Treatment of depression associated with the menstrual cycle: premenstrual dysphoria, postpartum depression, and the perimenopause

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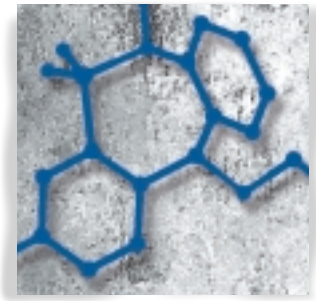

Several forms of depression are unique to women because of their apparent association with changes in gonadal hormones, which in turn modulate neuroregulatory systems associated with mood and behavior. This review examines the evaluation and treatment of depression that occurs premenstrually, postpartum, or in the perimenopause on the basis of current literature. The serotonergic antidepressants consistently show efficacy for severe premenstrual syndromes (PMSs) and premenstrual dysphoric disorder (PMDD), and are the first-line treatment for these disorders. The use of antidepressants for postpartum depression is compromised by concerns for effects in the infants of breast-feeding mothers, but increasing evidence suggests the relative safety of the antidepressant medications, and the risk calculation should be made on an individual basis. Estradiol may be effective for postpartum depression and for moderate-to-severe major depression in the perimenopause. In spite of its frequent use, progesterone is not effective for the mood and behavioral symptoms of PMS/PMDD, postpartum depression, or perimenopausal depressive symptoms.

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Approximately 20% of women experience an episode of major depression, a rate that is twice that of men.[1] The period of greatest vulnerability for women appears to be the childbearing years, with the initial onset of depression most likely to occur between the ages of 25 and 44.[2] Several forms of depression are unique to women because of their apparent association with changes in reproductive hormones: premenstrual dysphorias, including premenstrual syndromes (PMSs) and premenstrual dysphoric disorder (PMDD), postpartum depression (PPD), and depression in the perimenopausal period. The link among these depressive disorders appears to be a sensitivity to normal shifts in gonadal hormones, which affect neuroregulatory systems that play a role in affective disorders.[3,4] Such shifts occur during the menstrual cycle, in pregnancy and postpartum, and with ovarian aging in the years leading to the menopause.

Historically, depression has been underrecognized and undertreated. Until recently, diagnostic criteria were imprecise, clinical trials of purported treatments for menstrually related depressions were lacking or poorly done, and treatment options were generally unsupported

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Selected abbreviations and acronyms

ACTH	*adrenocorticotropic hormone*
GnRH	*gonadotropin-releasing hormone*
HRT	*hormone replacement therapy*
5-HT	*5-hydroxytryptamine (serotonin)*
m-*CPP*	m-*chlorophenylpiperazine*
OC	*oral contraceptive*
PMDD	*premenstrual dysphoric disorder*
PMS	*premenstrual syndrome*
PPD	*postpartum depression*
SSRI	*selective serotonin reuptake inhibitor*

by scientific data. Over the last two decades, considerable scientific research has focused on the depressions unique to women. This review examines the evaluation and treatment of depression that occurs premenstrually, postpartum, and in the perimenopause based on the current clinical literature.

Premenstrual dysphorias

Of the depressive disorders that affect only women, PMSs are the most extensively studied. Severe PMS is a chronic mood disorder that continues for many years in reproductive-age women.[5] The etiology remains unconfirmed. Moderate-to-severe forms of the syndrome result in diminished functioning and impaired relationships that cannot be dismissed as trivial. The *Diagnostic and Statistical Manual for Mental Disorders*, 4th ed (*DSM-IV*) provides specific diagnostic criteria for severe dysphoric PMS termed PMDD.[6]

Prevalence

Survey studies indicate that up to 40% of menstruating women experience some difficulty with premenstrual symptoms.[7,8] When premenstrual distress is dominated by emotional symptoms such as irritability, nervousness, tension, and depressed mood, it is a powerful predictor of treatment-seeking behavior. In a recent community-based study, 22% of menstruating women rated moderate-to-severe premenstrual distress on an analog measure of distress; this subjective distress was highly correlated with each of the impairment variables, occupation, leisure, partner, and friends.[9] Other studies show that approximately 3% to 10% of reproductive-age women met the specific criteria for PMDD.[10,11]

Depression and PMS/PMDD

By definition, PMDD is a severe and dysphoric form of PMS. Symptoms of irritability, emotional hypersensitivity, increased anxiety and food cravings, sleep difficulties, and decreased concentration characterize PMDD as well as depression, particularly atypical depression. A lifetime history of depression ranges from about 20% to 76% in samples of women diagnosed for PMS or PMDD,[12,13] with the higher rates substantially greater than the lifetime prevalence of about 20% for major depression in the female population of this age-group.[1] A family history of depressive illness is common in women with PMS/PMDD.[5] Women who seek treatment for premenstrual symptoms frequently have other emotional disorders, most commonly depressive disoders, substance abuse, or anxiety. Conversely, women who have mood disorders frequently experience worsening of symptoms premenstrually.[14]

In spite of these observable similarities, increasing evidence suggests that PMS/PMDD is not a simple variant of depression, but a distinct disorder. While depressive symptoms characterize a substantial number of women with severe perimenstrual distress, there is also a sizeable group of women who do not suffer from either depression or anxiety symptoms, but experience severe or moderate perimenstrual distress with symptoms of irritability, nervousness, and tension.[9] On the basis of epidemiologic findings, the researchers posited that the features of irritability and tension irrespective of the presence of depressive symptoms may form the core symptoms of the disorder, a premise also advanced by Eriksson, on the basis of results of antidepressant treatment studies.[15,16] Data from epidemiologically based twin studies indicated that the degree to which premenstrual symptoms shared generic and environmental risk factors with major depression was modest, a possible indication that there is no close etiologic relationship between the two disorders.[17] The evidence that severe PMS/PMDD responds much more robustly to serotonergic antidepressants than to other antidepressants that are clearly effective for depressive disorders suggests differences in underlying mechanisms. There is also empirical evidence that a good response of PMS/PMDD patients to serotonergic antidepressants is not explained by depressive symptoms or a history of depression.[18,19] The rapid response of several days rather than several weeks of PMS patients to selective serotonin reuptake

inhibitors (SSRIs), the efficacy of SSRIs at low doses, and the efficacy of other serotonin agonists, including fenfluramine[20] and buspirone,[21] which are not effective for depression, all suggest that the underlying mechanisms of severe PMS/PMDD differ from other depressive disorders.

Evaluation

The diagnosis of premenstrual dysphoria, PMS, or PMDD is made primarily on the basis of the symptom pattern and the exclusion of other possible diagnoses. The essential elements are confirmation of the expected relationship of the symptoms to the menstrual cycle, ie, that the symptoms occur premenstrually and remit with menses; that the symptoms are distressing and warrant treatment, ie, that the symptoms impair usual functioning; and that the symptoms are not due to another physical or mental disorder. These elements are incorporated in the diagnostic criteria for PMDD, which, in addition, requires at least 5 of 11 specified symptoms that are severe premenstrually and remit with menses.[6] It is underscored that the symptom *pattern*, rather than specific symptoms or the number of symptoms, defines the disorder.

For a PMS/PMDD diagnosis, it is essential to confirm the symptom pattern for two to three menstrual cycles with prospective daily symptom ratings maintained by the patient, especially if the symptoms are mild. Less than half the women who report PMS provide daily symptom reports that corroborate their retrospective reports,[22] which are less reliable when symptoms are not consistent and severe.[23]

The major consideration after identifying the symptom pattern is whether the condition is purely PMS/PMDD or a premenstrual exacerbation of other psychiatric problems or medical conditions. Premenstrual exacerbation of symptoms may occur in other conditions such as asthma,[24,25] migraine,[26] seizure disorders,[27] alcohol intake,[28,29] depression,[14] and schizophrenia.[30] There is no laboratory test that identifies PMS/PMDD, and such tests are useful only if there are other questions that might be answered. PMS and PMDD are based on regular menstrual cycles within the normal range of 22 to 35 days, and patients with irregular cycling should be examined for other conditions. Standard hematology and blood chemistry profiles are conducted to confirm general good health. A thorough examination includes a review of current and past psychiatric status, particularly mood and anxiety disorders that are commonly associated with PMS/PMDD. A gynecologic examination is important to rule out problems such as endometriosis, which might account for the symptoms.

Serotonergic antidepressants

The serotonergic antidepressants, particularly the SSRIs, appear to be the treatment of choice for severe PMS and PMDD at this time. Modulating serotonergic function is consistent with the dominant theoretical view that the normal gonadal steroid fluctuations of the menstrual cycle trigger an abnormal serotonergic response in vulnerable women. Indications of abnormalities in markers of serotonergic transmission in women with severe PMS include evidence of a lowered platelet imipramine binding (a peripheral marker of serotonin [5-hydroxytryptamine, 5-HT] function) in the luteal phase,[31] decreased platelet 5-HT content and 5-HT uptake during the luteal phase,[32,33] and significantly decreased whole blood 5-HT levels premenstrually.[34] PMS patients showed a lower 5-HT response to tryptophan (a 5-HT precursor) during the luteal phase compared with the follicular or midluteal phases.[35] Challenge tests depleting tryptophan provoked PMS symptoms,[36] while tryptophan supplementation relieved PMS symptoms in open-label treatment.[37] Following administration of the serotonin-releasing fenfluramine, the women with PMDD had a significantly blunted prolactin response compared with the normal controls.[38] Fenfluramine administered to PMS subjects improved depressed mood and food cravings.[20]

Administration of the serotonin agonist *m*-chlorophenylpiperazine (*m*-CPP) showed improvement of PMS symptoms in the luteal phase and a blunted response to cortisol and adrenocorticotropic hormone (ACTH) in both the follicular and luteal phases of the PMS subjects compared with normal controls.[39] Although existing information does not indicate a causal relationship between serotonin and PMS, the data suggest involvement of the serotonergic system in this disorder.

A meta-analysis of randomized controlled trials of SSRIs in treatment of PMS/PMDD concluded that these drugs were an effective first-line therapy, with the overall standard mean difference in favor of SSRIs equivalent to an odds ratio of 6.91.[40] Efficacy has been clearly

shown for fluoxetine,[41-46] sertraline,[18,47-50] paroxetine,[51] citalopram,[52] venlafaxine,[53] and clomipramine.[54,55] Open-label studies showed that nefazodone[56] and fluvoxamine[57] also had response frequencies in PMS treatment similar to those in the placebo-controlled studies of SSRIs. The only medication with Food and Drug Administration (FDA) approval for treatment of PMDD are fluoxetine and sertraline.

In all reports of SSRI and other serotonergic antidepressant treatments for PMS/PMDD, the effective doses have remained at the low end of the dose range. An adequate trial of a serotonergic antidepressant is at least two menstrual cycles with a third cycle if there is partial response. If a patient has an insufficient response or continuing side effects with an initial SSRI, another SSRI can be tried.[58] Side effects are common with the onset of treatment, but are usually transient and disappear during the first treatment cycle. The most common side effects include headache, nausea, insomnia, fatigue or lethargy, diarrhea, decreased concentration, and dizziness. Decreased libido is also a common side effect of SSRI treatment, although the few published reports of PMS patients identified a relatively low incidence of decreased sexual interest or reduced orgasm of 10% to 12%.[18,53] In contrast, the frequency of less sexual arousal reported by women in depression studies ranged from 32% (sertraline) to 40% (paroxetine).[59] Whether there is a true difference between PMS and major depression patients with respect to this side effect is not known, but the PMS/PMDD reports clearly are from acute treatment trials, do not represent a systematic assessment of sexual function, and may not represent experience with longer maintenance treatment.

Luteal phase dosing

The use of medication only in the symptomatic luteal phase of the menstrual cycle is of particular interest in PMS/PMDD because of the cyclic pattern of the symptoms, which includes a clear symptom-free interval each month, and the rapid response of these patients to SSRIs. A number of preliminary studies examined luteal phase dosing regimens of SSRIs and consistently reported efficacy.[48-50,52,60,61] Two large multicenter trials reported efficacy of fluoxetine[62] and sertraline[13] administered for the last 2 weeks of the menstrual cycle. As with daily dosing, the mean doses remained low and the medications were well tolerated. No studies to date have reported discontinuation symptoms with luteal phase dosing. Although several reports suggested superiority of luteal phase dosing over daily dosing, none were designed or sufficiently powered to answer this question. Overall, the studies indicate that luteal phase dosing is effective for clearly diagnosed PMS/PMDD; previous daily treatment with an SSRI is not required; response is usually at the low end of the dose range; side effects are similar to those seen in continuous dosing; and discontinuation symptoms do not appear to be a problem in the luteal phase dosing regimens.

Other antidepressants

The antidepressant response in PMS/PMDD appears to be associated with potent serotonergic activity and is not a general antidepressant effect. Other antidepressants, which are clearly effective for major depression, such as desipramine (a tricyclic noradrenergic antidepressant),[18] buproprion (with weak inhibition of both serotonin and norepinephrine reuptake),[45] and maprotoline (a selective noradrenaline reuptake inhibitor),[51] were no more effective than the placebo in PMS treatment.

Long-term treatment of PMS/PMDD

All published studies of treatment efficacy for PMS/PMDD are based on acute treatment of 2 to 3 months' duration. Anecdotal reports and several small pilot investigations[63-66] suggest that PMS symptoms return within several months if medication is stopped. It also appears that untreated symptoms do not resolve spontaneously, as may occur in depression, but continue for many years, based on information from clinical trials, which report that the duration of the disorder is in the range of 8 to 10 years prior to treatment. Well-designed, long-term maintenance studies have not been conducted for this disorder, but these observations suggest that long-term maintenance treatment may be appropriate for patients with severe PMS/PMDD, particularly if they experience a rapid return of symptoms after responding to medication.

Insufficient response to serotonergic antidepressants

The overall response of PMS/PMDD patients to SSRIs is approximately 60% in controlled trials, but up to 40% may not have sufficient response. No strong predictors

of response have been identified.[19] An expert consensus group recommended the common clinical practice of shifting to a second SSRI when the patient has an insufficient response or is intolerant to the initial SSRI.[58] Augmenting an SSRI with other medications has not been tested in PMS/PMDD studies. Switching to another class of medication that has shown efficacy for PMS/PMDD, such as anxiolytics or gonadotropin-releasing hormone (GnRH) agonists, is suggested, but there are no data that indicate whether nonresponders to an SSRI will respond to another class of medication. Nonresponse may also be due to other comorbid disorders. A thorough review of the diagnosis and adjustments of the premenstrual doses of medication for the primary disorder should be considered before pursuing other treatments for PMS.

Other treatments

Hormonal treatment

Hormonal treatments for PMS/PMDD are not supported by consistent scientific information in spite of evidence of hormonal involvement in the disorder.[67] GnRH agonists, such as depot leuprolide[68,69] and intranasal buserelin,[70,71] effectively reduce PMS symptoms, but are of limited use because of the risks associated with low estrogen levels, particularly osteoporosis, and these medications are viewed as appropriate only as a diagnostic tool or for patients who do not respond to other treatments. Results of preliminary investigations of add-back therapy using low-dose estrogen and progesterone in conjunction with a GnRH agonist are inconsistent and do not yet definitively indicate that this is a safe as well as effective approach for long-term treatment.[72-74] Limited data indicate that tibolone (a selective estrogen enzyme modulator) administered with a GnRH agonist in PMS treatment protects against the bone loss observed with GnRH agonists and does not reduce the therapeutic effect of the agonist.[75]

There are few randomized, placebo-controlled studies of oral contraceptives (OCs) as a treatment for severe PMS or PMDD, and no consistent scientific evidence of their efficacy for the disorder.[76,77] A triphasic OC was more effective than placebo only for physical symptoms of breast pain and bloating.[76] A recent trial of an OC containing a new progestin, an analog of spironolactone with antimineralocorticoid and antiandrogenic activity, showed a consistent reduction of both physical and behavioral PMS symptoms including dysphoric mood, but additional studies with sufficient statistical power are needed.[78]

From a clinical perspective, OCs are widely viewed as both improving and worsening PMS symptoms. Combination OCs have both estrogenic and progestational effects that vary considerably among the more than 40 compounds available in the USA. Relative absorption of the hormones, peripheral conversion, the degree of follicular development in the placebo interval, individual susceptibility to monophasic or triphasic formulations, and side effects have large variations among women and are not well understood in relation to PMS. Moreover, OCs can have side effects of water retention, bloating, appetite changes, and depressed mood, which are also PMS symptoms. Some studies showed that OC users had fewer PMS symptoms than nonusers overall,[79] but other investigations found few symptom differences between the two groups and no difference with respect to mood changes.[80] In sum, there is little empirical support or guidance for OCs as a treatment for PMS/PMDD,[81] although it is reasonable to try OCs, particularly when contraception is also required. If mood symptoms are predominant and persist, a serotonergic antidepressant is considered the first-line therapy.

Estrogen therapy with dose regimens sufficient to suppress ovulation significantly decreased the dysphoric mood and physical symptoms of PMS.[82-84] However, estrogen must be cycled with progesterone to reduce the risk of uterine cancer, and the extent to which exogenous progesterone results in return of PMS symptoms remains unclear. Progesterone treatment of PMS was advocated for many years, but numerous studies, including three large randomized controlled trials, failed to show improvement significantly greater than placebo for the mood and behavioral symptoms of PMS.[85-87]

Anxiolytics

Alprazolam and buspirone showed modest efficacy for PMS in some studies,[87-91] but not others.[92,93] The well-known risk of dependence with alprazolam must be considered, and this medication should be tried only when the patient has symptoms clearly limited to the luteal phase (so that the medication is stopped for at least 2 weeks in each cycle) and no history of substance abuse. These medications offer an alternative to antidepressants,

but the extent to which patients who fail to respond to antidepressants respond to these anxiolytics is not known.

Nonpharmacologic approaches

Numerous nonpharmacologic approaches have been advocated for PMS, but few are supported by solid empirical evidence.[94] A large study of calcium supplementation (600 mg twice daily) for PMS reduced premenstrual depression, fatigue, edema, and pain significantly more than the placebo. However, the severity of the dysphoric mood symptoms was not indicated, and further information is required to determine the efficacy of this treatment for premenstrual dysphorias.[95]

A meta-analysis showed that vitamin B_6 was about twice as likely as placebo to improve PMS symptoms overall, with an odds ratio for improvement in depressive symptoms of 1.69, but the researchers concluded that the quality of the studies was too poor to have confidence in the results.[96] There was no significant dose response, indicating that the amount of vitamin B_6 did not affect improvement, and reports of peripheral neuropathies with doses exceeding 200 mg preclude the use of megadoses.[96]

Several reports of cognitive therapies show improvement of premenstrual symptoms.[94] Other complementary and alternative therapies showed no convincing evidence of efficacy for PMS in a review of randomized controlled trials (dietary supplements, 13 trials; herbal medicines, 7 trials; biofeedback, 2 trials; homeopathy, relaxation, massage, reflexology, and chiropractic, 1 trial each).[97]

Emerging from a long history with little understanding and many treatments of doubtful effect, clinically significant PMS is now recognized as a chronic disorder that impairs functioning and personal relationships for a sizeable number of women. Serotonergic antidepressants are the first-line treatment at this time. Using these medications only in the symptomatic luteal phase is effective for women without other comorbid disorders. Hormonal treatments for PMS are not supported by consistent scientific data on efficacy and safety, in spite of evidence of hormonal involvement in the disorder.

Perimenopause

When women are in their forties, anovulation becomes more frequent and menstrual cycles are altered in length and frequency.[98] This reproductive transition extends for 2 to 8 years before the menopause, which is defined as the point where there was no menstrual bleeding for 12 months.[99] The mean duration of the perimenopausal transition is about 5 years; the onset occurs between the ages of 39 and 51 years for 95% of women.[100] Although cycle irregularity is the traditional clinical marker for perimenopause, it is increasingly clear that hormonal changes and distressing menopausal symptoms such as hot flashes can occur before observed cycle changes, which are an unreliable indicator of the perimenopause.[101]

Prevalence of depression

Among the most controversial issues in the transition to menopause is its association with depression. Whether there is an association, what the causes are, and how such depression should be treated are questions that continue to have no definitive answers. Epidemiologic studies based on self-report of menopausal status and dysphoric mood have consistently shown that most postmenopausal respondents do not report high rates of depressive symptoms and that reported depressive symptoms were not related to menopause per se but to other health problems,[102-104] and suggest that menopause does not cause depressive illness.[105] The National Comorbidity Study reported 30-day estimates of major depression of 5.0% and lifetime estimates of 21.8% for women aged 45 to 54 years, slightly lower than the estimates for the 35- to 44-year age-group, which had the highest rates of depression.[106] However, the rates of recurrent depression were highest in the 45- to 54-year age-group when compared with older women.[107] The Massachusetts Health Study[102] found that in the cohort of women aged 45 to 55 years at baseline prior depression was the variable most predictive of subsequent depression, based on self-report of depressive symptoms using the Center for Epidemiologic Studies–Depression (CES-D) scale.[108] The chance of a *recurrence* of depression is high (50% after a first episode, 70% after two episodes, and 90% after three episodes)[109] and may coincide with the perimenopausal years.

Most cross-sectional studies suggest that women in the 40- to 55-year age-group are more likely to report depressive symptoms than pre- and postmenopausal women. In the current Study of Women's Health Across the Nation (SWAN), 40.5% of the sample of women

aged 40 to 55 years reported that they had felt depressed within the past 2 weeks.[110] Dennerstein et al defined perimenopausal status from bleeding patterns and reported that 38% of late perimenopausal women reported depressive symptoms in the previous 2 weeks compared to 26% of the premenopausal and 28% of the postmenopausal women.[111] Bosworth et al reported that 28.9% of women aged 45 to 54 years had a high level of depressive symptoms based on an abbreviated CES-D scale, but found no association between the depressive symptoms and menopausal stage defined by the women's perceptions.[112] Soares et al identified 28.7% of women aged 40 to 58 years attending a menopause clinic as meeting *DSM-IV* criteria for depressive disorders.[113] While all these studies suggest an increased prevalence of depressive symptoms and possibly depressive illness in the transition to menopause, whether these depressive symptoms are associated with hormonal fluctuations or changes that characterize the transition to menopause remains unclear.

Estrogen as an antidepressant

Estrogen treatment is widely believed to improve depressive symptoms in menopausal women,[114-118] but study results are inconclusive because of large variations in study design and measures, hormonal status and diagnosis of the subjects, the estrogen compound, dose, and duration of use, and failure to find an effect greater than the placebo response.[119-122]

Burt et al[123] identified six studies that included perimenopausal women for estrogen treatment of depressive symptoms. Only two studies were placebo-controlled; only one of these showed significant improvement with estradiol compared with placebo after 4 months of treatment, but the treatment advantage over placebo was not sustained after 12 months of treatment.[124] In an uncontrolled study of women judged to be depressed or not depressed on the basis of the Beck Depression Inventory, only the group that was not depressed responded to standard replacement doses (0.3–0.625 mg/day) of conju-gated estrogen.[125] Pharmacologic doses of estradiol (5–25 mg/day) showed improvement greater than placebo in women diagnosed with depressive disorders[126] and in a study of postmenopausal women with scores signifying mental distress (1–4 mg/day).[127] Conclusions cannot be drawn from the conflicting results of these studies, which are limited by designs that do not clearly identify essential variables, such as menopausal status and diagnosis of depression, and also lack comparability in the form and dose of estrogen treatment.

Two recent well-designed studies found 17β-estradiol to be effective for depression in perimenopausal women. Both studies clearly diagnosed depression, endocrinologically defined perimenopausal status and administered transdermal 17β-estradiol (the major circulating estrogen in women) using randomized, placebo-controlled, double-blind designs and showed that estrogen may be an effective treatment for major or minor depression in perimenopausal women. Soares et al[128] reported remission of depression in 68% of the estradiol group compared with 20% of the placebo group after 12 weeks. Schmidt et al[129] showed a full or partial response for 80% of the estradiol group compared with 22% of the placebo group after 6 weeks of estradiol. A progestin added at 7 weeks did not negate improvement with one exception of worsening of early morning waking. Both studies indicated that the effect of estradiol on mood was independent of hot flashes—an important finding that suggests that the improvement of depressed mood with estrogen treatment was not simply a result of improving hot flashes. Both studies identified a rapid onset of antidepressant response in perimenopausal depression. However, the brief duration of the progestin use may be inadequate to determine whether long-term progesterone use reduces the beneficial estradiol effect on mood.[116] Further studies are needed to confirm these positive findings and determine long-term effects of estradiol treatment.

Estrogen administration throughout the cycle may be more effective than the standard OC regimen for decreasing depressive symptoms in perimenopausal women. Blümel et al compared a standard OC (20 µg ethinyl estradiol and 150 mg desogestrel for 21 days followed by placebo for 7 days) with the same OC followed by only 2 days of placebo and 5 days of 10 µg ethinyl estradiol in a randomized trial.[130] Depressive, vasomotor, and somatic symptoms and sexual function improved significantly more in the group with estrogen continued throughout the cycle. The results were interpreted by the researchers to indicate that increasing the days with estrogen in women using OCs restimulated estrogen receptors and improved cerebral neurochemistry.

Antidepressant medications

The SSRIs (fluoxetine, paroxetine, and sertraline) and other serotonergic antidepressants such as venlafaxine, nefazodone, and clomipramine are currently viewed as the first-line treatment for most depressive disorders because of extensive data supporting their efficacy, the minimal need for dose titration, and generally favorable side-effect profiles.[58] However, there is growing evidence of gender differences and effects of menstrual status in treatment response and tolerability to SSRIs. Women with chronic major depression were more likely to respond to sertraline compared with men, who were more likely to respond to the tricyclic antidepressant, imipramine.[131] Menstrual status affected this response, with premenopausal women significantly more likely to respond to the serotonergic than a tricyclic antidepressant, while the postmenopausal women responded similarly to both medications. The postmenopausal women who were taking imipramine also had significantly lower attrition rates than premenopausal women. Similar results were observed in a comparison of fluoxetine with maprotiline.[132]

Other observations of postmenopausal women identified an interaction between estrogen status and antidepressant therapies: women who were using estrogen replacement therapy and received fluoxetine had a greater antidepressant response than the women who received only fluoxetine[133]; similarly, older depressed women who received both estrogen and sertraline responded better than those who received only sertraline.[134] Another trial of fluoxetine in depressed menopausal women failed to find any effect of estrogen therapy, but the subjects were younger (≥45 years of age) and menopausal status was determined only by age, limiting interpretation and comparisons of the results.[135] Overall, these preliminary findings suggest that menstrual status is an important consideration in selecting an antidepressant for women, and that the estrogen status (which differs in pre-, peri-, and postmenopausal women) may be associated with the response to antidepressants.

Management of depression in perimenopausal women

Current consensus guidelines for treatment of depression in perimenopausal women recommend an antidepressant for severe depression.[58] Data indicate that an SSRI may be preferred to a tricyclic antidepressant for women who are not postmenopausal. For women with previous episodes of depression, the general guideline is to prescribe the antidepressant used in the previous episode if the patient had a satisfactory response.

Transdermal estradiol (0.05–0.10 mg/day) may be of benefit for perimenopausal women with major or minor depression, based on preliminary but consistent findings of two new studies.[128,129]

Minor mood symptoms associated with the perimenopause are also improved with estrogen therapy.[116] A progestin must also be prescribed for women with a uterus and may reduce the improvement of depressed mood in some women. Estrogen therapy is generally contraindicated for women with breast cancer, any potentially estrogen-dependent malignancy, active liver disease, and active thrombosis. Speroff et al indicate close surveillance for women with seizure disorders, familial hyperlipidemias, and migraine headaches.[136] Other considerations include a history of breast disease, history of stroke, myocardial infarction or thrombosis, and active gall bladder disease or gallstones.

The estradiol dose of hormone replacement therapy (HRT) does not suppress ovulation or provide contraception for perimenopausal women, who continue to be at risk of pregnancy until the menopause.[137] For contraceptive protection and for estrogen-related symptoms such as hot flashes, an OC with estrogen rather than HRT may be preferred for perimenopausal women. However, there is no evidence at this time that OCs effectively treat major or minor depression in perimenopausal women. Recent studies suggested that reducing the placebo interval of OCs and extending estradiol through the cycle improved depressive symptoms, but these findings do not extend to women diagnosed with depressive illness. The association of cardiovascular events with estrogen is dose-related and the current low-dose OCs (<50 µg ethinyl estradiol) can be used by perimenopausal women with normal blood pressure.[137] Smokers over age 35 should not use OCs.

A frequently asked question is whether estrogen and antidepressant therapies can be combined. The strongest rationale for using both medications is the known benefits of each. In addition to its psychotropic effect, estradiol reduces menopause-related hot flashes, improves vaginal dryness, is protective against bone loss, which may result in osteoporosis, and may be protective against cardiovascular disease.[137] Recent evidence indicates that estrogen can produce an antidepressant response in perimenopausal women with major or minor depression.[128,129]

Antidepressants are clearly effective for dysphoric mood. Although preliminary findings have suggested that the combined use of HRT and serotonergic antidepressants enhanced the antidepressant response, these observations pertained to elderly depressed women and cannot be generalized to perimenopausal women. There are no studies of combined estrogen and antidepressant therapies in women identified as perimenopausal.

To assess perimenopausal depression, the pattern and severity of the depressive symptoms should be determined. Perimenopausal status is suggested by the presence of vasomotor symptoms such as hot flashes or irregular menstrual cycles, although it is entirely possible that a perimenopausal woman has neither, particularly in the early stages of the menopausal transition. Careful physical examination and medical history should be obtained to determine other coexisting conditions, previous experience of any depressive disorder, the onset of the depressive symptoms in conjunction with menstrual cycle changes, and to identify risk factors and contraindications for estrogen therapy. A follicle-stimulating hormone (FSH) level greater than 20 IU/L is a hormonal marker of the perimenopause, but single measures are considered unreliable because of sporadic follicular activity and competence. The decline in mean estrogen levels occurs primarily in the year before menopause,[138] although there is considerable individual variability. Burger et al recently reported that mean estrogen levels started to decrease about 2 years before the final menstrual period, but fell substantially only in the year before the final menses with the most rapid decrease around the time of the final menstrual period.[139] Recognition that the perimenopause can extend over a number of years and that the hormonal shifts that occur in this transition may be associated with depressive symptoms is important for patient care. However, scientific data to guide treatment of depression in the perimenopause are limited and inconclusive. Estrogen therapy may be helpful for major or minor depression as well as for depressive symptoms linked to the menopause. OCs containing estrogen are another possible option for perimenopausal women, who still require contraceptive protection, but there is no consistent evidence at this time of their antidepressant effects. The hormone doses of OCs are considerably higher than those of HRT, but only the HRT dose levels of estrogen have shown antidepressant effects in perimenopausal women at this time. Serotonergic antidepressants are clearly effective for depressive illness, and are now widely considered the first-line treatment for moderate-to-severe depressive illness or a repeated episode of depression in perimenopausal women.

Postpartum depression

The months following childbirth have been recognized throughout history as a period of increased risk of depression for vulnerable women, although diagnostic criteria have emerged only in recent decades, and there are few well-designed controlled studies of treatment efficacy. Two defining characteristics of PPD are its occurrence at a time of large hormonal shifts and its high likelihood of recurrence with subsequent pregnancies.

Prevalence

PPD is a nonpsychotic depression that meets the diagnostic criteria for major depression and occurs within several months of delivery as defined in the *DSM-IV*.[6] The point-prevalence of PPD within 6 to 9 weeks of delivery is about 12%.[140,141] Postpartum psychosis is uncommon, but potentially lethal to the woman or the infant, and occurs in 1 to 2 per 1000 women following childbirth, with onset usually within 2 to 4 weeks of delivery.[142] Mood lability, or "baby blues" within the initial days following delivery is very common, with estimates up to 80% for brief periods of symptoms such as tearfulness, fatigue, and insomnia that occur within the first 2 weeks of childbirth, peaking at about 5 days postpartum.[143]

It was long believed that women were at decreased risk of depressive disorders during pregnancy, and few studies examined associations between depression during pregnancy and the postpartum period. However, studies show that depression can increase steadily from the second trimester of pregnancy to 9 weeks postpartum,[140,143] with little difference in prevalence (9% in the second trimester; 12% postpartum) or even greater prevalence during pregnancy than postpartum.[144,145] Data also indicate that the depressive symptoms differ when compared during pregnancy and in early and later postpartum periods, corroborating both the occurrence of depressive symptoms during pregnancy and identifying differing vulnerabilities to depression throughout pregnancy and the postpartum period.[146]

PPD is strongly associated with previous depressions. A recent review indicated that the increased risk was 25% for women with a history of depression, 50% for women with previous PPD, and 75% for women with depression during the current pregnancy.[58] Twenty-nine percent of women diagnosed with late luteal phase disorder and 43% of women diagnosed with PMS had experienced PPD, suggesting possible association with premenstrual syndromes.[147,148] Other risk factors for PPD include poor social support and chronic stressors.[149]

Treatment of postpartum depression

Reported treatments for PPD include antidepressants, hormones, and psychotherapy, but there is a paucity of well-designed controlled studies, samples are small and there are no definitive conclusions.

Antidepressants

Sertonergic antidepressants with reported efficacy for PPD include fluoxetine in double-blind study,[150] and sertraline, venlafaxine, and fluvoxamine in open studies.[151-153] Results in the sertraline study suggested that response is swift (by 2 weeks) and at low doses, but these findings were not supported in another retrospective record review.[154] The many antidepressants available are clearly effective for depression but are generally unstudied for PPD. Other considerations in the selection of an antidepressant are the patient's tolerability of side effects and the response to a previously prescribed antidepressant. For women with previous episodes of depression, the general guideline is to prescribe the antidepressant used in the previous episode if the patient had a satisfactory response.

A major concern about drug therapy for breast-feeding mothers is the effect of medication on the infant.[155] In small studies, amitriptyline, nortriptyline, desipramine, clomipramine, imipramine, sertraline, fluvoxamine, and paroxetine were not detected in quantifiable amounts in infant plasma and all infants were thriving.[156-161] The results are encouraging, but cannot be generalized to all infants exposed to these medications.

Because of the high risk of repeated PPD, the question of prophylactic treatment is important but unanswered. In the only controlled study of an antidepressant administered as a prophylactic, the tricyclic antidepressant, nortriptyline, initiated immediately postpartum in nondepressed women at risk of a subsequent PPD, was not better than placebo; 25% of the women in each group had a recurrence of PPD.[162]

Hormone treatments

Sublingual 17β-estradiol (1 mg, 3 to 8 times/day to achieve a serum concentration of 400 pmol/L) in open treatment for 8 weeks resulted in rapid and significant improvement for women with severe PPD.[163] The women had very low serum estradiol concentrations at the pretreatment baseline (mean = 21.7 pg/mL), but whether the low estradiol levels differed from those of asymptomatic postpartum women could not be determined in the absence of a control group. Women with postpartum psychosis also responded to 17β-estradiol treatment in a similar study conducted by the same researchers.[164]

Transdermal 17β-estradiol (delivery of 200 µg/day for 6 months) was significantly better than placebo for PPD, meeting criteria for major depressive disorder.[165] The response occurred in the first month of treatment and was sustained for the 6 months of the randomized, double-blind study. The effect on symptoms of a progestin added after 3 months was not reported; endometrial curettage at the end of treatment showed endometrial changes (sic) in three women, which resolved on follow-up.

A very small open pilot study administered estrogen immediately after delivery to prevent recurrent PPD.[166] A much lower relapse rate than expected in the ensuing year (9% versus an expected 35% to 60% without prophylaxis) suggested the utility of estrogen for high-risk women and supported the hypothesis that PPD may be triggered by rapid changes in the levels of estradiol in vulnerable women. However, possible problems with high-dose estrogen therapy such as the need to administer coagulants and the interference of estrogen with breast milk are not yet answered.[167]

Evidence does not support progesterone treatment for PPD.[168] Nor is there scientific evidence to support the prophylactic use of progesterone to prevent the recurrence of PPD. A randomized controlled trial of norethisterone enanthate given within hours of delivery reported an *increased* risk of developing PPD.[169]

Psychotherapy

Although there is increasing evidence that antidepressants are relatively safe, concerns for possible

effects of pharmacologic treatments in the infants supports psychotherapy as the treatment for PPD in breast-feeding mothers. Evaluation of women mild-to-moderate major depression, who were randomized to interpersonal psychotherapy (IPT) or wait-list condition for 12 weeks demonstrated significantly greater improvement in PPD and social adjustment for the psychotherapy group.[170] Another study reported that fluoxetine and six sessions of cognitive behavioral therapy were each effective for minor and major depression occurring in the first 6 to 8 weeks postpartum, but also found no advantage to receiving both treatment modalities.[171]

Management

The most serious problem in the management of PPD is its underrecognition and undertreatment. Maternal depression can impair mother–infant bonding and affect cognitive and emotional development.[172] Women with a history of PPD or another mood disorder require close observation and prompt treatment of depressive symptoms. However, detection of possible PPD has been poor in routine clinical evaluation.[173] Identification of possible PPD significantly increased when a simple screening scale was used (6% vs 35%).[173] Another study showed that the rate of diagnosis of PPD increased from about 4% to 11% following the implementation of a universal screening of postpartum women.[141] A brief screening scale (eg, the 10-item Edinburgh Postnatal Depression Scale)[171] appears to be an essential tool for identifying women who may have clinically significant depression in the postpartum period. Consensus guidelines indicate that the first-line treatment of PPD is antidepressants whether or not the mother is breast-feeding.[58] Although case-series comparisons have consistently reported no clinically significant differences in the infants of mothers taking or not taking antidepressant medications, relatively small numbers of women and their infants have been studied, and the findings are not sufficient to generalize to all infants at this time. Thus, it remains important to consider the risk/benefit equation for each woman in selecting treatment for PPD.

Conclusions

Serotonergic antidepressants are generally the first-line treatment for menstrually related depressions—PPD, premenstrual dysphorias, and depression in the perimenopause—using regimens that are proven for major depression. While there is increasing evidence that the reproductive hormones are involved in these disorders, knowledge of their use as effective and safe treatments is still limited. Preliminary studies indicate that estrogen replacement therapy is effective for major and minor depression in perimenopausal women with or without a history of depression. Pilot data suggest that estradiol may be effective for severe PPD. Progesterone is clearly not effective for depressive symptoms in PMS/PMDD, the postpartum or perimenopause. Safety concerns for medications during pregnancy and breast-feeding point to psychotherapy as the treatment for PPD, but the risk calculation of each treatment modality should be made on an individual basis. No one treatment entirely fits each of these complex disorders with their still-heterogeneous populations, and a one-fits-all treatment approach is not possible. Nonetheless, understanding knowledge of the causes and treatments of women's depressions is increasing, and many women with these disorders can obtain relief with effective medical treatment. ❑

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El tratamiento de la depresión asociada con el ciclo menstrual: disforia premenstrual, depresión postparto y depresión perimenopáusica.

Algunas formas de depresión son específicas de la mujer dada su aparente asociación con cambios en las hormonas gonadales, las que a su vez modulan los sistemas neurorreguladores asociados con el ánimo y la conducta. Esta revisión examina la evaluación y tratamiento de la depresión que ocurre en el período premenstrual, en el postparto o en la perimenopausia de acuerdo con la literatura actual. Los antidepresivos serotoninérgicos muestran una clara eficacia en algunos síndromes premenstruales severos (SPM) y en el trastorno disfórico premenstrual (TDP), y constituyen el tratamiento de primera línea para estos trastornos. El empleo de antidepresivos para la depresión postparto es discutido debido a los efectos que provoca en los niños de madres que están lactando, pero hay una creciente evidencia que sugiere que la seguridad relativa de los medicamentos antidepresivos y el cálculo del riesgo debe hacerse caso a caso. El estradiol puede ser eficaz en la depresión postparto y en la depresión mayor moderada a grave en la perimenopausia. A pesar de su uso frecuente, la progesterona no es eficaz para los síntomas anímicos y conductuales del SPM o del TDP, la depresión postparto o los síntomas depresivos perimenopáusicos.

Traitement de la dépression associée au cycle menstruel : dysphorie prémenstruelle, dépression du post-partum, et périménopause

Plusieurs formes de dépression propres aux femmes seraient dues à leur apparente association aux variations des hormones gonadiques, lesquelles en retour modulent les systèmes neuromédiateurs liés à l'humeur et au comportement. Cette revue de la littérature actuelle fait le point sur l'évaluation et le traitement de la dépression tant prémenstruelle que survenant au cours du post-partum ou de la périménopause. Les antidépresseurs sérotoninergiques ont une efficacité constante sur les syndromes prémenstruels sévères (SPM) et sur les désordres dysphoriques prémenstruels (DDPM), et représentent le traitement de première intention de ces troubles. La crainte des effets des antidépresseurs chez les enfants de mères qui allaitent fait obstacle à leur utilisation au cours de la dépression du post-partum, mais de plus en plus d'arguments suggèrent la relative sécurité des médicaments antidépresseurs, et l'évaluation du risque devrait être faite au cas par cas. L'estradiol pourrait être efficace dans la dépression du post-partum et la dépression majeure modérée à sévère de la périménopause. Malgré son utilisation fréquente, la progestérone n'est efficace ni sur l'humeur et les symptômes comportementaux des SPM/DDPM et de la dépression du post-partum, ni sur les symptômes dépressifs de la périménopause.

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