the objective of a current prospective study at our center.
The current literature reports few data about the effect of oral contraceptive therapy on DIE. A review by Vercellini et al [10] reported that in women with rectovaginal endometriosis, medical treatment is effective for pain relief, lesion reduction, and improvement in quality of life. However, only 1 of the published reports included in that review evaluated oral contraceptive therapy [22]; pain relief and lesion reduction were reported after 12-months of continuous COC therapy in women with recurrent rectovaginal endometriosis. In addition, continuous postoperative hormone treatment might prevent pain recurrence after surgical removal of deep infiltrating nodules [23].

In the present study, intensity of symptoms, nodule dimensions, and health-related quality of life remained stable in COC users throughout the preoperative period (mean [SD] duration, 5.8 [3.7] months), and none of the patients declined the surgical intervention. That longer duration of treatment could possibly provide better results cannot be ruled out. It must be stressed, however, that surgery is still the definitive treatment option because hormone therapy is not cytoreductive [24] and, therefore, is not curative [11]. Recently, some experienced authors adopted the concept that in the treatment of DIE, it is most likely that combined medical and surgical treatments should be used [25, 26].

The present study has 2 possible limitations. First, it was a retrospective study in patients scheduled for surgical interventions and included a smaller number of patients in the nonuser group. A larger randomized trial will be necessary to adequately power such a study. Second, although the results of this short-term study are encouraging, longer follow-up is needed to demonstrate hypothetical effects in suppression of nodule growth and pain associated with endometriosis.

In conclusion, COCs can have a role in restraining hypothesized clinical progression of DIE and preventing symptom worsening and nodule growth. However, larger prospective trials are needed to validate this effect.
REFERENCES


