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REVIEW

Continuous versus cyclic oral contraceptives for the treatment of endometriosis: a systematic review

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Abstract
Purpose Recurrence of endometriosis after conservative surgery has been observed in 40–50 % of patients within the first 5 years. A variety of regimens such as combined oral contraceptives, GnRH agonists, danazol, and progestins have been used postoperatively to reduce recurrence rates. Oral contraceptives (oCP) have been used either in a cyclic or in a continuous (no pill-free interval) fashion. The purpose of this article was to summarize the existing evidence on the efficacy and patient compliance for the use of oCP in a continuous versus cyclic fashion following conservative surgery for endometriosis.
Methods A systematic search of Medline identified four eligible studies. Studies were considered eligible, if they have evaluated oCP therapy, either in a cyclic or continuous regimen, after conservative surgery for endometriosis. Specifically, studies (1) reporting on women with endometriosis who were treated postoperatively with both continuous oCP and cyclic oCP, (2) written in English, (3) with minimum 6 months duration of medical treatment, and (4) with minimum 12 months duration of follow-up were considered eligible for our systematic review. Outcome measures of these eligible studies were tabulated and then analyzed cumulatively. A purely descriptive approach was adopted concerning all variables.
Results Postoperative use of continuous oCP was associated with a reduction in the recurrence rate of dysmenorrhea, delay in the presentation of dysmenorrhea, reduction in nonspecific pelvic pain, and reduction in the recurrence rate for endometrioma.
Conclusions Use of oCP in a continuous fashion following conservative surgery for endometriosis is more beneficial to cyclic use.

Keywords Endometriosis · Continuous · Cyclic · Oral contraceptives · Pelvic pain · Dysmenorrhea

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Introduction

Endometriosis, defined by the presence of endometrial-like tissue outside the uterine cavity, represents a major gynecological problem affecting women of reproductive age. According to Eskenazi et al. [1], the prevalence of endometriosis among women of reproductive age is as high as 10 %. The annual cost per woman suffering from endometriosis in North America (USA and Canada) and part of Europe (i.e., Denmark, Switzerland, Hungary, Belgium, Netherlands, Italy, France, UK, and Germany) has been estimated to 9,579€ (95 % CI 8,559€–10,599€) [2, 3]; however, this cost maybe smaller in other European countries.

The clinical manifestation of endometriosis is composed of the following three entities: (1) infertility, (2) pelvic mass, and (3) pelvic pain. Pelvic pain can be further characterized as dyspareunia, dysmenorrhea, and chronic pelvic pain. Rarely, endometriosis presents with dyschezia or dysuria when it infiltrates the rectum, the sigmoid colon, or the bladder, respectively. The pathogenesis of endometriosis is controversial, but the most predominant theory is that of the retrograde menstruation, which presented by Sampson et al. [4] in 1927. This theory explains only the presence of ectopic endometrium in the pelvic and abdominal cavity. Whereas retrograde menstruation may occur in up to 90 % of women of reproductive age only 10 % of those will develop endometriosis [5]. Alterations in the immune system of those women together with genetic variability may actually explain why some women develop endometriosis and others do not [5].

Endometriosis symptoms can be alleviated either with medication and/or surgery. Treatment goals include pain relief and/or enhancement of fertility and removal of ovarian endometriomas. For women of reproductive age, the treatment of choice is excisional surgery, as it provides pain relief and improves the quality of life in 67–80 % of the patients [6]. The role of surgery in the treatment of endometriosis-related infertility is still under evaluation [7]. In general, the operative management of endometriosis can be divided into three groups: (1) conservative management with preservation of all organs, (2) radical management with hysterectomy and bilateral salpingo-oophorectomy, and (3) hysterectomy with excision of all endometriotic foci but with retention of the ovaries.

The use of an adjunctive postoperative hormonal therapy following surgery for endometriosis-related pain has been used to reduce symptom recurrence mainly because of the hormonal-sensitive nature of the endometriotic tissue. Oral contraceptives (oCP) may represent one of the best available choices, as they are safe for long-term use, relative inexpensive, and well-tolerated drugs [8]. Several studies have shown the efficacy of oral contraceptives in the treatment of endometriosis recurrence and endometriosis-related symptoms [9–11]. oCP have been used for years in clinical practice, either in a cyclic or in a continuous (no pill-free interval) fashion.

Our aim was to summarize the existing evidence on the efficacy and patient compliance for the use of oCP in a continuous versus cyclic fashion following conservative surgery for endometriosis.

Materials and methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Table 1) and in line with the protocol agreed by all authors [12]. Eligible articles were identified by a search of MEDLINE bibliographical database from August 1962 to December 2014 (last search: December 15th, 2014) using the following search algorithm: [“endometriosis” (MeSH Terms) OR “endometriosis” (All Fields)] AND {“contraceptives, oral” (Pharmacological Action) OR “contraceptives, oral” (MeSH Terms) OR [“contraceptives” (All Fields) AND “oral” (All Fields)] OR “oral contraceptives” (All Fields) OR [“oral” (All Fields) AND “contraceptives” (All Fields)]}. Studies were considered eligible, if they have evaluated oCP therapy, either in a continuous or cyclic fashion, following conservative surgery for endometriosis. Specifically, studies (1) reporting on women with endometriosis who were treated postoperatively either with continuous or cyclic oCP, (2) written in English, (3) with at least 6 months duration of medical treatment, and (4) with at least 12 months of follow-up after treatment were considered eligible for our systematic review. Case reports, review articles, and meta-analyses were excluded.

For each one of the eligible studies, the following data were extracted: country of study; study type; mean age of patients; American Fertility Society classification for the severity of edometriosis; number of patients that were managed surgically for endometriosis and were administered oCP postoperatively; type of surgical and medical intervention; type of oCP pills used; duration of medical treatment; duration of follow-up; main outcome measures; methods of measurement of outcomes; definition of recurrence; and main results.

Outcome measures of eligible studies were tabulated and then analyzed cumulatively. A purely descriptive approach was adopted concerning all variables. Due to the differences in the treatment regimens being used and the different methods of measuring outcomes adopted by the authors, a meta-analysis of the available data was not deemed meaningful.

Results

Studies were selected by a total number of 1,171 articles that our search retrieved. The flow chart of the literature search is shown in Fig. 1. Four articles [13–16], which evaluated the effect of post-operative treatment with oCP on anatomical and/or pain recurrence, were finally included in this review. Patient and study characteristics of included articles are summarized in Table 1.

The two studies by Seracchioli et al. [13, 14] are both prospective, randomized, controlled trials, and the treatment allocation was performed in accordance with a computer-generated randomization sequence using

numbered, opaque, sealed envelops. However, Seracchioli et al. [13] utilize an intention-to-treat approach while Seracchioli et al. [14] do n ot. The study by Vercellini et al. [15] is a prospective, therapeutic, self-controlled trial with no treatment allocation. They compare the treatment of continuous oral contraceptives in a group of patients, which previously used cyclic oral contraceptives. The study by Vlahos et al. [16] is a prospective cohort trial, with 167 patients in the cyclic users group and 85 patients in the continuous users group.

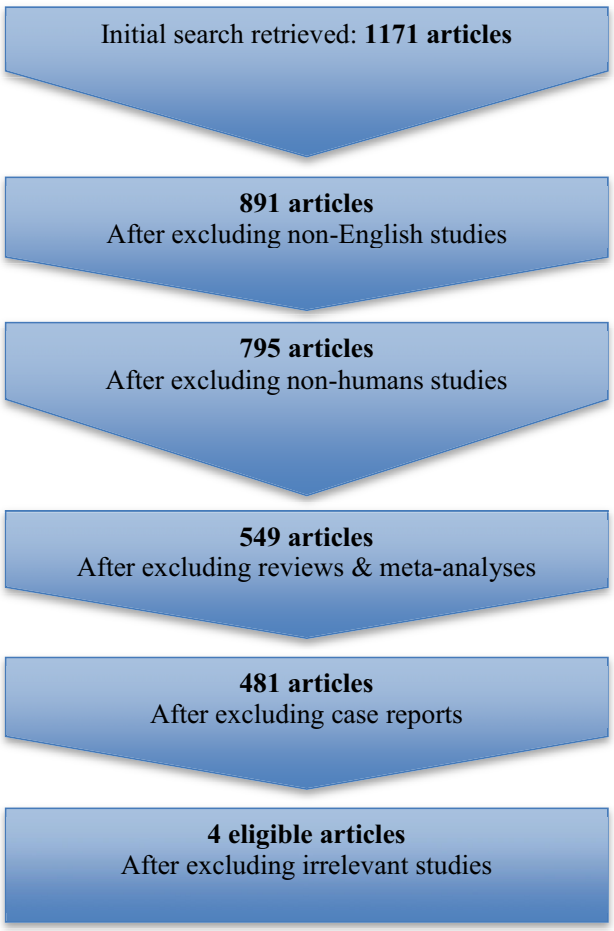

Fig. 1 Flow chart of the literature search

According to Jadad's scale [17], the studies of Vlahos et al. [16] and Vercellini et al. [15] scored with 1/5 stars since double blinding and randomization were not performed. The studies of Seracchioli et al. [13, 14] scored 5/5 stars, since appropriate randomization, double blinding, and description of withdrawals/dropouts were performed.

All studies evaluated the effect of cyclic versus continuous oCP, but only three of them evaluated the effect of cyclic versus continuous oCP in comparison with placebo treatment [13, 14, 16] (Table 2). Two studies assessed anatomical recurrence [13, 16], three studies assessed pain recurrence [14–16], and one of them examined both [16] (Table 3).

All studies have included women with endometriosis, which had undergone first-line conservative surgery for endometriosis. Among them, the studies by Vlahos et al. [16] and Seracchioli et al. [13, 14] included patients who underwent laparoscopic excision of endometriosis. On the other hand, Vercellini et al. reported on patients treated for endometriosis either laparoscopically or with an open surgery [15]. Regarding the definition of conservative surgery, Vercellini et al. do not describe the surgical procedure at all, while Seracchioli et al. describe a classic stripping technique [18–20]. Finally, Vlahos et al. [16] used the Hasson technique to enter the abdominal cavity, resected all visible endometriosis "with the use of standard laparoscopic equipment," and performed cystectomy in the cases of endometriomas. Subsequently, in all studies, a low-dose monophasic oral contraceptive pill was administered (Table 2). The duration of follow-up ranged from 6 months to 24 months (Table 2).

Table 1 Patient and study characteristics of included articles

References	Countries	Study type	Mean age (years)			AFS classification	Number of Patients CY/CON/NON/ TOTAL
			Patients with CO oCP	Patients with CY oCP	NON		
Vercellini [15]	Italy	Prospective, therapeutic, self-controlled clinical trial	32	NA	NA	NA	NA/50/NA 50
Seracchioli [13]	Italy	Prospective, randomized, controlled trial	29.6 ± 2.7	30.2 ± 2.4	28.7 ± 2.6	III/IV	75/73/69 217
Seracchioli [14]	Italy	Prospective, randomized, controlled trial	28.6 ± 2.4	29.7 ± 2.8	30.1 ± 2.7	III/IV	92/95/87 274
Vlahos [16]	Greece	Prospective cohort trial	28	27	NA	I–IV	167/85/NA 252

oCP oral contraceptives, *CO* continuous, *CY* cyclic, *NON* nonusers, *NA* not applicable, *AFS* American Fertility Society

Table 2 Therapeutic interventions of the included studies

References	Surgical intervention	Medical intervention	Type of oCP pills (CY/CON)	Duration of medical treatment (months)	Duration of follow-up CY/CON/NON in months
Vercellini [15]	Laparoscopy or Laparotomy	Continuous after cyclic use	Ethinylestradiol + desogestrel (0.02 + 0.15 mg)	24	NA/24/NA
Seracchioli [13]	Laparoscopy	Cyclic vs. continuous vs. nonusers	Ethinylestradiol + gestoden (0.020 + 0.075 mg)	24	24/24/24
Seracchioli [14]	Laparoscopy	Cyclic vs. continuous vs. nonusers	Ethinylestradiol + gestoden (0.020 + 0.075 mg)	24	24/24/24
Vlahos [16]	Laparoscopy	Cyclic vs. continuous	Drosperidone + ethinylestradiol (3 + 0.03 mg)	>6	23 ± 2.9/21 ± 2.7/NA

oCP oral contraceptives, *CO* continuous, *CY* cyclic, *NON* nonusers, *NA* not applicable

Table 3 Main outcomes and results of the included studies

References	Main Outcome measure(s)	Methods of measurement	Definition of recurrence	Main results			
Vercellini [15]	DYSM	VRS score and VAS score	Not defined	Reduction in	Baseline	2 years follow-up	
				Mean VAS score	75	31	
				Mean VRS score	2.4	0.7	
Seracchioli [13]	(1) DYSM (2) DYSP (3) NMPP	VAS score	VAS ≥ 4	Recurrence rate in[a]	CY	CON	NON
				DYSM	30 %	4 %	40 %
				DYSP	28 %	29 %	35 %
				NMPP	29.5 %	28 %	40 %
Seracchioli [14]	(1) END (2) Initial size of endometrioma (3) Growth rate of endometrioma	Ultrasonographic examination every 6 months	Presence of a cyst with a minimum diameter 1.5 cm		CY	CON	NON
				END	14.7 %	8.2 %	29 %
				Mean recurrent endometrioma diameter	2.17 cm	1.71 cm	2.73 cm
				Mean diameter increase every 6 months	0.31 cm	0.25 cm	0.48 cm
Vlahos [16]	(1) Endometriosis-related symptoms (2) Endometrioma recurrence	(1) WERF-WHSS (2) TV US and PE	According to the definitions proposed by Meuleman et al. [26][c]		CY	CON	NON
				DYSM[b]	20.9 %	9.4 %	NA
				DYSP[b]	17.3 %	10.5 %	NA
				NMPP[b]	23.9 %	9.4 %	NA
				END[b]	16.6 %	9.2 %	NA
				AUB[b]	12.5 %	23.5 %	NA
				DISC/R[b]	8.3 %	12.9 %	NA

VRS verbal rating scale, *VAS* visual analog scale, *WERF-WHSS* World Endometriosis Research Foundation-Women's Health Symptoms Survey, *CON* continuous, *CY* cyclic, *NON* non-oCP users, *TV US* transvaginal ultrasound, *PE* physical examination, *oCP* oral contraceptives, *NMPP* non-menstrual pelvic pain, *DYSM* dysmenorrhea, *DYSP* dyspareunia, *END* endometrioma recurrence, *AUB* abnormal uterine bleeding, *DISC/R* discontinuation rates

[a] Statistically significant differences between the two groups

[b] The numbers of the recurrence rates were estimated from the graphs provided

[c] Definition of recurrence according to Meuleman et al. [25]: (1) symptom recurrence based on patient history but no proof of recurrence by imaging and surgery; (2) endometriosis recurrence based on imaging: in patients with or without symptoms (pain and infertility). Recurrence is then likely based on noninvasive imaging (e.g., ultrasound and MRI); (3) surgical reintervention without recurrence of endometriosis: in patients with recurrent symptoms, surgery without visual diagnosis of endometriosis, and with either normal pelvis or other abnormalities (e.g., adhesions); (4) recurrence of visual endometriosis without histological proof: during laparoscopy, endometriosis is visually observed but either not biopsied or biopsied without histologically proven endometriosis; (5) recurrence of histologically proven endometriosis: during laparoscopy endometriosis is visually observed and confirmed histologically

In the trial by Vercellini et al. [15], the main outcome measure was dysmenorrhea measured with the Verbal Rating Scale (VRS) and the Visual Analog Scale (VAS). Women were experiencing moderate or severe recurrent dysmenorrhea despite postoperative use of oCP in a cyclic fashion. However, there was a statistically significant reduction both in VAS and in VRS score when they switched from the cyclic to continuous oCP regimens (Table 3). The mean dysmenorrhea VAS score at baseline was 75 ± 13 and at 2 years follow-up was 31 ± 17. Respectively, the VRS score was 2.4 ± 0.5 at baseline and 0.7 ± 0.6 at 2 years.

In the studies by Seracchioli et al. [13, 14], the outcome measures are listed in Table 3. Endometrioma recurrence after 24 months was 29 % (20 of 69) in the non-users, 14.7 % (11 of 75) in cyclic oCP users, and 8.2 % (6 of 73) in continuous oCP users (Table 3). The mean diameter of endometriomas at the first observation was significant smaller in continuous (1.71 ± 0.19 cm) and cyclic users (2.17 ± 0.45 cm) as compared with non-users (2.73 ± 0.56 cm) (Table 3). The growth rate of endometriomas after 6 months was significantly reduced in continuous users (0.25 ± 0.09 cm) and cyclic (0.31 ± 0.18 cm) as compared with the non-users (0.48 ± 0.3 cm). There were no statistically significant differences between cyclic and continuous users regarding the number, size, and growth of recurrent endometriomas (Table 3). Certainly, the dysmenorrhea recurrence was 4 % in the continuous group, 30 % in the cyclic group, and 40 % in the nonusers group, with statistically significant difference between the continuous group and the other two groups ($p < 0.001$). The dyspareunia recurrence rate was 29 % in the continuous group, 28 % in the cyclic group, and 35 % in the nonusers group. The non-menstrual pelvic pain or chronic pelvic pain was 28 % in the continuous group, 29.5 % in the cyclic group, and 40 % in the nonusers group. There were no significant differences among the three groups for the entire study period for chronic pelvic pain and dyspareunia (Table 3).

Vlahos et al. [16] reported on 293 patients who received either continuous or cyclic oCP for endometriosis. There were no differences between the two groups, except a difference in the incidence of non-menstrual pelvic pain, which was higher in the group of cyclic oCP administration (Table 3). The overall compliance with the treatment was 86 % (85 % in the cyclic group and 88 % in the continuous group). The outcome measures were endometrioma recurrence and the recurrence of endometriosis-related symptoms. Endometrioma recurrence rate was significantly higher in the group administered oCP in a cyclic fashion (16.6 %) compared with the continuous use of oCP (9.2 %) ($p = 0.025$), and endometriosis-related symptoms were significantly lower in the continuous group as compared with the cyclic group, with the exception of dyspareunia (Table 3). Specifically, the dysmenorrhea recurrence rate was 20.9 % in the cyclic group and 9.4 % in the continuous group ($p = 0.021$), the dyspareunia recurrence rate was 17.3 % in the cyclic users group and 10.5 % in the continuous users group ($p = 0.193$), and the non-menstrual pelvic pain recurrence rate was 23.9 % in the cyclic users group and 9.4 % in the continuous users group ($p = 0.006$). The abnormal uterine bleeding was 12.5 % in the cyclic users group and 23.5 % in the continuous users group ($p = 0.03$), and finally the discontinuation rate at 12 months was 7.1 % in the cyclic users group and 15.6 % in the continuous users group ($p = 0.035$).

Discussion

Endometriosis constitutes one of the greatest gynecological issues of our days, as it affects up to 10 % of the general population [1] and is a significant burden on the quality of life for women with the disease [2, 3]. A large portion of the patients with endometriosis ends up being treated with surgery. Women who desire to get pregnant usually attempt conception right after the operation [5, 21]. Those who do not wish to become pregnant most commonly use medications such as Progestins, Danazol, GnRH agonists, and oCP. Among them, oCP seem to be the best choice because they (1) can be administered long term, (2) do not have the major side effects of GnRH agonists, (3) provide contraception, (4) are relatively inexpensive, and (5) have been shown to reduce the risk of endometrial, ovarian, and colon cancers. Recently, dienogest has been proposed as a first-line treatment for endometriosis, and its use is increasing even if it is much more expensive than oCP [22]. One of the advantages of dienogest is that it differs from other progestins for the presence of a cyanometilic group in place of an ethinyl group in position 17-alpha, thus giving the advantages of nortestosterone derivatives [23].

Oral contraceptives act by blocking many pathways in the endometriosis recurrence cascade. First of all they reduce the menstrual flow and the possible retrograde menstruation; therefore, they can impede the reseeding of refluxed endometrial tissue [24]. They inhibit ovulation and reduce the risk of endometrioma development, as one theory supports that endometriotic cysts can develop from ovarian follicles [25]. Finally, oCP induce atrophy of the endometriotic tissue [26], enhance apoptosis in the ectopic endometrial tissue, and down-regulate the endometrial cell proliferation [27].

In the study by Vlahos et al. [16], there was a clear benefit with the use of continuous oCP regimen regarding endometrioma recurrence following surgery; however, no difference was noted in the time interval between surgery

and endometrioma reformation. In the studies by Seracchioli et al. [13, 14], there was no significant difference between cyclic and continuous users in terms of the number, size, and growth of recurrent endometriomas, but there was a positive trend toward favoring the continuous users regarding size and growth. The above findings are supported from the theory by Vercellini et al. [15] that continuous treatment with oCP may homogenize the hormonal milieu and increasing the efficiency of therapy.

Regarding dysmenorrhea, it seems that use of oCP in a continuous fashion is more effective as compared to the cyclic use [16]. In women with dysmenorrhea who did not respond to cyclic oCP, Vercellini et al. [15] observed a significant reduction in both the VAS and VRS scores with the administration of continuous oCP. Moreover, Seracchioli et al. [14] confirmed that dysmenorrhea recurrence rates in continuous users were significantly lower than cyclic and non-oCP users. A plausible explanation of this phenomenon is the achievement of amenorrhea with the continuous administration of oral contraceptives, a state that cannot coexist with dysmenorrhea.

Dyspareunia and nonspecific pelvic pain were evaluated only in two studies [14, 16]. In relation to dyspareunia, there were no significant differences between the two groups. This may be partially explained by the fact that dyspareunia is a cause of permanent endometriosis-related changes of pelvic anatomy, such as adhesions, that reduce the motility of the internal genital organs and cul-de-sac. In addition, it may be explained by the fact that dyspareunia may be influenced by psychological factors depending on woman's personality, marital, and psychosexual issues [28].

From the analysis of the studies included in this review, it seems that there is a growing body of evidence supporting continuous oCP regimens as a more effective treatment in the postoperative management of patients with endometriosis, compared with the cyclic oCP ones. According to Evans et al. [29], there are higher concentrations of activated immune cells (macrophages and mast cells), growth factors, and pro-inflammatory cytokines in peritoneal fluid of women with endometriosis. Probably with continuous oral contraceptive treatment, there is a continuous suppression of this proinflammatory process. The main drawbacks of the continuous administration of oCP are the increased discontinuation rate mainly due to erratic bleeding and cultural issues (women may desire to have periods as a sign of their femininity).

Some of the limitations of these studies are summarized below. First, the authors did not provide how many deep infiltrating endometriosis (DIE) lesions were identifying in the women before surgery and how many of them had recurrence after the treatment. The authors who studied the endometrioma recurrence rate failed to identify whether women had endometriomas only, without DIE lesions or both. In all eligible studies, there were no knowledge of the surgeons' skills and effectiveness in performing such surgeries. Furthermore, the study type is different between the eligible studies and only two studies out of four are randomized double-blind controlled trials [13, 14]. Vlahos et al. [16] used a prospective cohort design that suffers with group assignment imbalance (167 patients in the cyclic OC group and 85 patients in the continuous OC group), while Vercellini et al. [15] used a self-controlled study design that may suffer of the "regression toward the mean" phenomenon (as the patients may see a general improvement that has nothing to do with the therapy). Regarding population analysis, only two studies out of four have performed an intention-to-treat analysis. Likewise, the endometrioma recurrence rate is reported from three studies [13, 14, 16]. Finally, the severity of dysmenorrhea is measured with different scales from three out of four studies [14–16].

In conclusion, a growing body of evidence suggests that the administration of oCP in a continuous fashion following surgery for endometriosis seems to offer significant advantages as compared to the cyclic regimen. This is more evident in the cases of dysmenorrhea, chronic non-menstrual pelvic pain, and for women with endometriomas. Further, randomized trials with adequate power are required to confirm these findings and also to evaluate the preferred type of progestin that should be used in the future combined with oCPs.

Conflict of interest We declare that we have no conflict of interest.

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