ORIGINAL ARTICLE: ENDOMETRIOSIS

The use of combined hormonal contraceptives for the treatment of endometriosis-related pain: a systematic review of the evidence

Jeffrey T. Jensen, M.D., M.P.H.,[a] William Schlaff, M.D.,[b] and Keith Gordon, Ph.D.[c]

[a]Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, Oregon; [b]Department of Obstetrics and Gynecology, Thomas Jefferson University, Philadelphia, Pennsylvania; and [c]AbbVie, Inc., North Chicago, Illinois

Objective: To review the available clinical evidence on the use of combined hormonal contraceptive (CHC) agents (estrogen [E]-progestin combinations) for the treatment of endometriosis-related pain.
Design: A systematic review of the MEDLINE, Embase, and Derwent Drug File databases for prospective clinical studies.
Setting: Not applicable.
Patient(s): Women with endometriosis diagnosed by validated means.
Intervention(s): Combined hormonal contraceptive agents, active comparators, placebo, or no treatment.
Main Outcome Measure(s): Endometriosis-related pain (dysmenorrhea, pelvic pain, and dyspareunia).
Result(s): Nine randomized controlled trials and nine observational studies met the inclusion criteria. The quality of data was low: only two of the nine randomized trials were placebo controlled, and most trials were not blinded. The CHC agents were reported to significantly reduce dysmenorrhea, pelvic pain, and dyspareunia from baseline in most studies; continuous administration seemed to be more useful than cyclic administration. The effectiveness of CHC agents for pain reduction was similar to or less than that of oral progestins and GnRH agonists.
Conclusion(s): The available literature suggests that CHC treatment is effective for relief of endometriosis-related dysmenorrhea, pelvic pain, and dyspareunia; however, the supportive data are of low quality. Furthermore, insufficient data exist to reach conclusions about the overall superiority of any given CHC therapy, and the relative benefit in comparison to other approaches. Additional high-quality studies are needed to clarify the role of CHC agents and other treatments in women with endometriosis-related pain. (Fertil Steril® 2018;■:■–■. Copyright ©2018 The Authors. Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)
Key Words: Endometriosis, pain, estrogen, progestin, contraceptives

Although endometriosis represents one of the most common gynecologic diagnoses, considerable controversy exists regarding its evaluation and management. Endometriosis-related pain manifests primarily as dysmenorrhea, chronic pelvic pain, and dyspareunia (1). Endometriotic implants cause chronic inflammation with resultant increases in cytokines and prostaglandins (1, 2). Irritation or invasion of pelvic floor nerves by endometriotic lesions can occur (2, 3) and lead to propagation of central chronic pain loops and myofascial dysfunction (4). The complex nature of chronic pelvic pain in women (5, 6), the predominance of minimal and mild (i.e., stage 1 and 2) endometriosis and a high baseline prevalence of endometriosis in asymptomatic women (7, 8), and the confounding impact of central sensitization, which produces similar symptoms even in the absence of endometriosis (9), all help to explain why the extent of endometriotic lesions does not correlate well with pain severity (10).

Guideline-recommended therapies for endometriosis-related pain include combined hormonal contraceptive

Received November 13, 2017; revised March 8, 2018; accepted March 12, 2018.
J.T.J. reports grants and personal fees from AbbVie, Bayer Healthcare, Merck, and ContraMed; grants from Mirtha Women's Health and Medicines360; personal fees from Population Council outside the submitted work. W.S. reports grants from AbbVie, outside the submitted work. K.G. is a full-time employee of AbbVie, Inc., and may own stock and/or stock options.
Support provided by AbbVie, North Chicago, Illinois.
Reprint requests: Keith Gordon, Ph.D., Senior Scientific Director, Women's Health, AbbVie, Inc., 1 North Waukegan Road, North Chicago, Illinois 60064 (E-mail: keith.gordon@abbvie.com).

Fertility and Sterility® Vol. ■, No. ■, ■ 2018 0015-0282

https://doi.org/10.1016/j.fertnstert.2018.03.012

(CHC) agents (estrogen [E]-progestin combinations), progestins, danazol, GnRH agonists, nonsteroidal anti-inflammatory drugs, and aromatase inhibitors (1, 3, 11). The CHC agents are unique in that they are often initiated as empiric treatment when endometriosis is suspected, whereas a definitive diagnosis by laparoscopy is usually confirmed before initiation of most other therapies. However, evidence from well-designed, controlled studies to support CHC use is limited (3, 11). In addition, concerns about potential negative effects of CHC agents on endometriosis and fertility in the long term, as well as the risk of thromboembolism in certain populations, has led to some controversy on whether CHC agents should be considered first-line treatments (12). A recent review (13) found that the percent of patients with endometriosis-related pain remaining at end of treatment was higher with CHC agents (59%) than with progestins (34%), GnRH agonists (40%), danazol (31%), or gestrinone (28%).

The present systematic review examines evidence from prospective clinical studies (comparative and noncomparative) on the effectiveness of CHC agents. This effectiveness is compared with that of other interventions, placebo, or no treatment for the management of dysmenorrhea, pelvic pain, and dyspareunia in women with endometriosis diagnosed by validated means.

MATERIALS AND METHODS

The present literature review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (14). Institutional review board approval did not apply because this research was limited to published, deidentified data.

Literature Search

We searched the MEDLINE, Embase, and Derwent Drug File databases for articles on the use of CHC agents for the treatment of endometriosis-related pain. Titles, abstracts, and subject headings (MeSH or Embase terms) were searched using the following strategy: (endometriosis OR endometrioma OR endometrioses OR endometromata) AND (contraceptive OR hormone OR estrogen OR progesterone OR progestin OR estradiol OR hormonal therapy OR contraceptive pill OR contraceptive agent OR contraceptive agent, female OR contraceptives, oral, hormonal OR contraceptives, oral OR hormone replacement therapy OR hormonal therapy OR oral contraceptive agent) AND (dysmenorrhea OR dyspareunia OR dyschezia OR pelvic pain OR dysuria OR constipation OR pain symptom OR numeric rating scale OR visual analog scale OR pain assessment). The search was conducted on March 8, 2017, and results were limited to English-language, primary articles reporting results from human studies published after 1959.

Study Inclusion and Exclusion Criteria

We selected studies according to participants, interventions, comparators, outcomes, and study design (14). Although most studies enrolled participants with a surgical diagnosis of endometriosis (with or without microscopic analysis), we also included studies that established the diagnosis using validated imaging approaches with ultrasound or magnetic resonance imaging (1). Included studies compared the use of CHC agents with other active therapies, placebo controls, or no treatment. Outcomes of interest were the effect of treatment on dysmenorrhea, pelvic pain (including chronic and nonmenstrual), or dyspareunia. We included prospective randomized controlled trials (RCTs) and observational studies (comparative or noncomparative). Retrospective studies and studies that combined CHC agents with other treatments (no CHC-only group) or used CHC agents as an adjunct to surgery (i.e., immediate postoperative use) were excluded. In cases of uncertainty about study eligibility according to these prespecified criteria, study inclusion was decided by two investigators of the present study.

Outcome Measures

Mean or median values from pain scales in each study were used to summarize the effect of treatment on endometriosis-related pain. Results pertaining to patient quality of life (QoL) and satisfaction with treatment also were summarized, if available.

RESULTS

Literature Search Results

The literature search identified 518 records (Supplemental Fig. 1, available online). After removing duplicates, 516 records were reviewed and 498 were eliminated according to inclusion and exclusion criteria. A total of 18 studies (15-32) met the participants, interventions, comparators, outcomes, and study design inclusion criteria and are detailed in this review.

Characteristics and Methods of Included Studies

The included articles report results from nine RCTs [15-17, 23-28] and nine [18-22, 29-32] observational studies. Five [18-22] of the observational studies used a comparative design, and four [29-32] had no comparator group, instead comparing post-treatment pain scores with baseline values. Three (15–17) of the RCTs were double blind, and the rest were open label. All observational comparative studies (18–22) used a patient-preference design that allowed participants to choose their treatment group. The study methods are summarized in Table 1. The therapeutic modalities compared in each study are shown in Supplemental Table 1, available online.

Key Differences in Methods

Major methodological differences (Table 1) in eligibility requirements, treatment allocation, and outcome assessments should be considered in conjunction with the findings. Of the 18 studies, nine [16, 22-28, 32] required a surgical diagnosis of endometriosis, five [18, 20, 21, 29, 31] used radiologic criteria, and four [15, 17, 19, 30] allowed either method. Whereas surgery can detect endometriosis at any

TABLE 1

Methods of clinical studies of combined hormonal contraceptive use in women with endometriosis.

Study/setting	Key inclusion criteria[a]	Number of patients	Dropouts (n)	Method of diagnosis	Study intervention(s)	Treatment duration	Pain outcomes	Pain assessment	Data analysis
Randomized controlled trials									
Di Francesco & Pizzigallo 2014 (23) Italy	Chronic pelvic pain due to endometriosis	30	1	Laparoscopy	• Oral EE 0.03 mg + drospirenone 3 mg/d given cyclically (n = 10) • Leuprorelin acetate 11.25 mg IM every 3 mo (n = 10) • Oral PEA-m 400 mg + transpolydatin 40 mg twice a day (n = 10)	6 mo	• Dysmenorrhea • Chronic pelvic pain • Dyspareunia	NRS	ITT
Guzick et al., 2011 (16) United States	Endometriosis-associated pelvic pain	47	23	Laparoscopy or laparotomy	• Oral EE 0.035 mg + norethindrone 1 mg/d given continuously (n = 26) • Depot leuprolide 11.25 mg IM every 12 wk + hormonal add-back with oral norethindrone acetate 5 mg/d (n = 21)	48 wk	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	B&B pain score	NR
Harada et al., 2008 (17) Japan	Endometriosis-associated dysmenorrhea	100	4	Laparoscopy or laparotomy for endometriosis; ultrasound or MRI for endometrioma	• Oral EE 0.035 mg + norethisterone 1 mg/d given cyclically (n = 51) • Placebo (n = 49)	16 wk	• Dysmenorrhea • Nonmenstrual pelvic pain	VAS, VRS	PP
Harada et al., 2017 (15) Japan	Endometriosis-associated pelvic pain	312	43 (blinded treatment)	Clinical diagnosis of endometriosis (pelvic tenderness, induration in the cul de sac, or uterine immobility), or laparoscopy or laparotomy for endometriosis, or ultrasound for endometrioma	• Oral EE 0.02 mg + drospirenone 3 mg/d given continuously (4-d stop every 120 d) (n = 130) (blinded) • Placebo (n = 128) (blinded) • Oral dienogest 2 mg/d (n = 53) (open-label)	24 wk	• Pelvic pain	VAS	ITT
Parazzini et al., 2000 (24) Italy	Endometriosis-associated pelvic pain	102	3	Laparoscopy or laparotomy	• Oral EE 0.03 mg + gestodene 0.75 mg/d (n = 47) • Triptorelin 3.75 mg slow release every 28 d for 4 mo	12 mo	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	LAS, VRS	ITT

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.

TABLE 1

Continued.

Study/setting	Key inclusion criteria[a]	Number of patients	Dropouts (n)	Method of diagnosis	Study intervention(s)	Treatment duration	Pain outcomes	Pain assessment	Data analysis
					followed by Oral EE 0.03 mg + gestodene 0.75 mg/d for 8 mo (n = 55)				
Vercellini et al., 1993 (25) Italy	Endometriosis-associated pelvic pain	57	7	Laparoscopy	• Oral EE[b] 0.02 mg + oral desogestrel 0.15 mg/d given cyclically (n = 28) • Goserelin 3.6 mg SQ in a 28-d depot formulation (n = 29)	12 mo	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	LAS, VRS	PP
Vercellini et al., 2002 (26) Italy	Recurrent pelvic pain for >6 mo after surgery for endometriosis in past 12 mo	90	15	Laparoscopy or laparotomy	• Oral EE 0.02 mg + desogestrel 0.15 mg/d given continuously (n = 45) • Oral cyproterone acetate 12.5 mg/d given continuously (n = 45)	6 mo	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	VAS, VRS	ITT for patient satisfaction; PP for other outcomes
Vercellini et al., 2005 (27) Italy	Recurrent pelvic pain for >6 mo after surgery for rectovaginal endometriosis in past 12 mo	90	12	Laparoscopy or laparotomy (all patients), then transvaginal and transrectal ultrasound, vaginal and rectal exams	• Oral EE 0.01 mg + cyproterone acetate 3 mg/d given continuously (n = 45) • Oral norethindrone acetate 2.5 mg/d given continuously (n = 45)	12 mo	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	VAS, VRS	ITT for patient satisfaction; PP for other outcomes
Zupi et al., 2004 (28) Italy	Recurrent pelvic pain after surgery for endometriosis	133	NR	Surgery (all patients), then pelvic and vaginal ultrasound, hysteroscopy	• Oral EE 0.03 mg + gestodene 0.75 mg/d given cyclically (n = 43) • Leuprolide acetate 11.25 mg IM every 3 mo (n = 44) • Leuprolide acetate 11.25 mg IM every 3 mo + transdermal EE 0.025 mg and oral norethindrone 5 mg/d (n = 46)	12 mo	• Dysmenorrhea • Pelvic pain • Dyspareunia	VAS	NR
Observational comparative trials									
Caruso et al., 2016 (18) Italy	Chronic pelvic pain	96	10	Transvaginal ultrasound	• Oral EE 0.03 mg + dienogest 2 mg/d	6 mo	• Pelvic pain	VAS	NR

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.

TABLE 1

Continued.

Study/setting	Key inclusion criteria[a]	Number of patients	Dropouts (n)	Method of diagnosis	Study intervention(s)	Treatment duration	Pain outcomes	Pain assessment	Data analysis
					given continuously (n = 63) • Oral EE 0.03 mg + dienogest 2 mg/d given cyclically (n = 33)				
Grandi et al., 2015 (19) Italy	Endometriosis and dysmenorrhea >6 mo	40	6	Laparoscopy or laparotomy for endometriosis; transvaginal ultrasound for endometrioma	• Oral E_2 valerate (1–3 mg) + oral dienogest (2–3 mg/d) (quadriphasic) given cyclically (26/2) (n = 22) • Oral ketoprofen 200 mg PRN ≤3 times daily (n = 18)	24 wk	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	VAS	PP
Leone Roberti Maggiore et al., 2014 (20) Italy	Rectovaginal endometriosis infiltrating the rectum; endometriosis-related pain	143	18	MRI, vaginal and rectal examinations	• Vaginal ring delivering cyclic EE 0.015 mg and etonogestrel 0.12 mg (n = 83) • Oral desogestrel 0.075 mg/d given continuously (n = 60)	12 mo	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	VAS	ITT for patient satisfaction; PP for other outcomes
Morotti et al., 2014 (21) Italy	Rectovaginal endometriosis and migraine without aura; endometriosis-related pain	144	27	Ultrasound, vaginal and rectal examinations	• Oral EE 0.02 mg + desogestrel 0.15 mg/d given cyclically (n = 82) • Oral desogestrel 0.075 mg/d given continuously (n = 62)	6 mo	• Dysmenorrhea • Chronic pelvic pain • Dyspareunia	VAS	ITT for patient satisfaction; PP for other outcomes
Vercellini et al., 2010 (22) Italy	Recurrent pelvic pain for >6 mo after surgery for endometriosis in past 12 mo	207	95	Laparoscopy or laparotomy	• Vaginal ring delivering EE 0.015 mg + etonogestrel 0.12 mg/d given continuously (n = 123) • Transdermal system delivering EE 0.02 mg + norelgestromin 0.15 mg/d, given continuously (n = 84)	12 mo	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	VAS, VRS	ITT for patient satisfaction; PP for other outcomes

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.

TABLE 1

Continued.

Study/setting	Key inclusion criteria[a]	Number of patients	Dropouts (n)	Method of diagnosis	Study intervention(s)	Treatment duration	Pain outcomes	Pain assessment	Data analysis
Observational noncomparative trials									
Ferrari et al., 2012 (29) Italy	Colorectal endometriosis, endometriosis-associated pain	26	0	Rectal endoscopic ultrasonography, vaginal and rectal examinations	• Oral EE 0.015 mg + gestodene 60 μg/d given continuously (4-d stop every 3 mo) (n = 26)	12 mo	• Dysmenorrhea • Nonmenstrual pelvic pain • Dyspareunia	VAS	ITT (no dropouts)
Tanaka et al., 2016 (30) Japan	Endometriosis-associated dysmenorrhea	46	5	Surgery or MRI	• Oral EE 0.02 mg + drospirenone 3 mg/d given cyclically (24/4) (n = 46)	6 mo	• Dysmenorrhea • Chronic pelvic pain • Dyspareunia	VAS	NR
Taniguchi et al., 2015 (31) Japan	Unilateral ovarian endometriomas, dysmenorrhea	49	NR	Ultrasound or MRI	• Oral EE 0.02 mg + drospirenone 3 mg/d given cyclically (24/4) (n = 49)	6 mo	• Dysmenorrhea	VAS	NR
Vercellini et al., 2003 (32) Italy	Recurrent dysmenorrhea for >6 mo after surgery for endometriosis in past 12 mo, despite cyclic combined OC use	50	9	Laparoscopy or laparotomy	• Oral EE 0.02 mg + desogestrel 0.15 mg/d given continuously (n = 50)	2 y	• Dysmenorrhea	VAS, VRS	ITT

Note: Cyclic combined OC treatment was 21 d of active hormone and 7 d of placebo (21/7), unless otherwise specified. B&B = biberoglu and behrman; EE = ethinyl E_2; IM = intramuscular; ITT = intention-to-treat; LAS = linear analogue scale; MRI = magnetic resonance imaging; NR = not reported; NRS = numeric rating scale; OC = oral contraceptive; PEA-m = micronized palmitoylethanolamide (a fatty acid ethanolamide thought to have analgesic and anti-inflammatory effects); PP = per protocol; PRN = as needed; RCT = randomized controlled trial; SQ = subcutaneous; VAS = visual analogue scale; VRS = verbal rating scale.

[a] All studies included women of childbearing years.

[b] Patients could switch to EE 0.03 mg + desogestrel 0.15 mg for spotting or breakthrough bleeding.

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.

stage, radiologic methods only detect moderate-to-severe disease (33, 34). Thus, use of a radiologic diagnosis could identify a more affected, difficult-to-treat population compared with a surgically diagnosed population. On the other hand, studies requiring laparoscopic diagnosis of endometriosis may underestimate the true effectiveness of CHC agents for endometriosis-related pain, as CHC agents represent a common first-line therapy for dysmenorrhea, and women who fail therapy with CHC may disproportionately undergo laparoscopy for diagnosis. Unfortunately, only three studies reported past use of combined oral contraceptives (OCs) (74% [20], 37% [21], 13% (30)); none of these studies required a surgical diagnosis.

Pain assessment tools also varied between studies. Most used a visual analogue scale (VAS; 0–10 cm or 0–100 mm) or a verbal rating scale based on the Biberoglu and Behrman (35) and/or the Andersch and Milsom (36) scales. Unfortunately, neither the Biberoglu and Behrman nor the Andersch and Milsom scales have been validated (37), and many studies added to the confusion by administering modified forms of these instruments. In contrast, the VAS is a well-validated and precise measure of pain in patients with endometriosis (37). The minimum clinically significant difference in endometriosis-related pain is suggested to be $\geq$10 mm on a 100-mm VAS, but may be larger if considerable differences exist between medical interventions being compared (37). We applied a more stringent benchmark of a 13-mm reduction on a 100-mm VAS, which has been demonstrated to be clinically meaningful in patients with acute pain (38), for a conservative assessment of clinically important pain reductions in the nine studies (15, 17, 22, 26, 27, 29–32) using this scale.

Regional differences in practice and patient populations among the 18 included studies also limit the conclusions possible when comparing studies. Thirteen [18-29, 32] of the included studies were performed in Italy, four (15, 17, 30, 31) in Japan, and only one in the United States (16). Other important differences include treatment duration, CHC formulation used, and pattern of treatment (continuous or cyclic) (Table 1).

Summary of Pain Findings

Randomized controlled trials

Cyclic combined OCs versus placebo. Two studies (15, 17) by Harada et al. used a double-blind placebo-controlled design to assess the effects of CHC in Japanese women with endometriosis-related pain. In the first study, placebo-treated and combined OC-treated participants reported a significant reduction from baseline in dysmenorrhea according to VAS and verbal rating scale scores (Table 2) (17). However, the magnitude of reduction in dysmenorrhea VAS scores exceeded the minimum threshold for clinical significance (13 mm on a 100-mm VAS) only among subjects with active treatment (31.1 mm), with a threefold greater reduction than the placebo group (9.6-mm decrease). The statistically significant between-group difference favoring combined OC use emerged during the first treatment cycle and continued through the end of treatment (Table 2). The nonmenstrual pelvic pain scores were low and differed between the treatment groups at baseline, demonstrating the difficulty in evaluating this outcome even in an appropriately designed RCT. Combined OC treatment did not result in a clinically significant reduction in nonmenstrual pain (17). Although the double-blind placebo-controlled RCT design represents a considerable strength of this study, important limitations warrant consideration. Foremost, although the eligibility criteria allowed either a surgical (laparoscopic detection of endometriosis) or imaging (ultrasound detection of endometriomas) diagnosis, most of the enrolled participants (95%) had endometriomas diagnosed by imaging (17). This suggests that the population studied may have had more advanced disease than routinely observed in clinical practice. However, a similar reduction in endometrioma size occurred in the placebo and combined OC group, suggesting the possibility of diagnosis misclassification. Harada et al. (15) recently reported the results of a second placebo-controlled trial that examined a flexible regimen of combined ethinyl E_2 (EE) 20 μg/drospirenone 3 mg continuously for 120 days, with a 4-day tablet-free interval either after 120 days or after $\geq$3 consecutive days of spotting and/or bleeding during the 120 days. A third study arm received open-label dienogest (2 mg/d) for the 24-week study. The population was again exclusively Japanese and with predominately endometriomas diagnosed using imaging techniques. The evaluation of pain was reported as the absolute change in the most severe endometriosis-associated pelvic pain measured using a 100-mm VAS. Pain scores decreased more in the active combined OC treatment group (36.6-mm decrease) than in the group treated with placebo (10.7-mm decrease), but interestingly decreased even more in the parallel open-label group treated with dienogest (50.0-mm decrease) (Table 2) (15). Endometriosis-related pain improved after treatment despite no reduction in the number of bleeding/spotting days. As the CHC regimen involved quasi-continuous dosing, the study did not differentiate menstrual and nonmenstrual pain (15).

Cyclic combined OC versus GnRH agonist with and without hormonal add-back therapy. Four studies included a comparison of cyclic combined OC with GnRH agonist treatment. Di Francesco and Pizzigallo (23) randomized subjects to leuprolide acetate (LA), a cyclic combined OC, or micronized palmitoylethanolamide plus trans-polydatin (a food supplement anti-inflammatory agent). In this small study (n = 10/treatment group), all three treatments resulted in similar reductions from baseline in dysmenorrhea, chronic pelvic pain, and dyspareunia (Table 2). A larger 6-month study by Vercellini and colleagues (25) found cyclic combined OC treatment and monthly goserelin effective in reducing dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia scores (Table 2). Zupi et al. (28) randomized subjects to one of three groups; LA alone, LA with add-back therapy (low-dose transdermal E_2 plus oral norethindrone), or cyclic combined OC. All treatments resulted in statistically significant improvement in symptoms, with GnRH treatment statistically superior to combined OCs (Table 2). Lastly, Parazzini and colleagues (24) compared 12 months of combined OC use with 4 months of GnRH agonist followed by 8 months of combined OC treatment and found no significant differences between the groups in scores for dysmenorrhea or nonmenstrual pelvic pain

TABLE 2

Mean scores for endometriosis-related pain from randomized controlled trials.

		Dysmenorrhea		Nonmenstrual pelvic pain		Chronic pelvic pain		Dyspareunia	
Study	**Interventions**	**Baseline**	**Post-TX**	**Baseline**	**Post-TX**	**Baseline**	**Post-TX**	**Baseline**	**Post-TX**
VAS, LAS, or NRS, 0–10 scale: 0, no pain; 10, worst pain									
Di Francesco & Pizzigallo 2014 (23)	Combined OC (cyclic)	5.6	2.5[a,b]***	—	—	5.7	3.3[a,b]***	4.3	2.7[a,b]*
	GnRH agonist	5.2	3.1[a,b]***	—	—	4.0	2.2[a,b]***	3.1	2.3[a,b]*
	Fatty acid ethanolamide + medical food	7.5	2.3[a,b]***	—	—	5.3	2.2[a,b]***	5.0	1.8[a,b]*
Parazzini et al., 2000 (24)	Combined OC	6	6	5	4	—	—	—	—
	GnRH, followed by combined OC	6	4	6	6	—	—	—	—
Vercellini et al., 1993 (25)	Combined OC (cyclic)	8.0	3.7[b]**	4.2	1.9[b]**	—	—	6.1	3.9[b]**
	GnRH agonist	8.1	NA	4.4	2.1[b]**	—	—	6.4	2.1[b]**,[c]*
Zupi et al., 2004 (28)	Combined OC (cyclic)	6.0	0.9	—	—	6.3	0.8	5.6	1.3
	GnRH agonist	6.1	0[c]**	—	—	6.7	0.2[c]**	5.9	1.4
	GnRH agonist + add-back	5.8	0[c]**	—	—	6.9	0.3[c]**	5.8	1.2
VAS, 0–100 scale: 0, no pain; 100, worst pain									
Harada et al., 2008 (17)	Combined OC (cyclic)	58.7	27.6[b]***,[c]***	27.5	19.1[b]*	—	—	—	—
	Placebo	55.8	46.2[b]**	22.8	21.0	—	—	—	—
Harada et al., 2017 (15)	Combined OC (continuous)	—	—	—	—	77.2	40.5[b]*,[d]	—	—
	Placebo	—	—	—	—	77.7	66.4[b]*	—	—
	Progestin (reference arm)	—	—	—	—	76.3	25.9[b]*	—	—
Vercellini et al., 2002 (26)	Combined OC (continuous)	74	0	47	20	—	—	51	15
	Progestin	71	0	54	14	—	—	52	13
Vercellini et al., 2005 (27)	Combined OC (continuous)	72.3	8.7[e]	52.5	25.0[e]	—	—	46.5	10.8[e]
	Progestin	75.8	3.0[e]	57.5	14.5[e]	—	—	51.4	13.8[e]
VRS, 0–3 scale, based on modified Biberoglu & Behrman[f] grading scale									
Vercellini et al., 1993 (25)	Combined OC (cyclic)	—	—	—	—	—	—	1.8	1.2[b]**
	GnRH agonist	—	—	—	—	—	—	1.7	1.1[b]**
Vercellini et al., 2002 (26)	Combined OC (continuous)	2	0	1	0	—	—	1	0
	Progestin	2	0	1	0	—	—	1	0
Vercellini et al., 2005 (27)	Combined OC (continuous)	2.4	0.3[e]	1.8	0.8[e]	—	—	1.6	0.4[e]
	Progestin	2.5	0.1[e]	1.8	0.4[e]	—	—	1.7	0.5[e]
VRS, 0–6 scale, based on modified Biberoglu & Behrman[f] and Andersch & Milsom[g] grading scales									
Harada et al., 2008 (17)	Combined OC (cyclic)	4.4	2.4[b]***,[c]***	1.6	1.3	—	—	—	—
	Placebo	4.3	3.7[b]**	1.1	1.2	—	—	—	—
VRS, 0–7 scale, based on modified Andersch & Milsom[g] grading scale									
Parazzini et al., 2000 (24)	Combined OC	4	2	3	0	—	—	—	—
	GnRH agonist, then combined OC	3	0	2	0	—	—	—	—
Vercellini et al., 1993 (25)	Combined OC (cyclic)	5.0	2.4[b]**	2.9	1.6[b]**	—	—	—	—
	GnRH agonist	5.1	NA	3.0	1.2[b]**	—	—	—	—

Note: Results are presented as mean values for all studies except Vercellini et al., 2002, for which median values are shown. Three studies did not report statistical significance of within-group changes from baseline (Parazzini et al., 2000; Zupi et al., 2004; Vercellini et al., 2002). LAS = linear analogue scale; NA = not applicable (because treatment caused amenorrhea); NRS = numeric rating scale; OC = oral contraceptive; TX = treatment; VAS = visual analogue scale; VRS = verbal rating scale; —, not measured.

[a] Value estimated from chart in published article.

[b] Significant difference versus baseline at the following level of significance: *$P<.05$;**$P<.01$;***$P<.001$.

[c] Significant difference versus comparator at the following level of significance: *$P<.05$;**$P<.01$;***$P<.001$.

[d] Significant difference reported for combined OC versus placebo ($P<.001$); statistical significance of difference between combined OC and dienogest not reported.

[e] Vercellini et al., 2005 stated that all within-group changes from baseline were significant, but did not report P values for the comparisons.

[f] 0–3 points assigned for each of dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia, for a total score of 0–9; higher values indicate more severe symptoms (Biberoglu & Behrman 1981).

[g] 0–3 points assigned for work performance, the coexistence of systemic symptoms, and the use of analgesics, for a total score of 0–7; higher scores indicate more severe symptoms (Andersch & Milsom 1982).

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.

(Table 2). Common weaknesses in these studies include lack of appropriate blinding and no discussion of the randomization scheme. In addition, subjects receiving GnRH treatments reported more adverse effects such as hot flushes and vaginal dryness.

Continuous combined OC versus GnRH agonist plus hormonal add-back treatment. Guzick et al. (16) conducted a randomized double-blind study comparing continuous combined OC treatment with GnRH agonist plus hormonal add-back therapy. To conceal allocation, all subjects received a daily capsule containing the combined OC or add-back norethindrone and an injection of placebo or GnRH agonist every 12 weeks. These investigators assessed changes in pain during 48 weeks using the Biberoglu and Behrman pain score (for dyspareunia, dysmenorrhea, and noncyclic pelvic pain) and the numerical rating scale (for global pain). Both treatments resulted in significant reductions in pain scores from baseline, with no significant differences between therapies. In both groups, the reductions were apparent beginning with the first assessment at 4 weeks (16).

Continuous combined OC versus oral progestin. Two studies by the same Italian group compared the effects of continuous administration of a combined OC or an oral progestin. In the first study, Vercellini et al. (26) randomized women with recurrent pelvic pain after conservative surgical therapy for symptomatic endometriosis to a desogestrel-containing combined OC or oral cyproterone acetate. Both treatments resulted in a similar reduction in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia (Table 2). In the second study (27), the investigators treated women with symptomatic rectovaginal endometriosis with either a cyproterone acetate–containing combined OC or norethindrone acetate. Results were similar to those in the first study; both treatments reduced dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia (Table 2). In both studies, treatment with either therapy resulted in more complete improvement in dysmenorrhea than nonmenstrual pain. In the 2017 study by Harada and colleagues (15) women randomized to open-label dienogest showed more improvement in pain scores than women randomized to the flexible EE/drospirenone pill.

Observational comparative trials

Cyclic combined OC versus continuous combined OC. Caruso and colleagues (18) conducted the only study that compared continuous and cyclic administration of the same combined OC formulation (EE 30 μg/dienogest 2 mg) in women with endometriosis-associated pain. Continuous use resulted in a significant reduction in pain from baseline measured by VAS at 3 and 6 months, whereas a significant improvement with cyclic use was seen only at 6 months (Table 3). Although the magnitude of improvement with continuous combined OC use appeared more with cyclic use at both end points, the investigators did not report between-group statistical comparisons (18).

Cyclic combined OC versus nonsteroidal anti-inflammatory drug. A study by Grandi and colleagues (19) reported results from an observational study comparing the effects, during six cycles, of the quadriphasic E_2 valerate/dienogest combined OC to oral ketoprofen on endometriosis-related pain using a VAS. The combined OC, but not the nonsteroidal anti-inflammatory drug, resulted in significantly reduced dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia scores from baseline (Table 3).

Cyclic combined OC versus continuous progestin-only pill. An observational study of symptomatic rectovaginal endometriosis and migraine conducted by an Italian group led by Morotti (21) compared continuous use of an OC progestin-only pill (POP) containing desogestrel 75 μg to cyclic use of a desogestrel-containing combined OC during six cycles. Both treatments resulted in similar reductions in chronic pelvic pain and dyspareunia as evaluated by VAS. The combined OC also reduced dysmenorrhea, an end point not evaluable in the continuous POP group (Table 3).

Cyclic CHC vaginal ring versus continuous POP. Using a similar design as the Morotti study (21), another group (20) compared the desogestrel 75 μg POP to the combined EE/etonogestrel contraceptive vaginal ring (CVR) during 1 year in women with rectovaginal endometriosis. In this study (20), the POP resulted in cycle suppression and completely resolved dysmenorrhea, whereas use of the cyclic CVR resulted in a significant reduction from baseline in dysmenorrhea (Table 3). Although both treatments significantly reduced nonmenstrual pelvic pain and dyspareunia, the POP showed statistical superiority.

Continuous CHC vaginal ring versus continuous CHC transdermal patch. Vercellini and colleagues (22) used the same design to compare continuous use of the CVR (EE/etonogestrel) or the transdermal contraceptive patch (EE/norelgestromin). Both treatments resulted in improvement from baseline scores for dysmenorrhea, dyspareunia, and nonmenstrual pelvic pain (Table 3).

Observational noncomparative trials. Results from noncomparative observational trials of cyclic or continuous use of combined OCs are consistent with those observed in comparator studies. Cyclic combined OC use demonstrated statistically and clinically significant reductions from baseline in dysmenorrhea (30, 31) and chronic pelvic pain (30) (Table 3). Results from two observational studies (29, 32) examining the effects of continuous combined OC treatment showed statistically and clinically significant reductions in dysmenorrheal (29, 32), nonmenstrual pelvic pain (29), and dyspareunia (29) from baseline (Table 3). The study by Vercellini et al. (32) is notable, as they enrolled women who failed treatment with cyclic combined OCs, suggesting that switching to continuous use may improve outcomes in women who fail cyclic combined OC treatment.

Summary of QoL Findings

Quality of life was assessed in three RCTs (23,26,28) and three observational comparative trials (18, 19, 21). Five of the six studies used the Short Form-36 questionnaire, which measures eight domains of health (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/vitality, emotional well-being, social functioning, pain, and general health), with higher

TABLE 3

Mean scores for endometriosis-related pain from observational comparative and noncomparative trials.

		Dysmenorrhea		Nonmenstrual pelvic pain		Chronic pelvic pain		Dyspareunia	
Study	**Interventions**	**Baseline**	**Post-TX**	**Baseline**	**Post-TX**	**Baseline**	**Post-TX**	**Baseline**	**Post-TX**
VAS, 0–10 scale: 0, no pain; 10, worst pain									
Caruso et al., 2016 (18)	Combined OC (continuous)	—	—	—	—	7.3[a]	3.0[a,b]***	—	—
	Combined OC (cyclic)	—	—	—	—	7.1[a]	5.0[a,b]*	—	—
Grandi et al., 2015 (19)	Combined OC (cyclic)	6.33	2.47[b]***,[c]**	5.71	2.0[b]*,[c]*	—	—	5.71	2.74[b]*
	NSAID	5.98	6.3	5.32	4.55	—	—	6.01	5.95
Leone Roberti Maggiore et al., 2014 (20)	CHC vaginal ring (cyclic)	6.4	3.1[b]***	5.6	3.5[b]***	—	—	5.8	3.2[b]***
	POP (continuous)	6.7	NA	5.7	2.9[b]***,[c]*	—	—	5.4	2.5[b]***,[c]**
Morotti et al., 2014 (21)	Combined OC (cyclic)	7.3[a]	3.8[a,b]***	—	—	5.0[a]	3.3[a,b]**	5.1[a]	3.4[a,b]**
	POP (continuous)	NR	NR	—	—	4.8[a]	3.1[a,b]**	5.3[a]	3.9[a,b]**
VAS, 0–100 scale: 0, no pain; 100, worst pain									
Vercellini et al., 2010 (22)	CHC vaginal ring (continuous)	80	22[c]**	NR	NR	—	—	44	22
	CHC transdermal patch (continuous)	77	35	NR	NR	—	—	34	22
Ferrari et al., 2012 (29)	Combined OC (continuous)	90.4	26.9[b]**	65.0	18.5[b]**	—	—	63.1	18.5[b]**
Tanaka et al., 2016 (30)	Combined OC (cyclic)	71	24[b]***	—	—	30	5[b]***	10	0[b]***
Taniguchi et al., 2015 (31)	Combined OC (cyclic)	68	10[b]***	—	—	—	—	—	—
Vercellini et al., 2003 (32)	Combined OC (continuous)	75	31[b]***	—	—	—	—	—	—
VRS, 0–3 scale, based on modified Biberoglu & Behrman[d] grading scale									
Vercellini et al., 2003 (32)	Combined OC (continuous)	2.4	0.7[b]***	—	—	—	—	—	—

Note: Results are presented as mean values for all studies except Tanaka et al., 2016 and Taniguchi et al., 2015, for which median values are shown. One study did not report statistical significance of within-group changes from baseline, and reported some but not all statistical comparisons of end point values between treatment groups (Vercellini et al., 2010). Two studies reported no statistical comparison of end point values between treatment groups (Caruso et al., 2016; Morotti et al., 2014). CHC = combined hormonal contraceptive; NA = not applicable (because treatment caused amenorrhea); NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; OC = oral contraceptive; POP = progestin-only pill; TX = treatment; VAS = visual analogue scale; VRS = verbal rating scale; — = not measured by the given scale.

[a] Value estimated from chart in published article.

[b] Significant difference versus baseline at the following level of significance: *$P<.05$;**$P<.01$;***$P<.001$.

[c] Significant difference versus comparator at the following level of significance: *$P<.05$;**$P<.01$.

[d] 0–3 points assigned for dysmenorrhea; higher values indicate more severe symptoms (Biberoglu & Behrman 1981).

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.

TABLE 4

Mean quality-of-life scores from randomized controlled trials and observational comparative trials.

Study	QoL domain or summary score	Treatment group 1		Treatment group 2		Treatment group 3	
		Baseline	Post-TX	Baseline	Post-TX	Baseline	Post-TX
Di Francesco & Pizzigallo 2014 (23)		Combined OC (cyclic)		GnRH agonist		Fatty acid ethanolamide + medical food	
	PCS	39.5	46[a,b]***	46.9	49[a,b]***	43.4	51[a,b]***
	MCS	47.8	50[a]	41.3	44[a]	38.6	51[a,b]***,c*
Vercellini et al., 2002 (26)		Combined OC (continuous)		Progestin		NA	
	Physical functioning	79.9	85.1	81.3	93.6[b]***	—	—
	Role limitation (physical)	42.8	79.2[b]***	50.4	89.5[b]***	—	—
	Role limitation (emotional)	41.9	81.9[b]***	58.8	80.6[b]***	—	—
	Energy/vitality	47.5	52.3	49.2	63.3[b]***	—	—
	Emotional well-being	52.7	61.3[b]**	55.7	66.1[b]***	—	—
	Social functioning	56.4	67.3	58.9	77.0[b]*	—	—
	Pain	46.6	69.8[b]***	44.7	81.3[b]***,c*	—	—
	General health	55.0	60.6	52.5	65.8[b]***	—	—
Zupi et al., 2004 (28)		Combined OC (cyclic)		GnRH agonist		GnRH agonist + add-back	
	Physical functioning	52.8	55.6	51.6	57.6	52.6	66.4[b]***
	Role limitation (physical)	57.1	58.8	59.2	60.1	58.3	57.3
	Role limitation (emotional)	60.1	58.1	60.5	62.3	60.8	60.0
	Energy/vitality	52.3	56.1	53.4	57.8	52.7	68.0[b]*
	Emotional well-being	60.2	59.4	59.8	60.2	58.1	60.5
	Social functioning	58.5	56.7	55.6	54.5	56.4	58.3
	Pain	50.1	58.3	46.4	62.1[b]***	47.1	63.6[b]***
	General health	48.1	51.2	49.4	54.9	47.9	59.6[b]***
Caruso et al., 2016 (18)		Combined OC (continuous)		Combined OC (cyclic)		NA	
	Physical functioning	60[a]	78[a,b]***,c**	60[a]	70[a,b]*	—	—
	Role limitation (physical)	65[a]	80[a,b]***,c**	65[a]	75[a,b]*	—	—
	Role limitation (emotional)	70[a]	82[a,b]***,c**	70[a]	78[a,b]*	—	—
	Energy/vitality	70[a]	83[a,b]***,c**	70[a]	75[a,b]*	—	—
	Emotional well-being	67[a]	80[a,b]***,c**	66[a]	76[a,b]*	—	—
	Social functioning	70[a]	80[a,b]***,c**	70[a]	80[a,b]*	—	—
	Pain	50[a]	80[a,b]***,c**	50[a]	62[a,b]*	—	—
	General health	54[a]	80[a,b]***,c**	53[a]	63[a,b]*	—	—
Grandi et al., 2015 (19)		Combined (cyclic)		NSAID		NA	
	PCS	55.85	70.53[b]***	58[a]	62[a]	—	—
	MCS	57.17	67.72[b]**	51[a]	61[a]	—	—
	Physical functioning	67.63	80.53[b]**	79[a]	77[a]	—	—
	Role limitation (physical)	61.84	77.63[b]*	58[a]	77[a]	—	—
	Role limitation (emotional)	76[a]	81[a]	70[a]	73[a]	—	—
	Energy/vitality	48.42	56.84[b]*	42.08	56.94[b]*	—	—
	Emotional well-being	55[a]	63[a]	50[a]	54[a]	—	—
	Social functioning	49.87	70.39[b]**	42[a]	58[a]	—	—
	Pain	43.68	67.89[b]***	47[a]	54[a]	—	—
	General health	50[a]	57[a]	48[a]	40[a]	—	—

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.

TABLE 4

Continued.

Study	QoL domain or summary score	Treatment group 1		Treatment group 2		Treatment group 3	
		Baseline	Post-TX	Baseline	Post-TX	Baseline	Post-TX
Morotti et al., 2014 (21)		Combined OC (cyclic)		Progestin		NA	
	PCS	44.41	45.0[a]	43.03	47.0[a,b,*,c,*]	—	—
	MCS	49.69	48.5[a]	49.57	52.0[a,b,*,c,*]	—	—

Note: Results are presented as mean values. All studies used the Short Form-36 questionnaire, except the study by Di Francesco & Pizzigallo 2014, which used Short Form-12.
Combined OC = combined oral contraceptive (E + progestin); MCS = mental component summary; NSAID = nonsteroidal anti-inflammatory drug; PCS = physical component summary; QoL = quality of life; TX = treatment; NA = not applicable because there was no third treatment group in the study.

[a] Value estimated from chart in published article.

[b] Significant difference versus baseline at the following level of significance: *$P < .05$;**$P \leq .01$;***$P < .001$.

[c] Significant difference versus comparator at the following level of significance: *$P < .05$;**$P < .001$.

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.

scores indicating better QoL (range, 0–100). One study used the Short Form-12 survey, an abbreviated version of the Short Form-36 (23).

Taken together, the findings from the RCTs support that QoL is improved with cyclic combined OC (23), continuous combined OC (26), GnRH agonist (23, 28), and oral progestin treatment (26) (Table 4). Although between-group comparisons did not demonstrate consistent significant differences, one study showed a trend favoring treatment with GnRH agonist plus add-back therapy versus cyclic combined OC or GnRH agonist alone (28), and another favored oral progestin use versus continuous combined OC treatment (26).

Data from observational comparative trials demonstrated QoL improvements from baseline with cyclic combined OC (18, 19), continuous combined OC (18), and continuous desogestrel POP treatment (21) (Table 4). Between-group comparisons significantly favored continuous combined OC versus cyclic combined OC use (18) and continuous desogestrel POP versus cyclic combined OC treatment (21).

Summary of Patient Satisfaction Findings

Patient satisfaction with treatment was assessed according to a 5-point Likert scale that rated patients as "very satisfied," "satisfied," "uncertain," "dissatisfied," or "very dissatisfied" in seven studies: two RCTs (26, 27), three observational comparative studies (20–22), and two observational, noncomparative studies (29, 32). To summarize, the highest levels of satisfied or very satisfied ratings were observed with the use of continuous combined OCs (62% (27), 67% (26), 69% (29), and 80% (32)), oral progestins (73% (26, 27)), continuous CVR (71% [22]), and POP (61% (20, 21)), and the lowest levels were observed with use of a continuous CHC transdermal patch (48% [22]), cyclic OC (38% [21]), and cyclic CVR (36% [20]). One study used a 7-point scale ("very highly satisfied" to "very highly dissatisfied"); in that study, ratings of "very highly" or "highly" satisfied were achieved by 43% of patients treated with continuous combined OC (15). It is noteworthy that all eight studies (15,20–22,26,27,29,32) evaluating patient satisfaction used an intention-to-treat analysis for this end point (Table 1), which suggests a high degree of reliability for these estimates.

DISCUSSION

Our review of the available literature shows that CHC treatment, administered cyclically or continuously, results in clinically important and statistically significant reductions from baseline in endometriosis-related pain. We found clinically significant reductions in dysmenorrhea according to 100-mm VAS scores in all the reviewed studies using this scale (17, 22, 26, 27, 29–32). We also found clinically significant reductions in noncyclic pelvic pain (15, 26, 27, 29, 30) and dyspareunia (22, 26, 27, 29). CHC treatment also resulted in improvements from baseline in QoL in most studies that measured this outcome.

In RCTs comparing cyclic CHC with GnRH agonist treatment, the latter treatment showed superiority in most studies, likely due to the induction of amenorrhea that resulted in complete resolution of dysmenorrhea (24, 25, 28). However, by inducing amenorrhea, continuous CHC treatment may

improve dysmenorrhea to a similar degree as the GnRH agonists. A well-designed double-blind RCT comparing GnRH agonist with add-back to a continuous combined OC found clinically and statistically significant reductions in pain (nonmenstrual pelvic pain and dyspareunia combined due to amenorrhea-inducing approaches) with both treatments, with no significant difference between groups (16). In the two RCTs (26, 27) comparing continuous combined OC with continuous oral progestin treatment, both groups demonstrated significant and similar reductions from baseline in endometriosis-related pain. Quality-of-life improvements (26) and patient satisfaction with treatment (26, 27) favored progestin use.

Treatment-associated decreases in pain parameters from baseline are informative, but can be misleading because of the placebo effect, which often produces a high response rate, particularly in studies of short duration (39). Interpretation of study findings for endometriosis-related pain and their clinical application is also complicated by many superimposed conditions that contribute to pelvic pain in women with endometriosis (5), and by the possibility that different types of endometriotic lesions may respond differently to treatment—a concern that is not well addressed in therapeutic trials (13). Furthermore, many women with no laparoscopic evidence of endometriosis have symptoms and respond to treatment in a similar manner to those with early stage endometriosis. Specific to the studies in this review, the most critical concern limiting interpretation and application of the findings is the lack of high-quality evidence. Of the 18 studies, only 2 (15, 17) were placebo controlled, only 3 (15–17) were blinded, and 4 (29–32) had no control group. All observational comparative trials in this review used a patient-preference design. The resultant lack of blinding in these studies, and in most of the RCTs, represents a potential source of bias. Furthermore, selection bias may have resulted in enrollment of participants with forms of endometriosis that are more severe (radiologic diagnoses) or treatment resistant (surgical diagnoses). Other potential limitations include differences among the studies in pain assessment timing and rescue analgesic use. Although daily pain assessment is recommended in studies of endometriosis-related pain (37), only 1 (15) of the 18 studies did this. The timing of post-baseline pain assessments in the remaining studies ranged from monthly to every 6 months, or the assessments were completed at study end. These differences in pain recall periods may contribute to overall variability in pain findings. Regarding use of rescue analgesics, some studies (15, 18, 21, 22, 27) directly measured supplementary analgesic use, and others (17, 24, 25, 26) indirectly measured analgesic use as a component of the verbal rating scale scores; however, half of the studies either did not mention supplementary analgesic use or stated that it was allowed but did not measure it. Thus, the impact of rescue analgesic use on these findings is difficult to estimate.

CHC agents block endogenous ovarian E_2 production and ovulation and create a progestin-dominant hormonal milieu that down-regulates the local E receptor response that fuels the proliferation of endometriotic lesions (40, 41). This progestin-dominant hormonal environment has been shown to reduce nerve fiber density (42) and inhibit angiogenesis (43) in endometriotic lesions. These mechanistic studies support the clinical evidence of benefit observed in CHC trials for the treatment of endometriosis-related pain. The additional suppression maintained by continuous administration of CHC and POPs above and beyond cyclic use likely explains the superiority of this dosing approach.

Our review supports the efficacy of CHC treatment for certain types of endometriosis-related pain. However, insufficient data exist to reach conclusions about the overall superiority of any given CHC therapy and the relative benefit in comparison to other approaches (3, 11, 12, 44–46). Recently, the European Society of Human Reproduction and Embryology (ESHRE) issued revised guidelines for the diagnosis and treatment of endometriosis (11). These guidelines recognize the limitations of the available literature, but support use of CHC agents as one of the options for first-line treatment. Advantages include the favorable cost of treatment (compared with GnRH therapies) and contraceptive benefit. Building on the available evidence, a recent editorial (47) accompanying the study by Harada and colleagues (15) points out that many patients with endometriosis who are on first-line combined OCs are not getting adequate pain relief and could be offered more complete therapy. For patients who fail to adequately respond to combined OCs or develop progestin resistance with disease progression despite using a progestin-based therapy, this editorial (47) suggests the consideration of GnRH agonist or, in the future, GnRH antagonist treatment. Ultimately, treatment selection should be driven by a full consideration of demonstrated efficacy and safety in conjunction with practical considerations and secondary benefits such as contraceptive protection, anticipated duration of treatment, mechanism of action, tolerability, and cost (3, 11, 46, 48).

Combined and progestin-only hormonal contraception present affordable and effective treatment options for women with endometriosis. Our review supports that these methods reduce menstrual and nonmenstrual pain and improve QoL. Continuous use may result in amenorrhea and further improve outcomes compared with cyclic use. Overall, the available literature is limited, but a consistency of effect is observed supporting these recommendations. Additional well-designed, head-to-head, comparative trials are needed to develop an evidence-based hierarchy of treatments for the optimal management of endometriosis-related pain.

Acknowledgments: The authors thank Darlene J. Benson, R.Ph., E.L.S., and Lamara D. Shrode, Ph.D., C.M.P.P., of JB Ashtin, for assistance in preparing this manuscript for publication based on the authors' input and direction. Michelle Koutsantonis, Ph.D., of AbbVie contributed to the literature search design and acquisition of the data.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fertnstert.2018.03.012.

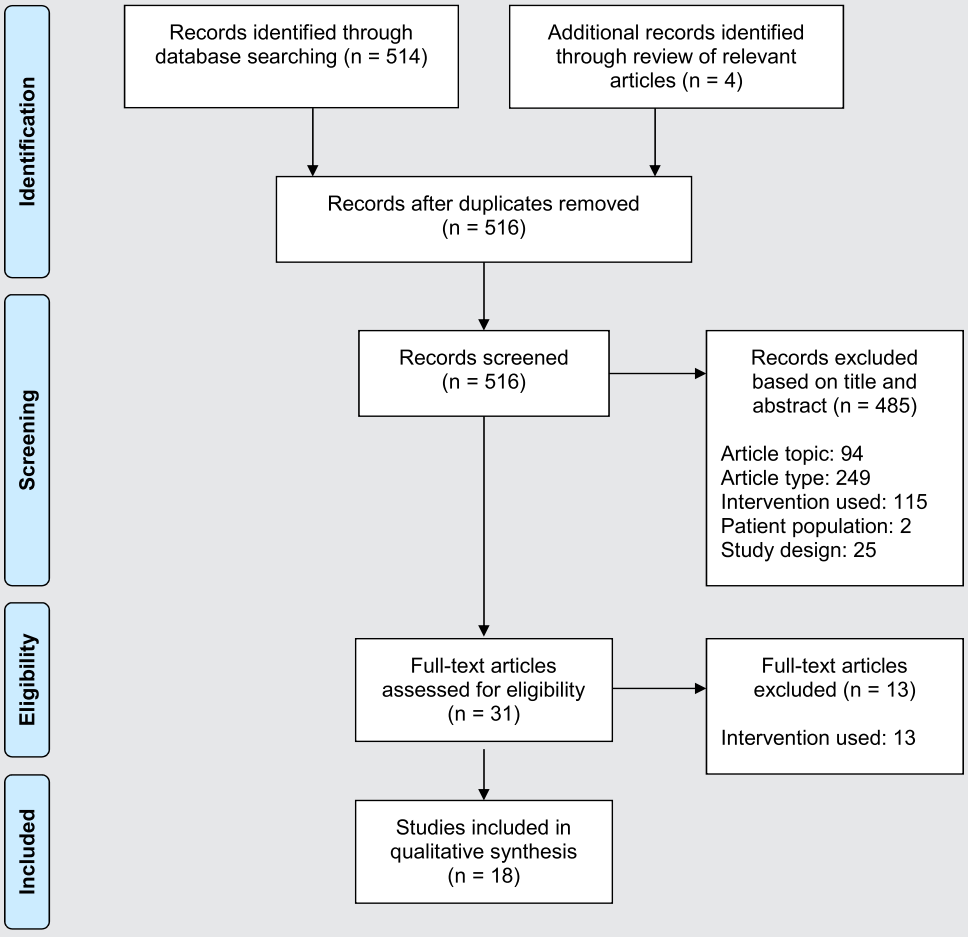
REFERENCES

1. American College of Obstetricians and Gynecologists (ACOG). Practice bulletin no. 114: management of endometriosis. Obstet Gynecol 2010; 116:223–36.

2. Howard FM. Endometriosis and mechanisms of pelvic pain. J Minim Invasive Gynecol 2009;16:540–50.
3. American Society for Reproductive Medicine (ASRM), Practice Committee. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril 2014;101:927–35.
4. Aredo JV, Heyrana KJ, Karp BI, Shah JP, Stratton P. Relating chronic pelvic pain and endometriosis to signs of sensitization and myofascial pain and dysfunction. Semin Reprod Med 2017;35:88–97.
5. Yosef A, Allaire C, Williams C, Ahmed AG, Al-Hussaini T, Abdellah MS, et al. Multifactorial contributors to the severity of chronic pelvic pain in women. Am J Obstet Gynecol 2016;215:760.e1–14.
6. Mowers EL, Lim CS, Skinner B, Mahnert N, Kamdar N, Morgan DM, et al. Prevalence of endometriosis during abdominal or laparoscopic hysterectomy for chronic pelvic pain. Obstet Gynecol 2016;127:1045–53.
7. Balasch J, Creus M, Fábregues F, Carmona F, Ordi J, Martinez-Román S, et al. Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: a prospective study. Hum Reprod 1996;11:387–91.
8. Buck Louis GM, Hediger ML, Peterson CM, Croughan M, Sundaram R, Stanford J, et al, ENDO Study Working Group. Incidence of endometriosis by study population and diagnostic method: the ENDO study. Fertil Steril 2011;96:360–5.
9. Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. Hum Reprod Update 2011;17:327–46.
10. 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;22:266–71.
11. Dunselman GAJ, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, de Bie B, et al. European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400–12.
12. Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. Fertil Steril 2017;107:533–6.
13. Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertil Steril 2017;108:125–36.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
15. Harada T, Kosaka S, Elliesen J, Yasuda M, Ito M, Momoeda M. Ethinylestradiol 20 μg/drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-associated pelvic pain: a randomized controlled trial. Fertil Steril 2017;108:798–805.
16. Guzick DS, Huang LS, Broadman BA, Nealon M, Hornstein MD. Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. Fertil Steril 2011;95:1568–73.
17. Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril 2008;90:1583–8.
18. Caruso S, Iraci M, Cianci S, Fava V, Casella E, Cianci A. Comparative, open-label prospective study on the quality of life and sexual function of women affected by endometriosis-associated pelvic pain on 2 mg dienogest/30 μg ethinyl estradiol continuous or 21/7 regimen oral contraceptive. J Endocrinol Invest 2016;39:923–31.
19. Grandi G, Xholli A, Napolitano A, Palma F, Cagnacci A. Pelvic pain and quality of life of women with endometriosis during quadriphasic estradiol valerate/dienogest oral contraceptive: a patient-preference prospective 24-week pilot study. Reprod Sci 2015;22:626–32.
20. Leone Roberti Maggiore U, Remorgida V, Scala C, Tafi E, Venturini PL, Ferrero S. Desogestrel-only contraceptive pill versus sequential contraceptive vaginal ring in the treatment of rectovaginal endometriosis infiltrating the rectum: a prospective open-label comparative study. Acta Obstet Gynecol Scand 2014;93:239–47.
21. Morotti M, Remorgida V, Venturini PL, Ferrero S. Progestogen-only contraceptive pill compared with combined oral contraceptive in the treatment of pain symptoms caused by endometriosis in patients with migraine without aura. Eur J Obstet Gynecol Reprod Biol 2014;179:63–8.
22. Vercellini P, Barbara G, Somigliana E, Bianchi S, Abbiati A, Fedele L. Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertil Steril 2010;93:2150–61.
23. Di Francesco A, Pizzigallo D. Use of micronized palmitoylethanolamide and trans-polydatin in chronic pelvic pain associated with endometriosis. An open-label study. Giorn It Ost Gin 2014;36:353–8.
24. Parazzini F, di Cintio E, Chatenoud L, Moroni S, Ardovino I, Struzziero E, et al. Estroprogestin vs. gonadotrophin agonists plus estroprogestin in the treatment of endometriosis-related pelvic pain: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. Eur J Obstet Gynecol Reprod Biol 2000;88:11–4.
25. Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60:75–9.
26. Vercellini P, de Giorgi O, Mosconi P, Stellato G, Vicentini S, Crosignani PG. Cyproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. Fertil Steril 2002;77:52–61.
27. 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;84:1375–87.
28. Zupi E, Marconi D, Sbracia M, Zullo F, de Vivo B, Exacustos C, et al. Add-back therapy in the treatment of endometriosis-associated pain. Fertil Steril 2004;82:1303–8.
29. Ferrari S, Persico P, DI Puppo F, Vigano P, Tandoi I, Garavaglia E, et al. Continuous low-dose oral contraceptive in the treatment of colorectal endometriosis evaluated by rectal endoscopic ultrasonography. Acta Obstet Gynecol Scand 2012;91:699–703.
30. Tanaka Y, Mori T, Ito F, Koshiba A, Kusuki I, Kitawaki J. Effects of low-dose combined drospirenone-ethinylestradiol on perimenstrual symptoms experienced by women with endometriosis. Int J Gynaecol Obstet 2016;135:135–9.
31. Taniguchi F, Enatsu A, Ota I, Toda T, Arata K, Harada T. Effects of low dose oral contraceptive pill containing drospirenone/ethinylestradiol in patients with endometrioma. Eur J Obstet Gynecol Reprod Biol 2015;191:116–20.
32. Vercellini P, Frontino G, de Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. Fertil Steril 2003;80:560–3.
33. Zanardi R, del Frate C, Zuiani C, Bazzocchi M. Staging of pelvic endometriosis based on MRI findings versus laparoscopic classification according to the American Fertility Society. Abdom Imaging 2003;28:733–42.
34. Peterson CM, Johnstone EB, Hammoud AO, Stanford JB, Varner MW, Kennedy A, et al, ENDO Study Working Group. Risk factors associated with endometriosis: importance of study population for characterizing disease in the ENDO Study. Am J Obstet Gynecol 2013;208:451.e1–11.
35. Biberoglu KO, Behrman SJ. Dosage aspects of danazol therapy in endometriosis: short-term and long-term effectiveness. Am J Obstet Gynecol 1981;139:645–54.
36. Andersch B, Milsom I. An epidemiologic study of young women with dysmenorrhea. Am J Obstet Gynecol 1982;144:655–60.
37. Bourdel N, Alves J, Pickering G, Ramilo I, Roman H, Canis M. Systematic review of endometriosis pain assessment: how to choose a scale? Hum Reprod Update 2015;21:136–52.
38. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med 2001;38:633–8.

39. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of endometriosis-associated pain with Elagolix, an oral GnRH antagonist. N Engl J Med 2017;377:28–40.
40. Somigliana E, Vercellini P, Vigano P, Abbiati A, Benaglia L, Fedele L. Endometriosis and estroprogestins: the chicken or the egg causality dilemma. Fertil Steril 2011;95:431–3.
41. Maia HJ, Casoy J. Non-contraceptive health benefits of oral contraceptives. Eur J Contracept Reprod Health Care 2008;13:17–24.
42. Tarjanne S, Ng CHM, Manconi F, Arola J, Mentula M, Maneck B, et al. Use of hormonal therapy is associated with reduced nerve fiber density in deep infiltrating, rectovaginal endometriosis. Acta Obstet Gynecol Scand 2015;94:693–700.
43. Laschke MW, Menger MD. Anti-angiogenic treatment strategies for the therapy of endometriosis. Hum Reprod Update 2012;18:682–702.
44. Brown J, Farquhar C. An overview of treatments for endometriosis. JAMA 2015;313:296–7.
45. Davis L, Kennedy SS, Moore J, Prentice A. Oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev 2007;(3):CD001019.
46. Vercellini P, Buggio L, Berlanda N, Barbara G, Somigliana E, Bosari S. Estrogen-progestins and progestins for the management of endometriosis. Fertil Steril 2016;106:1552–71.
47. Taylor HS. Clinical diagnosis of endometriosis and optimal medical therapy. Fertil Steril 2017;108:759–60.
48. Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain 2009;146:238–44.

SUPPLEMENTARY FIGURE 1



Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

Jensen. Hormonal contraceptives in endometriosis. Fertil Steril 2018.