

Ovulation Suppression of Premenstrual Symptoms Using Oral Contraceptives

Patricia J. Sulak, MD

Abstract

Managing premenstrual symptoms at the most fundamental level necessitates careful consideration of female reproductive biology. Inhibiting ovulation using hormonal agents is a reasonable approach for reducing premenstrual symptoms, but the benefits of agents such as gonadotropin-releasing hormone agonists and the synthetic androgen danazol are largely offset by their adverse effects and costs. Combination oral contraceptives provide an alternative that is widely accepted by women experiencing premenstrual symptoms and by their physicians; and newer formulations with lower levels of estrogen and progesterin, administered using a monthly regimen with a shortened pill-free interval, appear promising for alleviating patient distress from severe premenstrual symptoms.

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The biology of menstrually related symptoms involves either direct or indirect interaction of the ovarian cycle with key hormones, neurotransmitters, or other substances.¹ A menstruating woman may experience symptoms in the late luteal phase of her ovulatory cycle throughout her childbearing years. To provide relief for women who suffer moderately or severely from any combination of these symptoms, it would seem prudent to seek a solution that works in tandem with female physiology to restore health-related quality of life and an overall sense of well-being with the fewest possible adverse effects.

Symptoms related to the menstrual cycle may be limited to mild discomfort or extend to premenstrual syndrome (PMS) or to premenstrual dysphoric disorder (PMDD), which would include severe emotional and somatic impairment. Only limited research on alleviation of menstrual symptoms has been conducted to date on women meeting

the diagnostic criteria published by the American College of Obstetricians and Gynecologists² for PMS and by the American Psychiatric Association for PMDD.³ However, research on premenstrual symptoms in general may provide strategies for effective treatments for PMS and PMDD.

Ovulation Suppression

Premenstrual symptoms occur almost exclusively in ovulatory cycles; therefore, inhibiting ovulation could be expected to reduce or eliminate these symptoms. Gonadotropin-releasing hormone (GnRH) agonists can be used to suppress ovulation and effectively alleviate premenstrual symptoms. However, because using GnRH agonists leads to a hypoestrogenic state, "add-back" hormone therapy with estrogen or estrogen/progesterone is necessary to prevent menopausal symptoms such as hot flashes and to minimize bone loss that could occur with steady use.⁴ These agents are costly and are not recommended for long-term use.

Another hormonally mediated possibility, the synthetic androgen danazol, suppresses ovulation as well, but its use is limited by an array of adverse effects. These include weight gain; decreased high-density lipoprotein cholesterol, which may increase the risk of cardiovascular disease; and, at higher doses, the possibility of greater facial hair growth and severity of acne.⁴ Like GnRH agonists, danazol is not recommended for long-term use.

Combination oral contraceptives (OCs), which contain estrogen and one of several

Address correspondence to: Patricia J. Sulak, MD, Scott & White Hospital and Clinic, 2401 S. 31st Street, Temple, TX 76508.

progestins, are commonly prescribed hormonal agents providing a variety of noncontraceptive health benefits, aside from preventing pregnancy. Combination OCs have been widely used to treat physical premenstrual symptoms. Women and their physicians have a high level of comfort with their use, and OC users benefit from their relatively low cost and positive effects on the menstrual cycle.

Few controlled trials have evaluated OCs for their effects on premenstrual symptoms, and past studies demonstrated little difference in the experience of OC users and nonusers in this regard.^{5,6} Evidence for OC effects on premenstrual symptoms is weakened, according to a recent review of the medical literature, by the fact that early studies were conducted using OCs with the high estrogen doses commonly employed at that time. The reduced estrogen doses in current OC formulations may result in a decreased degree of ovarian inhibition compared with that afforded by older OCs, especially during the pill-free interval.⁷

In the female reproductive system, the degree of follicular activity during OC use is dependent on the type and dose of steroids used, the type of regimen, user adherence, and individual metabolic responsiveness to the OC prescribed.⁷ Early OC formulations with high doses of estrogen and progestin caused many adverse effects, including nausea, breast tenderness, and fluid retention. These symptoms resulted in a high rate of premature discontinuation of use, and therefore hormone doses in combined OCs have been reduced. OCs inhibit follicular development, and high-dose OCs maintain steroid levels sufficient to suppress ovarian function during the pill-free interval; with low-dose OCs, however, effective serum levels of ethinyl estradiol (EE) are maintained for only 2 to 3 days after administration is suspended, and follicular development may resume because of inadequate endocrine suppression.⁸

Patient adherence is another crucial factor when low-dose OCs are used. The risk of ovulation is at its maximum during the 7-day pill-free interval, and the risk of pregnancy increases substantially for a woman using these formulations if she does not

start her new pill pack on time. In addition, individual women metabolize medications differently, and faster metabolism may jeopardize the efficacy of low-dose pills.

The Standard OC Regimen

In studies of women with premenstrual symptoms, OCs have typically been administered using a standard regimen (21/7 regimen) consisting of 21 days of estrogen-plus-progestin pills, followed by 7 pill-free days (in some regimens, placebo pills may be taken on pill-free days to increase the likelihood of timely resumption). This 21/7 regimen closely mimics a woman's average 28-day cycle—indeed, the regimen was developed with this average cycle in mind—and is also used with other contraceptive methods, such as the patch and the vaginal ring. Women who take hormonal contraceptives using this standard regimen have a monthly withdrawal bleed that traditionally has assured them that they are not pregnant.

However, the standard regimen's 7-day pill-free interval is associated with significant drawbacks. For example, commonly used low-dose OC formulations have a very real potential for reduced ovarian inhibition during this interval. Also, OC users may experience an increase in monthly hormone-withdrawal symptoms—pelvic pain, headaches, bloating, and breast tenderness—during the pill-free interval.

Hormone-related symptoms were assessed in a study of women of childbearing age who used OCs and kept daily symptom diaries.⁹ Women who requested OCs were recruited from an obstetrics and gynecology practice without regard to the presence of premenstrual symptoms. Of the 262 evaluable women, 193 were current OC users at study entry and 69 women were categorized as new starts because they had had no recent OC use (26 had not previously used OCs and 43 were former OC users). The various low-dose OCs used by the study participants contained 35 µg EE or less as the estrogen component plus different progestins and were administered in the standard 21/7 regimen. Participants were significantly more likely to experience hormone-withdrawal symptoms during the 7 pill-free days than during the 21 days of

Table 1. Commonly Reported Hormone-withdrawal Symptoms in Women Using OCs

Symptoms	Hormone Treatment (21 days, %)	Pill-free (7 days, %)	P Value
Pelvic pain	21	70	<.001
Headaches	53	70	<.001
Breast tenderness	19	58	<.001
Bloating/swelling	16	38	<.001
Use of pain medications	43	69	<.001

OCs indicates oral contraceptives.
Source: Reference 9.

active hormone use. The percentage of women reporting hormone-withdrawal symptoms during the 21 days of pill use and the 7-day pill-free interval is shown in **Table 1**.

Women who were current OC users of more than 12 months' duration experienced headaches more commonly during the pill-free interval than during active-pill use. New-start OC users had significantly more headaches during the pill-free interval than during active-pill use in cycle 2 (71% vs 49%, $P < .001$) but not in cycle 1 (71% vs 62%). This increase in the incidence of headaches probably stemmed

from the effect of estrogen withdrawal on the vasculature.

Current and new-start OC users both experienced significantly more pelvic pain or cramps during the pill-free interval than while taking active pills (each $P < .001$). In addition, current and new-start OC users both reported an increase in bloating and swelling that started during the active-pill week before the pill-free interval. For all cycles studied, current and new-start OC users both reported significantly more bloating or swelling during the pill-free interval compared with active-pill weeks (58% vs 19%, $P < .0001$).

In this study, breast tenderness was also more common in new-start than in current OC users. The current OC users tended to experience a greater degree of breast tenderness during the week before the pill-free interval that peaked during the pill-free interval; 16% experienced breast tenderness during active-pill weeks versus 38% during the pill-free interval ($P < .001$).⁹

Using a Shorter Pill-free Interval

Low-dose OC formulations provide a lesser degree of ovarian inhibition during the standard 7-day pill-free interval compared with higher doses.¹⁰ Shortening the pill-free interval would be logical in an attempt to maintain ovulation suppression with low-dose OC formulations. However, the first

Table 2. Studies on Effects of Shortening the Pill-free Interval

Study	Agent	Pill Regimen	Results
Spona et al 1996	EE 20 µg + gestodene 75 µg	21 + 5 or 7 days	Group with 5-day interval had greater ovarian suppression; serum estradiol level increased earlier and more extensively than in 7-day group
Sullivan et al 1999	EE 15 µg + gestodene 60 µg	24 + 4 or 21 + 7 days	Ovulation suppressed in all cycles of women with 4-day interval and in 74/75 cycles of women with 7-day interval; no luteinized unruptured follicles were seen in women with 4-day interval and in 6/75 cycles of women with 7-day interval
Sulak et al 2000	EE 30 µg + various progestins	Standard (21 + 7 days) for 1 cycle, then 21 + 3 or 21 + 4 days	Luteinizing hormone, FSH, estradiol and inhibin B increased much more with 7-day interval than with either 3- or 4-day interval

EE indicates ethinyl estradiol; FSH, follicle stimulating hormone.
Sources: References 9-11.

low-dose and OC formulations (35 µg EE or less) were not introduced with a recommendation for shortening the pill-free interval. Three studies conducted on the feasibility of shortening the pill-free interval are summarized in **Table 2**. In all of these studies, women in the groups receiving regimens with shorter pill-free intervals showed greater ovarian suppression than women who received the standard 21/7 regimen.⁹⁻¹¹

Recently, Mishell published comments on the rationale for decreasing the pill-free interval for women using low-dose OCs, pointing out that clearance of estrogen and progesterone from the circulation could lead to ovulation if a new cycle of OCs was not started promptly. He noted that "It appears prudent and reasonable to reduce the pill-free interval from 7 to 4 days with OC formulations containing the current lowest doses of EE (20 mg) combined with low doses of the most recently synthesized progesterin[s]."⁸ Mishell proposed that a shorter pill-free interval should lead to a decrease in the adverse symptoms that many women experience during that time.⁸

New Research

Currently, Sulak and colleagues are conducting a study in women aged 18 to 50 who have been using OCs with the standard 21/7 regimen for at least 3 cycles at study entry, who have no contraindications to continued OC use, and who reported experiencing hormone-withdrawal symptoms in association with the 7-day pill-free interval but have not been diagnosed with PMS or PMDD.⁹ Participants are asked to complete an adapted version of the Daily Symptom Report (DSR-17), a validated 17-item daily record that rates premenstrual symptoms on a scale of 0 to 4.¹² **Figure 1** shows a sample of the adapted DSR-17 used in this study.¹²

During the study's preextension phase, women continued to take a variety of OCs containing EE 35 µg or less plus 1 of several 19-nortestosterone-based progestins for 1 cycle, while they monitored their hormone-withdrawal symptoms. Subsequently, they were switched to an OC containing EE 30 µg plus drospirenone 3 mg for 2 cycles. **Figure 2** shows the total mean score for the DSR-17

Figure 1. Sample Daily Symptom Report (17 Items)

Date (month/day/year) _____

____ Check if menstruating

____ Study medication; no pills taken

____ Check if taking other medications (list on back)

0 = not present at all
 1 = mild, only slightly apparent to you
 2 = moderate, aware of symptom, but it doesn't affect daily activity at all
 3 = severe, continuously bothered by symptoms
 4 = very severe, symptom is overwhelming and/or interferes with daily activity +

____ Fatigue, lack of energy

____ Poor concentration

____ Feeling out of control/overwhelmed

____ Feeling hopeless, worthless, or guilty

____ Headache

____ Anxiety, tension, "on edge"

____ Aches

____ Irritability, persistent anger

____ Mood swings

____ Swelling, bloating, weight gain

____ Craving foods, increased appetite, overeating

____ Decreased interest in usual activities

____ Cramps

____ Depression, feeling sad, down, or blue

____ Breast tenderness

____ Insomnia or hypersomnia

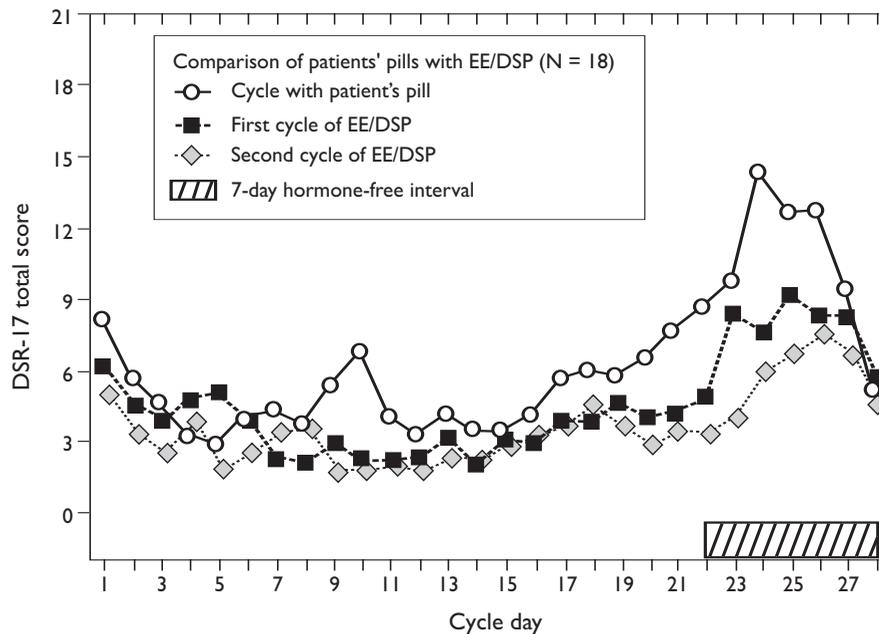
____ Difficulty concentrating

Note: The actual form includes spaces for 31 days.

Source: Adapted from Freeman EW et al. *Psychiatry Res.* 1996;65:97-106. Copyright 1996, with permission from Elsevier.

over the 3 cycles of the study. Compared with the other low-dose OCs, there were reduced hormone-withdrawal symptoms during the pill-free interval in the 2 cycles of the drospirenone-containing OC.

Figure 2. Mean DSR-17 Scores With Low-dose OCs Containing 19-Nortestosterone-based Progestins Versus a Drospirenone-containing OC



DSR indicates Daily Symptom Report; OC, oral contraceptive; EE, ethinyl estradiol; DSP, drospirenone.
 Source: Adapted from Spona J. *Contraception*. 1996;54:71-77. Copyright 1996, with permission from Elsevier.

Participants in the study's preextension phase were invited to take part in an extension phase, in which the drospirenone-containing OC was taken for 168 consecutive days without a pill-free interval.¹³ A total of 111 women began the study extension; of these, 102 (92%) completed phase I. Hormone-withdrawal symptoms (eg, headache and mood swings) that occurred when the drospirenone-containing OC was taken using the standard regimen were compared with symptoms that occurred using a 168-day extended regimen with the same OC. These symptoms were much more common in the 7-day pill-free interval of the standard 21/7 regimen than during the 168-day extension of active pills.

Extended OC Regimens

Extended-cycle OC regimens are associated with potential decreases in hormone-withdrawal symptoms, such as menstrually related headaches, cyclic mood swings, pelvic pain, and dysmenorrhea. In addition, use of an extended regimen may lessen

bleeding, anemia, and functional ovarian cysts, as well as decrease the possibility of unintended pregnancies.

Currently, the combination OC containing EE 30 µg plus levonorgestrel 150 µg is the only extended-regimen OC with a US Food and Drug Administration indication. The regimen for this OC consists of 84 days of active treatment, followed by a 7-day pill-free interval. New formulations with other extended regimens, such as EE 20 µg plus drospirenone 3 mg administered 24/4, are being developed. Drospirenone, an analogue of the diuretic spironolactone, has been shown to exhibit progestogenic, antiminer-
 alocorticoid, and antiandrogenic properties. OCs with prescribing instructions calling for a standard regimen are sometimes used in an extended regimen, which constitutes an off-label use. Trends in OCs are summarized in **Table 3**.

Summary

Ovulation suppression is a recognized treatment for premenstrual symptoms, which

occur essentially only during ovulatory cycles. Hormonal approaches, such as GnRH agonists and danazol, have both advantages and disadvantages, and in previous studies OCs have had mixed results in reducing premenstrual symptoms, with the differences possibly depending on the type and dose of steroids used. However, more recent research indicates greater promise for low-dose formulations in use and in development.

The standard regimen used for most OCs includes a 7-day pill-free interval, which has been associated with a decrease in ovarian inhibition and an increase in hormone-withdrawal symptoms. Use of a regimen with a shortened, 4-day, pill-free interval has the potential to maintain a constant level of ovarian suppression, inhibit follicle formation, and decrease the incidence of hormone-withdrawal symptoms.

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Table 3. Traditional and Current OC Formulations and Regimens

Traditional	Current
Active hormones on days 1-21; hormone-free pills on days 22-28	Extension of days of active pills Shortened pill-free interval
Shift to lower doses of estrogen and progestin	Use of newer progestins
Shift to less androgenic progestins	

OC indicates oral contraceptive.

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