ORIGINAL ARTICLE: ENDOMETRIOSIS

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

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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

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(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