Treatment of Premenstrual Worsening of Depression With Adjunctive Oral Contraceptive Pills: A Preliminary Report

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Objective: Despite the efficacy of antidepressants, depression can break through premenstrually. Oral contraceptive pills (OCPs) stabilize reproductive hormones and treat premenstrual dysphoric disorder. Management of depression that breaks through premenstrually has not been studied.

Method: Women taking antidepressants with successfully treated depression, except during the late luteal phase (Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 15) and high late-luteal phase (Daily Rating of Severity of Problems scores) were randomly assigned to open-label ethinyl estradiol (EE) 30 μg/day plus drospirenone 3 mg/day (EE/DRSP) for 21 days and double-blinded treatment with EE 30 μg/day or placebo for days 22 through 28 of 2 cycles. Participants were recruited from community and psychiatry outpatient clinics and enrolled into this study in 2004–2005.

Results: Of 25 subjects who received EE/DRSP (N = 12 with EE and N = 13 with placebo), 21 completed treatment. For study completers, premenstrual MADRS ($p = .0019$) and Daily Rating of Severity of Problems scores ($p = .0001$) improved significantly in both groups. Outcome did not differ between groups.

Conclusion: This study provides preliminary evidence that addition of EE/DRSP (± EE) to antidepressants may treat premenstrual breakthrough of depression. Stabilizing hormone levels with EE/DRSP may provide an important therapeutic option for women taking antidepressants whose symptoms break through premenstrually.

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Women with mood disorders frequently report premenstrual worsening of depression.[1,2] Depression symptoms can break through premenstrually, even when the underlying depression is treated effectively throughout the remainder of the menstrual cycle. However, the hormonal basis of premenstrual worsening of depression is not well understood, and treatment strategies for premenstrual worsening of depression have not been evaluated systematically.

Current understanding of the mechanisms underlying premenstrual worsening of depression is confined to studies of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). In such women, mood symptoms are restricted to the luteal phase of the menstrual cycle. However, despite the association between PMDD and the specific hormonal dynamics of the luteal phase, reproductive hormones are normal and are not different from the fluctuating pattern across the menstrual cycle in women without premenstrual problems.[3] These findings suggest that PMS and PMDD are a consequence of a heightened sensitivity of mood to fluctuations of estradiol and progesterone.[4]

One approach to treating PMS and PMDD involves stabilization of reproductive hormones with oral contraceptive pills (OCPs) or gonadotropin-releasing hormone (GnRH) agonists.[5] Oral contraceptive pills and GnRH agonists have both been shown to be more effective than placebo in treating PMS and PMDD,[6,7] although some

clinical trials with OCPs have shown no benefit relative to placebo.[8] Oral contraceptive pills stabilize estradiol and progesterone levels during the 21 days of each 28-day cycle when they are administered followed by a 7-day hormone-free interval (21/7-day regimen).[9] The importance of hormonal stabilization in treating premenstrual symptoms is highlighted by the observation that administration of OCPs in an extended regimen (continuous administration of estradiol and progesterone for 168 days) is more effective than a 21/7-day regimen.[10]

Approaches to treating premenstrual worsening of depression have been extrapolated from PMDD studies. Increasing the dose of a serotonergic antidepressant either in a continuous fashion or transiently during the luteal phase has been recommended.[2,11] However, no systematic studies have been conducted to date in women with premenstrual worsening of depression.

The purpose of the current study was to determine preliminarily whether stabilization of estradiol and progesterone levels with an OCP treats depression symptoms that break through premenstrually in women with depression that is otherwise well controlled by antidepressants. We hypothesized that hormonal stabilization with a 21/7-day OCP regimen would be an effective augmentation strategy for these women. We also hypothesized that maximal stabilization of estrogen levels with the addition of estradiol during days 22 through 28 of each OCP cycle would confer further therapeutic benefit. Levels of exogenous and endogenous estrogens were measured to determine the stability of hormone levels with treatment.

METHOD

Subjects and Screening Phase

Study participants were recruited from the community and psychiatry outpatient clinics and enrolled into this study in 2004–2005. Informed consent was obtained from all participants, and all study procedures were approved by the Partners Health Care Institutional Review Board.

Initial eligibility criteria included (1) women aged 18 to 45 years; (2) regular 26- to 35-day menstrual cycles predictable within 7 days; (3) no hormonal contraceptive use for the past 6 months; (4) onset of a depressive disorder (major or minor depressive disorder, dysthymia) at least 3 months prior to study participation, as diagnosed by the Structured Clinical Interview for DSM-IV[12] (SCID); (5) use of current antidepressant for at least 3 months, with stable dose for at least 2 months; (6) depressive disorder in full remission for at least 2 months, with the exception of the premenstrual week, when depressive symptoms recurred intermittently and resolved with onset of menses; and (7) willingness to use barrier contraceptive methods.

After initial eligibility screening, mood symptoms were assessed prospectively during a 1-month run-in phase to establish that significant depression symptoms were present only premenstrually (Figure 1). Eligible participants met the following criteria during the run-in phase: depression and premenstrual symptoms were present during the late luteal phase (final 5 days prior to the onset of menses) of the menstrual cycle, but not during the midfollicular phase (cycle days 6–10). To meet such criteria, subjects were required to have a score on the clinician-rated Montgomery-Asberg Depression Rating Scale[13] (MADRS; range, 0–63) greater than or equal to 15 during the late luteal phase and less than 10 during the midfollicular phase. Premenstrual symptoms were defined as a greater than or equal to 50% increase in the Daily Rating of Severity of Problems[14] score from the midfollicular to the late luteal menstrual cycle phase. This 24-item instrument is a daily diary that incorporates the psychological, physical, and functional DSM-IV symptoms of PMDD and is used widely to document treatment response in PMDD studies.[15]

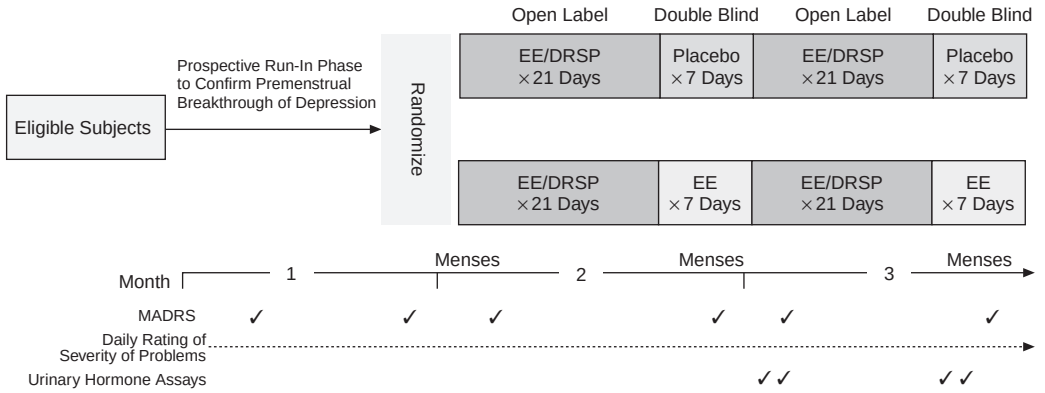
Women were excluded if they (1) had contraindications to ethinyl estradiol (EE) or drospirenone (DRSP) or took medications that interfered with EE/DRSP metabolism, (2) were pregnant, (3) were lactating, (4) increased the dose of their antidepressant during the luteal phase, (5) smoked cigarettes (if aged ≥ 35 years), (6) had psychotic symptoms or suicidal ideation, or (7) met SCID criteria for lifetime bipolar disorder, lifetime psychotic disorder, or alcohol or substance use disorder within the past year.

Treatment Phase

Participants who met eligibility criteria during the run-in phase were randomly assigned to open-label treatment with 21 days of EE 30 μg/day plus DRSP 3 mg/day with double-blinded assignment to daily EE 30 μg (EE/DRSP + EE) or placebo (EE/DRSP + placebo) during the remaining 7 days of each 28-day cycle (Figure 1). The first cycle of EE/DRSP was added to each subject's antidepressant within the first 5 days after menses began, and treatment was continued for 2 cycles. Randomization was conducted in a double-blind fashion and in a 1:1 ratio in blocks of 4 to maintain a balance in the randomization. Withdrawal bleeding occurred in all participants because the progestin was withdrawn during days 22 through 28 of each cycle for both treatment groups, thereby maintaining the double-blind design.

While receiving OCP treatment, all participants were evaluated for depressive symptoms (MADRS scores) twice monthly during the "premenstrual" and "postmenstrual" phases of each cycle and continued to complete the Daily Rating of Severity of Problems daily. The MADRS was used to measure depression symptoms during the previous week. The premenstrual assessments were conducted during the third to sixth day of taking double-blinded EE or placebo (days 25–28 of the OCP). The postmenstrual assessments were conducted immediately prior to initiation of EE/DRSP (days 1–5 of the OCP cycle) during the first

Figure 1. Study Design[a,b]



[a]EE/DRSP + EE = open-label EE 30 µg/day plus DRSP 3 mg/day for days 1–21 followed by double-blinded EE 30 µg/day for days 22–28 of 2 consecutive cycles.
[b]EE/DRSP + placebo = open-label EE 30 µg/day plus DRSP 3 mg/day for days 1–21 followed by double-blinded placebo for days 22–28 of 2 consecutive cycles.
Abbreviations: DRSP = drospirenone, EE = ethinyl estradiol, MADRS = Montgomery-Asberg Depression Rating Scale.

treatment month and on days 6 through 10 of EE/DRSP during the second month. The self-administered Beck Depression Inventory (BDI; range, 0–63)[16] was also completed at each of these timepoints. The Quality of Life Inventory (QOLI; range, 0%–100%; higher score signifying better quality of life)[17,18] was completed during the premenstrual phase at baseline and at study end.

Hormone Measures

Levels of estrogens were measured to determine the stability of exogenous and endogenous estrogens with treatment in each group. Urinary levels of the endogenous estradiol hormone metabolite estrone-glucuronide (E_1C) and exogenous EE were measured in first-morning spot urine samples obtained at 2 separate timepoints during the final treatment month. Two samples were collected between days 2 and 5 of EE/DRSP, and another 2 samples were collected between days 2 and 5 of EE or placebo (Figure 1). Mean E_1C and EE levels were calculated to establish more stable estimates of E_1C and EE levels. E_1C levels were analyzed using enzyme-based immunoassays,[19] and EE levels were analyzed using an extraction/radio-immunoassay method (Immunometrics, Ltd., London, U.K.). All urine specimens were analyzed during a single run and were standardized to urinary creatinine (Cr) to normalize for urine concentration.

Statistical Analysis

The primary outcome measure was defined as the percent change in the mean premenstrual MADRS score from baseline (average of last 5 days prior to menses during the run-in period) to the second treatment month (obtained on days 25–28 of the OCP cycle and reflecting the week prior to the withdrawal bleed). The secondary outcome measure was the percent change in the mean premenstrual Daily Rating of Severity of Problems score from baseline (average of last 5 days prior to menses during the run-in period) to the second treatment month (average of last 5 days prior to withdrawal bleed).

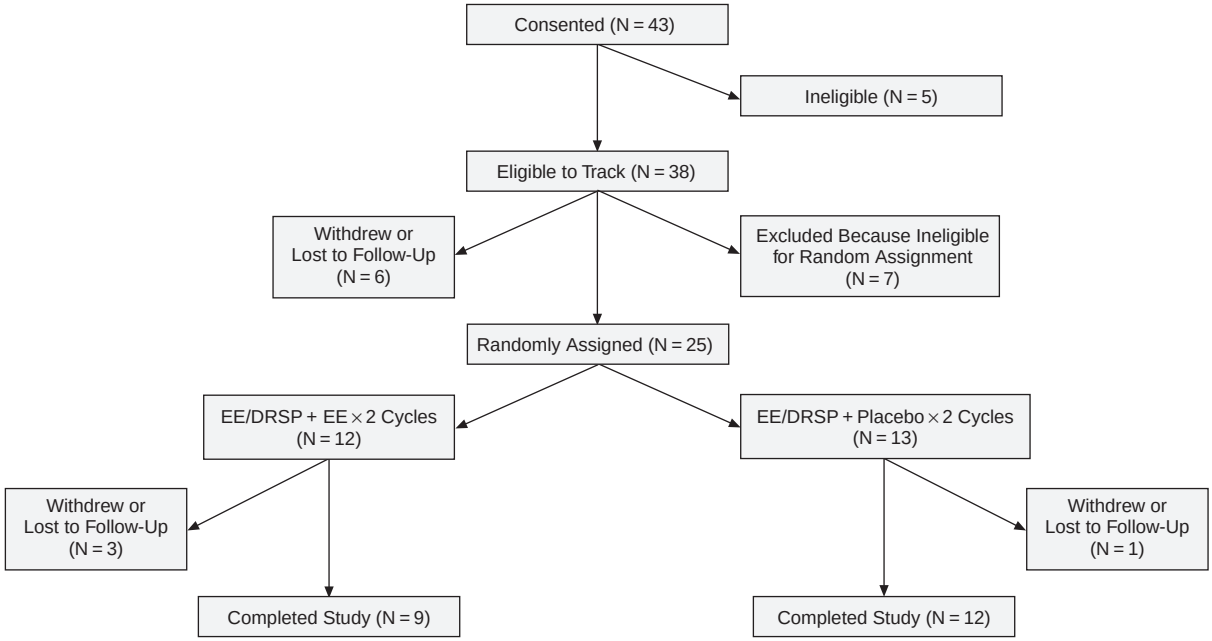
For the primary analysis, the Wilcoxon signed-rank nonparametric t test was used to examine the change in premenstrual MADRS and Daily Rating of Severity of Problems scores from baseline to study end for all subjects together. In the secondary analysis, the Mann-Whitney nonparametric test was used to examine the specific effect of continued EE administration during days 22 through 28 by comparing the change in premenstrual MADRS and Daily Rating of Severity of Problems scores from baseline to study end between the groups assigned to EE/DRSP + EE and EE/DRSP + placebo. The urinary hormone data were analyzed using unpaired t tests to compare EE levels and E_1C levels between the 2 treatment groups. Parametric analyses were conducted after checking assumptions of normality.

Sample size was determined based on data from previous studies that used selective serotonin reuptake inhibitors (SSRI) to treat PMDD and the Daily Rating of Severity of Problems to measure treatment effects. Only subjects who completed the entire study were included in the analysis because the primary outcome measure was based on a change score from baseline to study end. Analyses were conducted using STATA version 8 (StataCorp, College Station, Tex.) with 2-sided hypotheses and $\alpha = .05$.

RESULTS

Of 43 women evaluated for the study, 38 (88.4%) were eligible to participate in the run-in phase of the study

Figure 2. Subject Flowchart[a,b]



[a]EE/DRSP + EE = EE 30 µg orally/day plus DRSP 3 mg orally/day for first 21 of 28-day cycle + EE 30 µg orally/day for final 7 days of 28-day cycle.
[b]EE/DRSP + placebo = EE 30 µg orally/day plus DRSP 3 mg orally/day for first 21 of 28-day cycle + placebo for final 7 days of 28-day cycle.
Abbreviations: DRSP = drospirenone, EE = ethinyl estradiol.

(Figure 2), and 30 (78.9%) of those completed this phase. Twenty-five (83.3%) of the women who completed the run-in phase were confirmed to have depressive symptoms that broke through premenstrually and initiated treatment. Of those, 12 were randomly assigned to EE/DRSP + EE and 13 were randomly assigned to EE/DRSP + placebo. Twenty-one (84.0%) of those who initiated treatment completed the study. Analyses were performed on these 21 subjects. There was no difference in the study completion rate between those who were randomly assigned to EE/DRSP + EE and those treated with EE/DRSP + placebo (9/12, 75% vs. 12/13, 92%, respectively, p = .24).

Subject Characteristics

There were no differences in demographic, psychiatric, or gynecological characteristics between the 2 treatment groups (Table 1). For the 25 study participants who initiated treatment, the mean ± SD age was 36 ± 7.4 years, approximately half had never married or borne children, and the majority were white, employed, college-educated nonsmokers.

Eighty-eight percent of subjects (22/25) were being treated for a major depression and had their first episode of depression in their 20s. All subjects were taking a serotonin-based antidepressant (sertraline [N = 9], fluoxetine [N = 4], venlafaxine [N = 4], paroxetine [N = 3], citalopram [N = 2], or escitalopram [N = 2]) except 1 participant, who was taking bupropion. The median duration of antidepressant use was 18 months (interquartile range [IQR] of 8–36 months). The mean (SD) age at onset of premenstrual symptoms was 24 (9.1) years. Two thirds of subjects reported that they developed PMS before they had their first problem with depression, and over 80% reported that PMS symptoms occurred when they were not depressed.

Treatment Effects

Prior to treatment, there was a 7-fold increase in MADRS scores from the follicular (median score = 3; IQR, 1.5–6.0) to the luteal (median score = 22; IQR, 19.0–24.5) phase, consistent with premenstrual breakthrough of depression symptoms (Figure 3). After 2 months of OCP treatment, premenstrual depression symptoms decreased significantly, from a median MADRS score of 22 (IQR, 19.0–24.5) to a median score of 4 (IQR, 3–7) for the group as a whole (p = .0019). With OCP treatment, premenstrual depression symptoms were reduced to postmenstrual levels. Improvement in premenstrual depression symptoms observed on the MADRS were consistent with changes in premenstrual BDI scores, which also improved significantly with OCP therapy (from a median score of 16.5 [IQR, 13.0–23.5] to a median score of 4 [IQR, 1–9], p = .0005). After 2 months of

Table 1. Demographic, Psychiatric, and Gynecological Characteristics at Baseline for All Subjects Together and by Treatment Assignment (ethinyl estradiol/drospirenone [EE/DRSP] + estradiol vs. EE/DRSP + placebo)[a,b]

Characteristic	All (N = 25)	EE/DRSP + Estradiol (N = 12)	EE/DRSP + Placebo (N = 13)
Demographic			
Age, mean ± SD, y	36 ± 7.4	36.6 ± 7.6	35.5 ± 7.5
Nonwhite, N (%)[c]	6 (24.0)	2 (16.6)	4 (30.8)
College degree, N (%)	21 (84.0)	11 (91.7)	10 (76.9)
Marital status, N (%)			
Never married	14 (56.0)	6 (50.0)	8 (61.5)
Married	7 (28.0)	4 (33.3)	3 (23.1)
Divorced/separated	4 (16.0)	2 (16.6)	2 (15.4)
Birth children, N (%)	11 (44.0)	7 (58.3)	4 (30.8)
Full/part-time employment, N (%)	23 (92.0)	12 (100)	11 (84.6)
Current smoker, N (%)	1 (4.0)	1 (8.3)	…
Psychiatric			
Depression diagnosis, N (%)			
Major depressive disorder	22 (88.0)	10 (83.3)	12 (92.3)
Dysthymia	1 (4.0)	1 (7.7)	…
Minor depression	2 (8.0)	1 (7.7)	1 (7.7)
Duration of current depressive disorder, median (interquartile range), mo[d]	15 (4.5–37.5)	36 (9–48)	12 (4–36)
No. of lifetime major depression episodes, median (interquartile range)[e]	4 (2–5)	2 (1–5)	4 (2–5)
Age at first major depression episode, mean ± SD, y[f]	21.7 ± 8.1	23.7 ± 9.4	20 ± 6.8
Taking an SSRI/SNRI as antidepressant, N (%)	24 (92.0)	12 (100)	12 (92.3)
Duration of antidepressant use, median (interquartile range), mo[g]	18 (8–36)	22 (10–42)	16 (8–24)
Gynecological			
Cycle length off OCP, mean ± SD, d[g]	28.6 ± 1.5	29 ± 2	28 ± 1
Premenstrual syndrome history, N (%)			
Preceded first onset of mood disorder	16 (64.0)	8 (66.7)	8 (61.5)
Present when not depressed[h]	20 (83.3)	10 (83.3)	10 (76.9)
Age at onset of premenstrual syndrome, mean ± SD, y[g]	24 ± 9.1	25.1 ± 10.8	22.8 ± 7.1
Prior OCP use, N (%)	20 (80.0)	11 (91.7)	9 (69.2)

[a]Categorical variables are presented as N (%) and continuous measures as mean (SD) if normal distribution and median (interquartile range) if nonnormal distribution.
[b]p Value > .05 for all comparisons of EE/DRSP + continuous estradiol vs. EE/DRSP + placebo.
[c]Includes black, Asian, and Hispanic women.
[d]Missing data for N = 9.
[e]Missing data for N = 4.
[f]Restricted to women with ≥ 1 episode of major depression in their lifetime (N = 23); missing data for N = 1.
[g]Missing data for N = 2.
[h]Missing data for N = 1.
Abbreviations: OCP = oral contraceptive pill, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.
Symbol: … = no patients had that characteristic.

OCP treatment, QOLI score improved significantly (from a median score of 18 [IQR, 5–38] to a median score of 44 [IQR, 16–55]), indicating improvement in overall quality of life (p = .02).

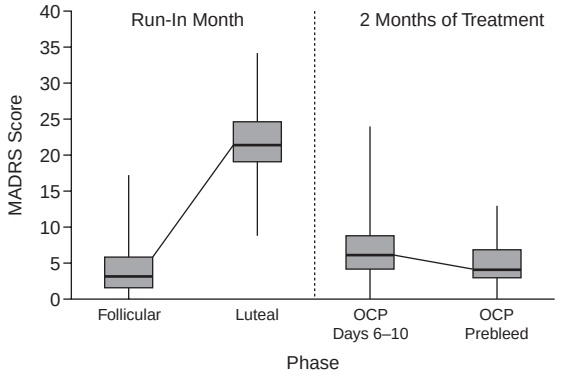
Premenstrual symptoms also improved significantly with OCP therapy for the group as a whole (p = .0001, Figures 4A–C), as indicated by a reduction in premenstrual Daily Rating of Severity of Problems scores from the run-in phase (median score = 58; IQR, 43.4–80.8) to the second month of treatment (median score = 37.9; IQR, 26.3–55.0).

There were no statistically significant differences in the effect of treatment on MADRS and Daily Rating of Severity of Problems scores between the groups treated with EE/DRSP + EE and EE/DRSP + placebo (p > .05). The median change in MADRS scores was 16 (IQR, 11–19) for the EE/DRSP + EE group and 17 (IQR, 15.0–20.5) for the EE/DRSP + placebo group (p > .05). The median change in Daily Rating of Severity of Problems scores was 19.2 (IQR, 14.3–28.8) for the EE/DRSP + EE group and 20.2 (IQR, 10.2–32.8) for the EE/DRSP + placebo group (p > .05).

Urinary Hormones

Urinary EE levels were higher overall in the subjects randomly assigned to EE/DRSP + EE than to EE/DRSP + placebo (Figure 5, p < .001), while urinary E_1C levels were lower (Figure 5, p < .001). In the group randomly assigned to EE/DRSP + placebo, maximum E_1C levels were observed during days 2 through 5 of the second OCP month, which followed a 7-day hormone-free interval. Urinary E_1C levels during days 2 through 5 of the second OCP month were significantly higher in the EE/DRSP + placebo group (mean ± SE = 48.3 ± 2.9 ng/mg Cr) than in the EE/DRSP + EE group (mean ± SE = 5.4 ± 2.2 ng/mg Cr), whose levels were measured after 7 days of EE treatment (p < .001). These differences reflect the effect of a 7-day hormone-free interval on

Figure 3. Median MADRS Scores Indicating Significant Improvement in Depression Symptoms During the Luteal/Premenstrual Phase From the Pretreatment Run-In Cycle[a] to the End of the Second Month of Treatment With an OCP[b] (p = .0019)[c]



[a]During the run-in, the MADRS was administered during the postmenstrual/follicular (cycle days 6–10) and premenstrual/luteal (last 5 days prior to onset of menses) phases of the menstrual cycle.
[b]During the second month of treatment, the MADRS was administered during days 6–10 on the OCP to reflect the postmenstrual phase and prior to the OCP-induced withdrawal bleed (during days 3–6 on estradiol or placebo) to reflect the premenstrual phase.
[c]Box plots present median (dark horizontal line), interquartile range (grey box), and range of data points (dark vertical line).
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OCP = oral contraceptive pill.

follicle development and endogenous estradiol secretion during the hormone-free interval in 21/7-day OCP regimens.[20]

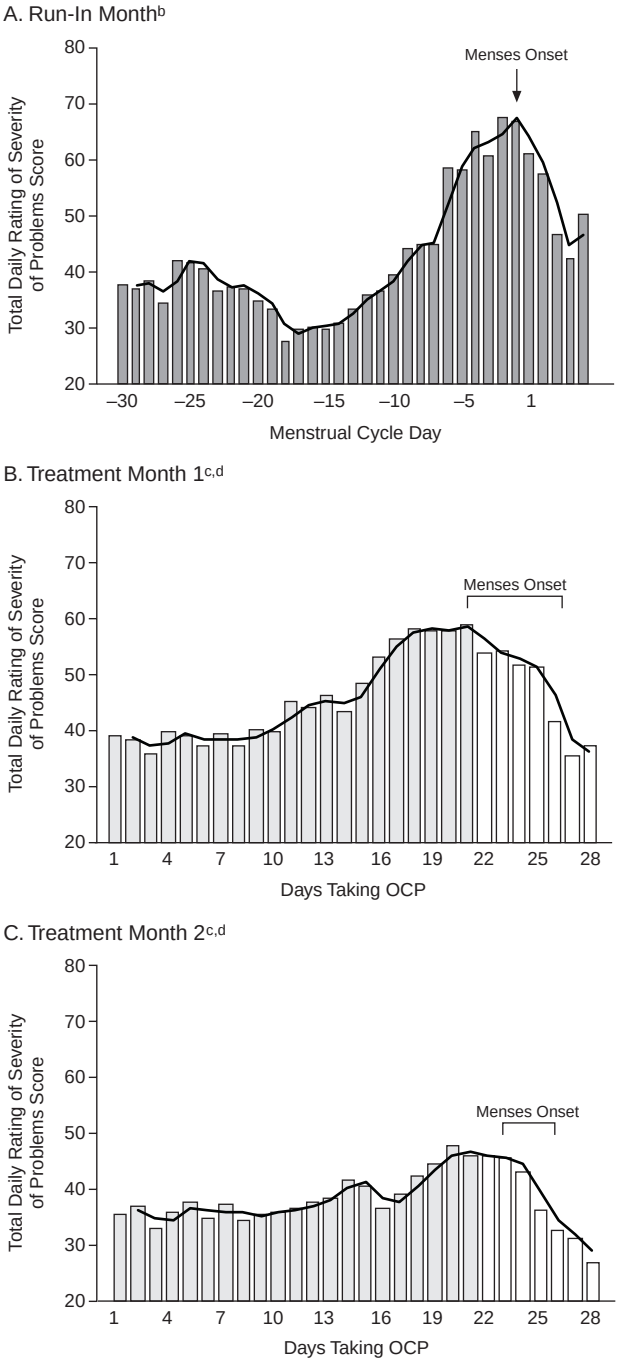
Medication Tolerability

The study medication was well tolerated. All women had a withdrawal bleed. The most common side effects were nausea (N = 9), headache (N = 5), and breast tenderness (N = 4). Of 25 women treated with the OCP, 3 withdrew because of side effects, 1 (4%) as a result of acute worsening of depression within the first week taking the OCP.

DISCUSSION

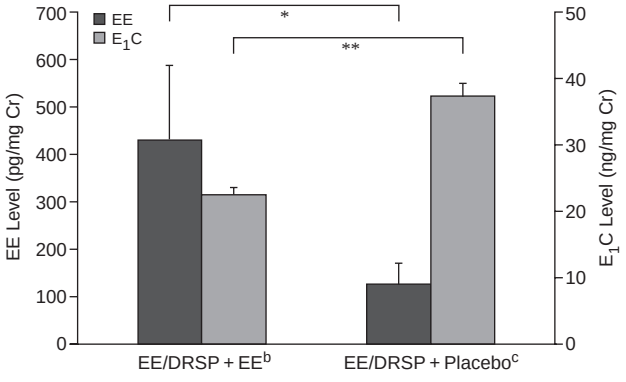
In this study, augmentation with open-label use of the OCP containing ethinyl estradiol and drospirenone improved depression symptoms that broke through premenstrually in the setting of antidepressant treatment. However, double-blinded randomization to continued use of ethinyl estradiol during the typical 7-day hormone-free interval of the OCP did not confer any additional therapeutic benefit when compared with placebo. These results provide preliminary evidence that adding hormonal contraceptives to antidepressants treats depression symptoms that break through premenstrually in women who are euthymic during the follicular phase but who nonetheless

Figure 4. Median Daily Premenstrual Symptoms, as Measured by the Daily Rating of Severity of Problems Scale[a]



[a]Significant improvement (p = .0001) from the pretreatment run-in cycle to the end of the second month of OCP treatment.
[b]Premenstrual Daily Rating of Severity of Problems scores were calculated based on the average of the last 5 days prior to menses beginning during the run-in cycle (indicated by an arrow).
[c]Premenstrual Daily Rating of Severity of Problems scores were calculated based on the average of the last 5 days prior to the withdrawal bleed during the 2 OCP treatment months (indicated by a bracket).
[d]White bars indicate days 22–28, when either estradiol or placebo was administered.
Abbreviation: OCP = oral contraceptive pill.

Figure 5. Mean (SE) Urinary Levels of the Exogenous Ethinyl Estradiol (EE) and the Endogenous Estradiol Metabolite Estrone-Glucuronide (E_1C)[a]



[a]Mean values of EE and E_1C were calculated for each treatment group after first determining the mean level of the 4 samples for each subject.
[b]EE 30 µg/day plus DRSP 3 mg/day for days 1–21 followed by EE 30 µg/day for days 22–28 of 2 consecutive cycles (EE/DRSP + EE).
[c]EE 30 µg/day plus DRSP 3 mg/day for days 1–21 followed by placebo for days 22–28 of 2 consecutive cycles (EE/DRSP + placebo).
*EE levels were significantly higher in the group randomly assigned to EE/DRSP + EE ($p < .001$).
**E_1C levels were significantly higher in the group randomly assigned to EE/DRSP + placebo ($p < .001$).
Abbreviations: Cr = creatinine, DRSP = drospirenone.

experience recrudescence of depression symptoms during the luteal phase of the menstrual cycle.

To our knowledge, this is the first study to systematically examine treatments for premenstrual worsening of depression. In 1 previous depression study, a post hoc analysis conducted on a subset of women with premenstrual worsening of depression showed that premenstrual depression symptoms improved when depression improved with antidepressant therapy overall.[21] Other reports suggest that increasing the dose of serotonergic antidepressants during the luteal phase, particularly nefazodone, may be helpful to treat depression that worsens premenstrually.[2,22]

The rationale for using OCPs to treat depression symptoms that break through premenstrually derives from the putative hormonal basis of premenstrual worsening of depression.[2,23] Like PMDD, premenstrual worsening of depression may result from susceptibility to the mood effects of changing levels of endogenous estradiol and progesterone on neurotransmitters involved in mood regulation.[24] PMDD symptoms remit when fluctuations in reproductive hormones are eliminated by GnRH agonists and re-emerge when either estradiol or progesterone is added back.[4] Such studies demonstrate that changes in estrogen and progesterone play independent roles in the etiology and management of PMDD.

Studies using OCPs to treat PMDD suggest that stabilization of estradiol and progesterone treats this hormonally based mood disorder. The monophasic OCP EE/DRSP has been shown to be effective for treatment of PMDD when administered for 24 days followed by a 4-day hormone-free interval,[7,25] and for treatment of premenstrual symptoms when administered without a hormone-free interval,[10] presumably because estrogen and progesterone levels are stabilized.

In our study, subjects received treatment with an OCP for the first 21 days of two 28-day cycles and were randomly assigned to continued treatment with estradiol or placebo during days 22 through 28 of each cycle. We hypothesized that continuous use of EE would confer additional therapeutic benefit by stabilizing levels of estradiol throughout the month. The absence of an additional benefit from this approach has several interpretations. One explanation is that central nervous system levels of estrogens are maintained at stable levels regardless of whether additional estradiol is given. In women taking OCPs, circulating estrogens are comprised of a mixture of endogenous and exogenous estrogen sources, both of which are likely to have effects on brain regions involved in mood regulation. This explanation is supported by our observation that urinary EE levels were higher in the EE/DRSP + EE group, whereas urinary E_1C levels were higher in the group treated with EE/DRSP + placebo. The increase in E_1C levels in women randomly assigned to EE/DRSP + placebo, particularly during the days immediately following a 7-day hormone-free interval, is consistent with previous studies demonstrating development of follicles and secretion of endogenous estradiol during the hormone-free interval in 21/7-day OCP regimens.[20,26] Thus, increased secretion of endogenous estradiol in women randomly assigned to EE/DRSP + placebo may maintain stable central nervous system levels of estrogens at a similar effective level as those maintained by continuous EE administration.

An alternative explanation for the absence of a difference between the effect of continued EE administration and placebo is that drospirenone may exert an ongoing therapeutic effect during days 22 through 28 of the OCP cycle when no progesterone is administered because of its long half-life.[27] Drospirenone also has unique antiandrogenic and antimineralocorticoid properties that distinguish it from other progestins and may contribute to the efficacy of EE/DRSP for the treatment of premenstrual symptoms.[28] If the half-life or unique properties of drospirenone contribute independently to the efficacy of EE/DRSP for the treatment of premenstrual symptoms, the absence of an effect of continued EE administration may be explained because drospirenone was dosed identically in the 2 groups. These potential interpretations are both plausible because estrogen and progesterone can independently lead to worsening of depression symptoms

premenstrually, as they do in PMDD.[4] Future studies examining the length of different hormone-free intervals and the independent effects of ethinyl estradiol and specific progestins are needed to further elucidate these possible explanations.

The absence of a therapeutic advantage from continuing estradiol during the traditional hormone-free interval may appear to be at odds with studies showing that extended OCP regimens are more effective than 21/7-day regimens at treating premenstrual symptoms.[9,10] However, these studies cannot be compared because the study populations and treatment approaches differ significantly between our and other studies.[10] We administered EE/DRSP with estradiol alone in a continuous fashion to women with depressive disorders that were prospectively confirmed to break through premenstrually. In contrast, other investigators have observed a reduction of premenstrual-like symptoms when women without previously established premenstrual symptoms were swapped from 21/7-day regimens to continuous administration of both estradiol and drospirenone.[10]

An important observation in this study is that OCP treatment led to worsening of depression infrequently, a finding that is consistent with epidemiologic studies.[29] In the current study, depression symptoms worsened in only 1 subject (4%) shortly after starting the OCP, suggesting OCP-induced dysphoria.[30] This subject had never taken an OCP previously and had rapid resolution of depression after the OCP was discontinued. Thus overall, data from this small study support the use of OCPs in women with treated depression while monitoring for OCP-induced dysphoria.

There are several limitations of this study. First, treatment with EE/DRSP was administered in an open-label fashion and placebo-controlled studies are required to confirm our findings. In addition, because of the small sample size, the number of subjects completing treatment with the 2 different OCP regimens may be too small to detect a meaningful difference between the groups. Another limitation is that subjects were treated naturalistically with different antidepressants at a range of doses for varying periods of time prior to enrollment. All subjects, with the exception of 1 subject, were receiving treatment with serotonin-based antidepressants. The specific role of a serotonergic (versus nonserotonergic) antidepressant when augmenting with an OCP requires further investigation.

In summary, this report provides preliminary evidence that augmentation of antidepressants with an OCP containing EE/DRSP and potentially other OCPs improves depression symptoms that break through premenstrually when the OCP is administered in a standard 21/7-day regimen with or without continuous estradiol administration. These results provide the first experimental evidence that hormonal contraceptives may offer important therapeutic advantages for such patients. This work adds to the body of literature indicating that stabilizing estrogen and progesterone may have therapeutic benefits in women with heightened sensitivity to the negative effects of fluctuating hormones on their mood.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac, Sarafem, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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