

Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills

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For decades, combined estrogen-progestin oral contraceptive pills (OCPs) have been the first-line treatment for menstrual and pelvic pain associated with endometriosis without any clinical evidence of efficacy. Initial relief provided by OCPs is likely a result of improvement in primary dysmenorrhea. Biologic data and limited clinical evidence support a potential adverse effect of long-term use of OCPs on the progression of endometriosis. In contrast, there is randomized, controlled trial data to support the use of oral progestin-only treatment for pelvic pain associated with endometriosis and for suppressing the anatomic extent of endometriotic lesions. Both norethindrone acetate and dienogest have regulatory approval for treating endometriosis and may be better than OCPs as a first-line therapy. (Fertil Steril® 2017;107:533–6. ©2017 by American Society for Reproductive Medicine.)

Key Words: Dienogest, endometriosis, norethindrone acetate, oral contraceptives, progestins

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Combined estrogen-progestin oral contraceptive pills (OCPs) have been used for decades as the first-line treatment for endometriosis despite an absence of controlled data regarding their effectiveness. In my opinion, based on assessment of the scientific and clinical data, OCPs should be supplanted by oral progestin-only therapy as the first line of treatment for chronic pelvic pain associated with endometriosis. Readers should note that my opinion in this regard runs contrary to the guidelines for the management of endometriosis from every gynecologic society, including the American College of Ob-

stetrics and Gynecology (ACOG), the American Society for Reproductive Medicine (ASRM), the European Society for Human Reproduction and Endocrinology (ESHRE), and the Canadian Fertility and Andrology Society (CFAS) (1–4), all of whom regard OCPs as the initial treatment option for endometriosis-associated pelvic pain and dysmenorrhea not responsive to nonsteroidal anti-inflammatories. My opinion is also in conflict with the recent comprehensive review published by Vercellini et al. (5) in which they suggested that combined estrogen and progestin should be the first-line therapy of endometriosis pain, followed by

progestin-only treatment in the case of a contraindication to estrogen.

Oral contraceptive pills are an intuitive choice for treatment of pain associated with endometriosis. In women with primary dysmenorrhea, OCPs thin the endometrium, thereby reducing the amount of bleeding and inhibiting the metabolism of arachidonic acid to prostaglandins (6, 7), effectively relieving cramping and pain. Because endometriotic implants have the morphologic appearance of endometrium, containing both epithelial glands and stroma, the natural assumption is that OCPs will have the same effect of decreasing the growth of implants as they do with eutopic endometrium. This assumption may not be correct, as I will explain later. In addition, OCPs generally have a high safety level and are inexpensive, and most family doctors and general gynecologists feel comfortable prescribing them. Patients also have a high comfort level with

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OCPs because many of their friends may be taking them for birth control or even for painful periods with good success. In addition, OCPs can be used to stop periods if given continuously. Based on this anecdotal evidence, OCPs have been used (off label) for decades to treat endometriosis.

Surprisingly, only one randomized, placebo-controlled clinical trial has ever been published to investigate the effectiveness of OCPs for pelvic pain and dysmenorrhea in patients with endometriosis (8). In this study, 100 women were randomized to an OCP or placebo, and a statistically significant though modest improvement was found in dysmenorrhea with OCP administration for 4 months when compared with placebo. The OCP resulted in about a 50% reduction in dysmenorrhea as determined by linear analogue pain scoring (shown in Fig. 1). One could argue that all the improvement in pain may be attributed to the reduction of primary dysmenorrhea (PG-related), which may still occur in women with endometriosis, without any effect on the pain associated with endometriosis. This speculation is supported by the lack of any beneficial effect of the OCP on non-menstrual pelvic pain and dyspareunia in these endometriosis patients (8).

There are other, relatively old, noncontrolled studies of OCPs in the treatment of pelvic pain and dysmenorrhea in women with documented endometriosis, and these show that about 50% of patients have partial or no improvement in symptoms (9). Of interest, an international study of women's perception of pain and bleeding in endometriosis enrolled 441 women between the ages of 15 to 49 years in eight countries, including Canada and the United States (10). The women were interviewed using an online questionnaire. The responses about OCP use by patients with diagnosed endometriosis demonstrated that about 70% of women had used multiple OCPs for relief of endometriosis pain and over 40% had been prescribed between 3 and 10 different OCPs for endometriosis (Table 1). These data suggest that there was recurrence of pelvic

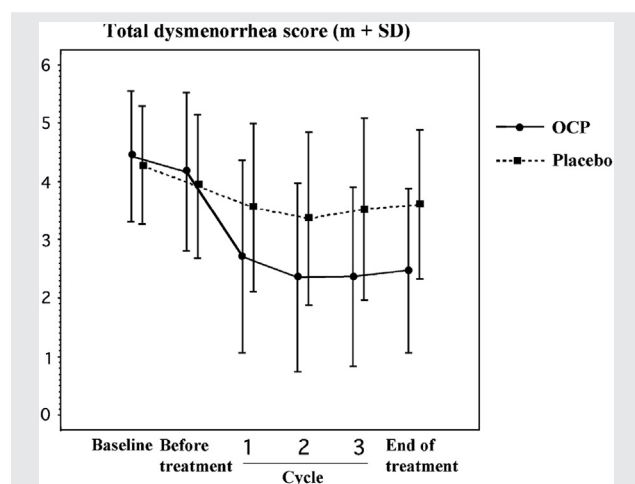
pain while taking an OCP and that the patients were switched to a different OCP in the hope of alleviating the pain. This further supports the concept that OCP use is not completely effective in the treatment of endometriosis. Furthermore, switching from one OCP to another because of ineffectiveness of pain relief may lead to a delay in the diagnosis of endometriosis. Nevertheless, OCPs have remained the first line of treatment for endometriosis pain.

Why might an OCP be relatively ineffective in diminishing the activity of endometriosis implants when it is so effective in thinning the eutopic endometrium? Basic research findings suggest the answer to this question, and these studies are summarized nicely in two review articles by Bulun et al. (11, 12). In normal eutopic endometrium, estrogen in the follicular phase acts through the estrogen receptor (ER) to increase transcription and protein levels of the progesterone receptor (PR), especially the PR-B isoform (13). During the luteal phase, progesterone acts through PR-B to down-regulate ER and increase the transcription and secretion of the enzyme 17 β -hydroxysteroid dehydrogenase type 2 (HSD17B2) (12), which catalyzes the conversion of estradiol to the less active estrone. This effect is transcriptionally regulated by downstream PR-B signaling involving retinoic acid and Sp1/Sp3-dependent pathways (14). In endometriotic implants, ER- α is reduced but ER- β activity is markedly up-regulated (15, 16), leading to complete loss of PR-B (17) and the inability to induce HSD17B2 (12). Endometriosis implants, therefore, demonstrate resistance to progesterone and have augmented estrogen activity.

Low-dose OCPs contain 20 to 30 μ g of ethinyl estradiol (EE). Basic research (18) and data from clinical menopausal hormone therapy (19) suggest that 5 μ g of EE is equivalent to about 1 mg of micronized estradiol or 0.625 mg of conjugated equine estrogen. Therefore, the dose of EE in a low-dose OCP is equivalent to 4 to 6 times the physiologic dose of estrogen. The OCPs also contain a progestin designed to antagonize the estrogen effect on the endometrium. Based on the previously described evidence for ER and PR alterations in endometriosis, it is likely that administering a high dose of estrogen and progestin in an OCP is counterproductive, resulting in estrogen dominance in the presence of progesterone resistance. In fact, based on their review of earlier work by Dizerega et al. (20), Vercellini et al. (21) suggested that the presence of supraphysiologic concentrations of estrogen with the OCP, during what should be the low-estrogen menstrual phase, may rescue endometrial cell clusters deposited in the pelvis during retrograde menses.

There are other, albeit limited, data suggesting an adverse effect of OCPs on endometriosis. A recent meta-analysis looked at the risk of developing endometriosis in women who were current or past users of OCPs. The investigators showed a reduced risk of endometriosis in current users of OCPs but an increase in endometriosis risk in past users of OCPs (21). Chapron et al. (22) also reported an increased incidence of endometriosis in past users of OCPs. It may seem incongruous that there is an observed increased risk of endometriosis in past but not present users of OCPs. However, this finding is consistent with the fact that the large majority of women currently using OCPs are taking them for

FIGURE 1



Changes in mean dysmenorrhea score determined by linear analogue scale comparing an oral contraceptive pill (OCP) with placebo. Source: Harada et al. 2008 (8). Copyright Elsevier, and the American Society for Reproductive Medicine.

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TABLE 1

Number of different oral contraceptive pills (OCPs) used for relief of symptoms in 441 women with diagnosed endometriosis globally and broken down by country.

| No. of OCPs tried | Global (n = 441) | United States (n = 110) | Canada (n = 53) | Italy (n = 60) | France (n = 25) | Germany (n = 32) | United Kingdom (n = 48) | Brazil (n = 76) | South Korea (n = 7) |
|-------------------|------------------|-------------------------|-----------------|----------------|-----------------|------------------|-------------------------|-----------------|---------------------|
| 1 | 28 | 28 | 34 | 40 | 52 | 32 | 25 | 20 | 46 |
| 2 | 28 | 23 | 22 | 35 | 36 | 15 | 36 | 33 | 29 |
| 3–5 | 28 | 29 | 28 | 16 | 8 | 41 | 31 | 27 | 24 |
| 6–10 | 15 | 15 | 16 | 8 | 4 | 13 | 6 | 20 | 0 |
| >10 | 2 | 3 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |

Note: Values are percentages unless otherwise indicated.

Source: Bernuit et al. 2011 (10). With permission from Bayer Global; data on file.

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contraception or for relief of primary dysmenorrhea and are completely satisfied. One could speculate that those women with underlying endometriosis may eventually stop the OCP because of incomplete relief of pain and then eventually have a laparoscopy for diagnosis. This explanation suggests that the increase in endometriosis in past users is an artifact of OCP ineffectiveness in treating endometriosis.

In the study of Chapron et al. (22), an additional finding was a large increased risk of deep infiltrating endometriosis (adjusted odds ratio 16.2; 95% confidence interval, 7.8–35.3) in women who had taken OCPs in the past because of what was diagnosed as primary dysmenorrhea. This finding not only suggests the eventual failure of the OCP to relieve the pain associated with endometriosis but also supports the hypothesis that the large dose of estrogen in the OCP could lead to progression of the disease to a more invasive type.

Finally, there are some practical limitations to the use of combined oral contraceptives, which are contraindicated in women older than 35 years who smoke or who may be at increased risk of myocardial infarction, stroke, or venous thromboembolism (23). We have also demonstrated that the use of OCPs for several years may result in endometrial thinning that is nonresponsive to estrogen (24). This previously unrecognized side effect of long-term OCP use may be important for women with endometriosis who wish to conceive in the future.

Given these uncertainties about the appropriateness of using OCPs for managing the pelvic pain and dysmenorrhea associated with endometriosis, I believe that the time has come to replace the OCP as the first line of treatment for endometriosis with oral progestin-only medications such as norethindrone acetate (NETA) or dienogest. One could ask why progestins alone would work if endometriosis represents a progesterone-resistant condition. Progestins alone, in milligram per day doses, generally inhibit ovulation (25, 26) and induce amenorrhea, which should prevent dysmenorrhea. The decrease in gonadotropin secretion induced centrally by the action of potent progestins will result in a relatively hypoestrogenic state that could help suppress endometriosis and certainly should prevent progression of the disease. Generally, these treatments still result in enough endogenous estrogen to spare bone mineral density (27), and the oral progestins themselves may have a positive

effect on bone formation (28). In addition, progestins have been shown to have anti-inflammatory and antiangiogenic activity (29–32), both of which will have a beneficial effect on the progression of endometriosis and the pain associated with the condition. Progestins also may decrease expression of matrix metalloproteinases, thereby decreasing the invasiveness of endometriosis implants (33).

In contrast to the OCP for endometriosis, there are several placebo-controlled trials showing the efficacy of progestins alone in alleviating the chronic pelvic pain and dysmenorrhea associated with endometriosis (27,34–36). Orally administered medroxyprogesterone acetate, one of the earliest studied progestins, was shown to be better than placebo in relieving endometriosis pain (37). Norethindrone acetate (NETA) has been approved by the U.S. Food and Drug Administration for the treatment of endometriosis. Early studies showed a beneficial effect in endometriosis at doses of 2.5 to 5.0 mg daily (26). Medroxyprogesterone acetate and NETA in these early studies, unlike OCPs, completely eliminated pelvic pain and dysmenorrhea in women with endometriosis and decreased implant size on second-look laparoscopy (25) or decreased endometrioma size on ultrasound (26). Similarly, dienogest is a 19-nortestosterone derivative that has more recently received regulatory approval for treatment of endometriosis in Europe and Canada after placebo-controlled (27) and other comparative trials (38). Dienogest and NETA appear to be equally effective in alleviating pain and decreasing lesion size in endometriosis (39). Although NETA is less expensive, dienogest is slightly better tolerated because of fewer side effects (39). In addition, there is evidence that progestin-only therapy may be as effective for pain relief as second-line therapies such as gonadotropin-releasing hormone agonists (40, 41).

In conclusion, once endometriosis is suspected or proven as the cause of chronic pelvic pain, an OCP may not be the best treatment option and could potentially lead to progression of the disease. The beneficial effect of OCPs observed in the past may have been entirely due to relief of primary dysmenorrhea with little or no beneficial effect on the underlying endometriosis. Based on controlled trial data, it appears that women with suspected or confirmed endometriosis may do better with oral progestin-only treatment as the first-line therapy because progestins have demonstrated benefits in

reducing pain and suppressing the anatomic extent of endometriotic lesions. Oral progestins alone can be used at any age, do not increase the risk of thrombosis, and are capable of inhibiting ovulation and inducing amenorrhea with very few side effects.

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