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Options for relief from symptoms suggesting endometriosis

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INTRODUCTION

Many women experience vague symptoms of pelvic pain or discomfort that may stem from endometriosis. Rather than undergo laparoscopy for a definitive diagnosis, patients may prefer to focus on symptom relief. For these patients, clinicians should focus on agents and regimens that control symptoms and reduce menstrual bleeding and endometrial stimulation.

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THE CASE

- 25-year-old gravida 0, para 0
- Significant premenstrual abdominal pain interferes with daily activities
- Pain occurs prior to onset of menses, is accompanied by lower back pain, and continues for several days beyond cessation of menses
- Duration of menses is 7 to 8 days, and her menstrual cycle averages 26 days
- Frequent sense of bloating and premenstrual syndrome is associated with her menstrual cycle
- Acne is associated with menstrual cycle

LEARNING OBJECTIVES

Upon completion of this case study, the reader should be able to:

- Evaluate clinical signs that suggest endometriosis
- Discuss treatment options in terms of patient preferences; that is, definitive diagnosis or relief of symptoms irrespective of diagnosis
- Select appropriate contraceptive agents for symptom relief, with consideration of patient needs relative to contraception
- Evaluate currently available contraceptive agents and regimens regarding relief of symptoms, including pelvic pain, bloating, and other symptoms

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TABLE 1

Symptoms and Hormone Withdrawal (n = 262)

	21 Active Pill Days (% Sx)	7 Hormone-free Days (% Sx)	P value
Pelvic pain	21	70	<.001
Headaches	53	70	<.001
Breast tenderness	19	58	<.001
Bloating/swelling	16	38	<.001
Use of pain meds	43	69	<.001

Sulak PJ, et al. *Obstet Gynecol.* 2000;95:261-266.

TABLE 2

Reasons for Extending Active Pills (n = 292)

	Primary Reason*	% with Sx**
Headache	35%	46%
Dysmenorrhea	21%	41%
Hypermenorrhea	15%	30%
Premenstrual Sxs	13%	22%
Other	12%	100%

*Most severe symptom
**Most had more than one Sx.
Sulak PJ, et al. *Obstet Gynecol.* 2002;186:1142-1146.

PATIENT HISTORY

The patient reports that her mother and sister have had treatment for endometriosis. For her mother, repeated surgical interventions including hysterectomy were required. Her older sister opted for treatment with oral contraceptives (OCs) in lieu of a definitive surgical diagnosis and treatment. She has remained pain free for several years.

The patient had wanted to become pregnant and was unsuccessful; however, new job responsibilities have made her decide to postpone pregnancy. She is unsure as to when she might desire pregnancy in the future. She experiences increasingly annoying episodes of acne.

DIAGNOSTIC WORKUP

This patient likely has endometriosis, although laparoscopy is required for confirmation. While the etiology of endometriosis remains unclear,[1] factors associated with increased risk of developing endometriosis include having first- or second-degree relatives with the disease, menstrual cycles less than or equal to 27 days, and a duration of menses of 7 or more days. Dysmenorrhea, outflow obstruction, and younger age at menarche also increase risk.[2] Additionally, this patient's prior unsuccessful attempts at pregnancy may have been the result of endometriosis; endometrial implants often result in pelvic scarring and adhesions that distort normal anatomy and prevent normal tubal function.

OPTIONS FOR THIS PATIENT

A laparoscopy should be encouraged to document endometriosis in this patient, although she is primarily concerned about symptom relief and is not interested in obtaining a definitive diagnosis. Thus, it may be most useful to begin a trial of treatment with contraceptive agents: She does not wish to become pregnant and is already interested in using such agents for symptom relief. Available agents should be considered that may offer symptom relief as a result of beneficial effects on the endometrium.

Oral contraceptives

Continuous OCs have been used for decades to treat endometriosis. Administration of OCs result in suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). They also have direct atrophic effects on endometrial tissue. It is generally believed that the disease progresses with repetitive menstrual cycles; therefore, the effects of OCs on regulation of the menstrual cycle and on reducing the duration and amount of bleeding may be important for this patient. Improved control of the menstrual cycle will reduce menstrual volume and likely result in decidualization of endometrial implants and reduction in menstrual reflux.[3-5] Probably for these reasons, OCs provide pain relief.

Patients experiencing the symptoms of endometriosis often are instructed to use OCs without a hormone-free interval, unless they develop bothersome breakthrough bleeding or spotting.

When that occurs, they are advised to cease OC use for 3 to 4 days and then resume active pills.

The relation between the hormone-free interval and menstrual symptoms has been studied by Sulak's group (**FIGURE, TABLES 1 AND 2**).[6,7] Most recently, these investigators evaluated a shortened hormone-free interval of 0 to 4 days in 181 women. Menstruation-related side effects were reduced significantly. Further, most women who used a shortened hormone-free interval did not discontinue OC use because of breakthrough bleeding.[8]

Traditionally, OCs that are progestin-dominant, such as those containing levonorgestrel, have been chosen to treat endometriosis; however, no OC has been shown to be superior to others for such treatment. The choice of OC for this patient should address her menstruation-related symptoms of bloating, premenstrual syndrome (PMS), and acne.

She considers her symptoms severe. Therefore, modification of the standard OC regimen may be appropriate: Patients with severe symptoms or symptoms that persist during OC therapy should consider continuous use of OCs in a regimen that includes shortening the standard 7-day hormone-free interval. Recent investigations have demonstrated that severity and duration of menstrual symptoms can be reduced by shortening the traditional 7-day hormone-free interval.

The levonorgestrel-releasing intrauterine system (LNG-IUS)

This device also represents a viable option for control of her bleeding and dysmenorrhea. Like OCs, the LNG-IUS regulates the menstrual cycle and reduces menstrual bleeding. Of the women who choose this regimen, 20% typically become completely amenorrheic[9] and others experienced significantly reduced bleeding, generally 1 day of bleeding/spotting after 1 year.

The LNG-IUS may not be appropriate for this patient. It may cost more initially. Given this patient's lack of certainty regarding childbearing, the LNG-IUS could represent an unnecessary expense. However, for patients looking for long-term contraception, the LNG-IUS is more cost-effective than OCs.[10] In discussion of the available options, the patient elects to strongly consider this option once her plans for future pregnancy become more finalized.

Medroxyprogesterone acetate

Ovarian suppression and a direct effect on the endometrial implants are obtained with this drug; however, the slow return to fertility following discontinuation would be a disadvantage to a woman such as the patient in question who wishes to conceive in the future.

Gonadotropin-releasing hormone analogues

Leuprolide acetate and goserelin acetate are certainly effective means of treating endometriosis. Because of their cost, however, they should be reserved for laparoscopically confirmed cases of endometriosis and for those patients with significant symptoms.

SELECTION OF OC AGENT FOR CONTROL OF SIDE EFFECTS

Oral contraceptives have traditionally contained progestin formulations derived from 19-nortestosterone. One OC includes a new progestin, drospirenone (DRSP) that is not derived from 19-nortestosterone and is an analogue of spironolactone. It provides antiandrogenic and antimineralocorticoid activities that should ameliorate this patient's side effects. For this reason, it represents the most appropriate choice for this patient. A review of its properties follows.

The perception of weight gain and bloating

When asked about their concerns regarding OCs, most women will mention the fear of weight gain. Drospirenone, as an analogue of spironolactone, reduces the menstruation-related bloating effect and perception of weight gain. This may be because its antimineralocorticoid action increases sodium and water excretion, resulting in a diuretic effect. Potassium retention may be a side effect; therefore, DRSP would be inappropriate for use in patients with kidney, adrenal, or liver disease. A European randomized, open-label trial compared the effects of EE, 30 µg/DRSP, 3 mg, with EE, 30 µg/desogestrel, 150 µg. Over 26 cycles, the EE 30 µg/desogestrel 150-µg group appeared to demonstrate a weight change likely to be consistent with an expected normal change over time in reproductive-age women (mean increase of 0.2 kg at 1 year and 1 kg at 2 years). The EE 30 µg/DRSP 3-mg

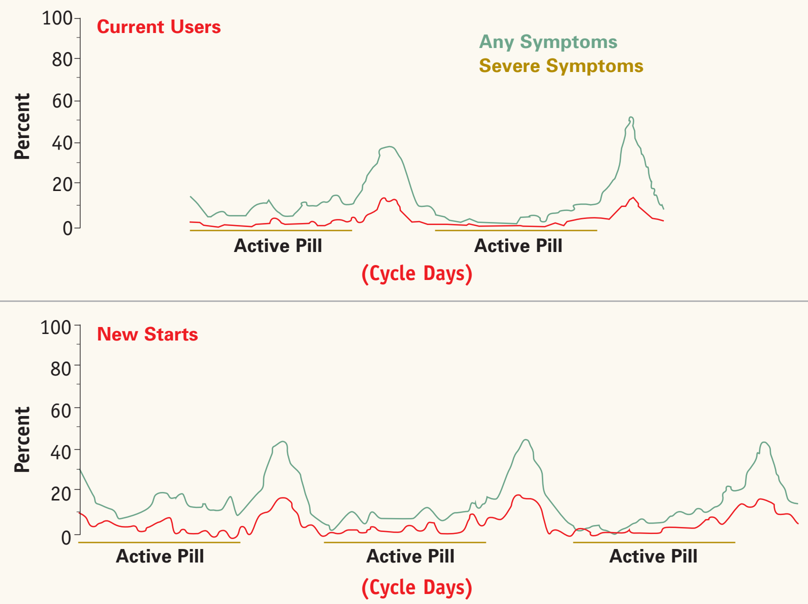
group, however, had a mean decrease of approximately 0.5 kg at 1 year, which remained below baseline at 24 months. Additionally, after 2 years of EE 30 µg/DRSP 3-mg use, the population average had decreased by approximately 0.2 kg as compared with baseline.[11]

DRSP and reduction in PMS/PMDD symptoms

It has been estimated that PMS affects up to 80% of women.[12] Androgenic effects have been theorized to be responsible for PMS and premenstrual dysphoric disorder (PMDD) symptoms such as irritability and mood swings. In several small trials, spironolactone, with its antiandrogenic activity, has shown benefits for PMS/PMDD symptoms.[13-16]

FIGURE

Pelvic pain and OC use: timing and severity of symptoms (n = 262)



Sulak PJ, et al. Obstet Gynecol. 2000;95:261-266.

Recent studies have shown that EE/DRSP treats PMS/PMDD. In a trial of 80 patients, DRSP and EE were administered on a 21/7 regimen.[17] Although the trial was not sufficiently powered, statistically significant improvements were shown in one aspect of the Calendar of Premenstrual Experiences scale.

A larger study[18] enrolled 858 women to evaluate the effects of EE/DRSP on such premenstrual symptoms as water retention, negative effect, and health-related quality of life. Significant improvement was reported for all 13 Menstrual Distress Questionnaire items during the late luteal phase and menses. Over the remainder of the cycle, most items showed improvement. The mean Mental Component Summary scale scores of the Short Form 12-Item Health Survey (SF-12) also were improved.

DRSP and improvement in acne

This patient reports increasingly annoying episodes of acne. All OCs will improve acne, but DRSP has shown results surpassing the effects of another antiandrogenic progestin, cyproterone acetate (CPA), which is approved for treatment of acne in many countries but not in the United States. The latter progestin has been shown to be effective in treating pronounced forms of acne and those accompanied by seborrhea or by inflammation or formation of nodes (acne papulopustulosa, acne nodulocystica), androgenetic alopecia, and mild forms of hirsutism. The effects of DRSP and CPA were compared in a recent study.[19] Another study comparing an OC that contains DRSP with a triphasic norgestimate OC also demonstrated superiority of the DRSP-containing OC for acne.[20]

DISCUSSION

This patient is fairly typical, in that onset of endometriosis usually occurs between the ages of 25 and 29 years.[21] Approximately 24% of women who complain of pelvic pain are diagnosed with endometriosis.[22] However, prevalence is difficult to determine: Many asymptomatic women are diagnosed with endometriosis at

the time of unrelated surgical intervention.

It should also be noted that the etiology of endometriosis is unknown. Theories include retrograde menstruation, vascular spread, coelomic etaplasia, and immunologic causes. Retrograde menstruation likely accounts for the presence of endometrial cells within the peritoneal cavity. Normal immunologic response allows for the clearing of these cells; however, an altered response may encourage development of endometriosis.[23-25] Of concern to clinicians is the fact that severity of symptoms does not always correlate with severity of disease. A patient who is asymptomatic or has very mild symptoms may have extensive disease, and a woman with few visible lesions may experience extensive pain.

CONCLUSION

This case represents a challenge for the physician: While a definitive diagnosis through laparoscopy would be ideal, the patient is interested in symptom relief. Therefore, a trial of OC therapy represents an appropriate treatment. The clinician should consider the agent that is most likely to resolve her symptoms of pelvic pain, as well as other symptoms associated with menstruation.

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Options for relief from symptoms suggesting endometriosis

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1. Factors associated with increased risk for endometriosis include
- a) First- or second-degree relative with the disease
- b) Menstrual cycles longer than 27 days
- c) Duration of menses of 8 or more days
- d) All of the above

2. Only oral contraceptives containing progestins with antimineralocorticoid properties provide relief of which menstrual symptom(s)?
- a) Bloating
- b) Pelvic pain
- c) Acne
- d) All of the above

3. Oral contraceptives improve endometriosis through
- a) Atrophic effects on endometrial tissue
- b) Suppression of luteinizing hormone
- c) Suppression of follicle-stimulating hormone
- d) All of the above

4. Approximately what percentage of women who complain of pelvic pain are diagnosed with endometriosis?
- a) 18
- b)32
- c) 5
- d) 24

5. The etiology of endometriosis is uncertain but may include
- a) Retrograde menstruation
- b) Vascular spread
- c) Immunologic factors
- d) All of the above

6. Symptoms of endometriosis generally correlate with disease severity.
- a) True
- b) False

7. Symptoms of endometriosis generally appear in women of what ages?
- a) Teens
- b) 20s
- c) 30s
- d) 40s

8. In a recent study, pelvic pain was experienced by what percentage of women during the 7-day hormone-free interval?
- a) 50
- b) 60
- c) 70
- d) 80

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