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# A Reproductive Subtype of Depression: Conceptualizing Models and Moving Toward Etiology

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## Abstract

The lifetime risk for major depression in women is well known to be twice the risk in men and is especially high during the reproductive years between menarche and menopause. A subset of reproductive-age women experience depressive episodes that are triggered by hormonal fluctuations. Such “reproductive depressions” involve episodes of depression that occur specifically during the premenstrual, postpartum, and perimenopausal phases in women. These reproductive subtypes of depression can be conceptualized as a specific biological response to the effects of hormonal fluctuations in the brain. The different types of reproductive depressions are associated with each other, have unique risk factors that are distinct from nonreproductive depression episodes, and respond to both hormonal and nonhormonal interventions. This review uses a PubMed search of relevant literature to discuss clinical, animal, and genetic evidence for reproductive depression as a specific subtype of major depression. Unique treatment options, such as hormonal interventions, are also discussed, and hypotheses regarding the underlying biology of reproductive depression—including interactions between the serotonergic system and estrogen, as well as specific effects on neurosteroids—are explored. This review will provide evidence supporting reproductive depression as a distinct clinical entity with specific treatment approaches and a unique biology that is separate from nonreproductive depression.

### Keywords

estrogen; major depression; neurosteroids; perimenopause; postpartum; premenstrual; reproductive; serotonin



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The pathophysiology underlying major depressive disorder (MDD) remains unclear. Currently, the etiology of MDD is considered multifactorial, with environmental factors interacting with biological factors, and sometimes personality factors, to produce the illness that we recognize clinically as MDD. It is likely that there are several biological factors resulting in MDD. One important vulnerability for some women is susceptibility to hormonal changes that occur during the reproductive life cycle, leading to a “reproductive subtype” of depression.

It is well known that MDD is twice as common in women as in men. This increased risk begins in early adolescence and closes by the end of the fifth decade,1 corresponding to a woman's reproductive years. Within the reproductive life cycle, time periods associated with hormonal change (premenstrual, postpartum, and perimenopause) are known to precipitate mood symptoms in a subgroup of women. While mild depressive symptoms are common in the general population during periods of hormonal fluctuation, a minority of women experience severe depressive episodes during the premenstrual, postpartum, or perimenopausal time periods. Most women who experience severe symptoms also have underlying mood disorders and therefore experience depressive episodes at other, non-reproductive-associated times of their lives.2-5 “Reproductive-related depressive disorders” have been hypothesized to result from an affective vulnerability to the hormonal changes that occur during the premenstrual, postpartum, and perimenopausal phases of a woman's reproductive life.6

The reproductive subtype of depression can be conceptualized as a specific biological response to hormonal fluctuation in the brain that leads to depression. A growing body of literature has demonstrated the modulatory effects of estrogen on both the central nervous system, in general, and the serotonergic system, in particular.7 While the use of estrogen may have antidepressive effects for some women, fluctuations in estrogen and other hormonal levels may also trigger a vulnerability to mood disorders in other women.7 Reliably identifying this subgroup of women is difficult, however, because not every MDD episode that occurs at a time of hormonal change meets this definition, which requires that hormonal fluctuation specifically trigger a biological vulnerability. Some “reproductive” MDD episodes may simply be coincidences due to timing and may not reflect a biological response to hormonal change. Identification and study of the subgroup of women that actually experiences depressive episodes biologically triggered by hormonal change— that is, “reproductive depression”—may lead to a better understanding of the biological underpinnings of MDD in general. In this review we use the term “reproductive depression” to imply a MDD episode that occurs as a biological response to hormonal change, specifically premenstrual dysphoric disorder (PMDD), postpartum depression (PPD), and perimenopausal depression. While this definition cannot be directly applied clinically, we will demonstrate that clinical clues that a MDD episode is a type of reproductive depression include timing, a personal or family history of reproductive depressions, and a quick or preferential response to selective serotonin reuptake inhibitors (SSRIs).

This review will focus on the evidence supporting the reproductive subtype of depression, including associations between different types of reproductive depression as well as preliminary genetic studies of reproductive depression. We conducted a computerized literature search on PubMed through October 2008 using the following search terms: PMS, PMDD, postpartum depression, perimenopausal depression, and reproductive depression.

We discuss the potential biological underpinnings of reproductive depression, including the neuromodulating effects of endogenous estrogen and evidence derived from clinical, neuroimaging, and animal studies. We will also discuss the specific use of hormonal

therapies to treat reproductive, but not nonreproductive, depression—evidence that reproductive depression is a distinct entity. Finally, we will explore evidence that serotonergic antidepressants may have superior efficacy in reproductive depression, and discuss potential explanations for these clinical observations. In summary, this review will provide evidence supporting reproductive depression as a distinct clinical entity with specific treatment approaches and a unique biology separate from nonreproductive depression.

## EVIDENCE FOR THE "REPRODUCTIVE" SUBTYPE OF DEPRESSION

Three lines of evidence support the idea of a reproductive subtype of depression: (1) correlations between reproductive depressions at different stages of reproductive life, (2) genetic studies, and (3) evidence that the risk for depression is elevated for women during times of hormonal change and decreased during times of hormonal stability.

### Correlation Studies

Correlation studies have demonstrated that depressions occurring at different stages of reproductive life are associated with each other. A number of studies have shown that a history of one type of reproductive depression predicts depressive episodes at other times of hormonal change (Table 1),8-20 suggesting that sensitivity to hormonal change may be a stable trait that persists across the reproductive life cycle.

In the most common approach used to study the association between depression at different reproductive life stages, a group of women is identified who experience one type of reproductive depression, and it is then determined retrospectively whether these women had a history of other types of reproductive depressions. A number of the studies contrast findings with a control group of women without presenting complaints (Table 1: Studies 1, 2, 9) or to women without such complaints within a larger sample or cohort (Table 1: Studies 3, 5, 6, 7, 8, 10). The majority of the studies assessed for depressive *symptoms* occurring at the same times as reproductive life events (Table 1: Studies 1, 3, 4, 7, 10, 11) rather than MDD episodes that met DSM criteria. Other studies established a diagnosis for the current, but not the prior, reproductive depression episode (Table 1: Studies 2, 5, 6, 8, 9, 12). Most studies were conducted retrospectively for at least one reproductive episode (Table 1: Studies 1, 2, 3, 4, 5, 7, 8, 9, 11, 12), whereas a minority established a depression diagnosis prospectively for reproductive events (Table 1: Studies 6, 10). Though most studies examined only two reproductive life events, two studies examined a population of women with mood disorders, assessing for mood symptoms at all reproductive life events (Table 1: Studies 4, 11).

Association between a history of premenstrual symptoms and PPD symptoms was demonstrated in 5 of 7 studies (Table 1: Studies 1, 2, 7, 8, 11). Most of the studies that found a significant association were large (200–1800 women) (Table 1: Studies 7, 8, 11). In contrast, the negative studies (Table 1: Studies 4, 10) were generally smaller. Among women seeking treatment for premenstrual symptoms, approximately 40% of those with a prior pregnancy reported a history of PPD, as compared to 12% of women with no premenstrual symptoms (Table 1: Study 2). In another study that identified women with PPD, 43% reported a history consistent with PMDD (retrospectively determined), compared to 28% of women without PPD (Table 1: Study 8). One of the two negative studies (Table 1: Study 4) included women with bipolar disorder in the sample. Notably, unlike in MDD, there is evidence that premenstrual symptoms may not reliably predict postpartum mood symptoms in women with bipolar disorder.19 The weight of the evidence from these correlation studies therefore suggests that premenstrual symptoms appear to be associated with the development of postpartum mood symptoms in a subgroup of women with MDD.

Of eight studies examining whether premenstrual symptoms predict perimenopausal depressive symptoms, six (Table 1: Studies 1, 3, 4, 5, 6, 11) describe a statistically significant association between these reproductive depression episodes, and a seventh (Table 1: Study 9) found a trend supporting the association. The eighth study (Table 1: Study 12) reported that a history of premenstrual symptoms was not a consistent finding in women with perimenopausal depression, though 55% of women with perimenopausal depression reported a history of premenstrual symptoms.

Another four studies (Table 1: Studies 1, 4, 11, 12) examined the association between postpartum mood symptoms and perimenopausal depressive symptoms. Of these, three (Table 1: Studies 1, 4, 11) reported a positive association. In the only study to examine whether all three states were associated (Table 1: Study 11, data not shown), an association between premenstrual, postpartum, *and* perimenopausal depressive symptoms was found in 509 women with MDD. These women met DSM criteria for MDD and had a history of nonreproductive MDD in addition to reproductive depression.

One issue that limits interpretation of these studies is that most were conducted retrospectively. Retrospective recall of premenstrual symptoms does not consistently predict PMDD assessed prospectively.21-23 In addition, determination that criteria for specific DSM-IV diagnoses of PMDD or PPD were present was not always achievable because standardized psychiatric interviews were not necessarily conducted.

One final study examined whether women who experienced a PPD after their first child went on to have further postpartum and non-postpartum depressive episodes.24 Those who experienced their first episode of depression when they were postpartum ($n = 34$) had an increased risk for PPD but not for non-postpartum depression. In contrast, those women who had both a history of MDD prior to the birth of their first child and a PPD episode ($n = 21$) did not have an increased risk of PPD, but they did have an increased risk for future nonreproductive MDD. These data suggest that women whose first episode of depression presents postpartum are specifically susceptible to reproductive depressions, thus supporting the notion that PPD is a specific type of reproductive depression that has a distinct clinical course from nonreproductive depression.

In summary, a history of one type of reproductive depression or depressive symptoms appears to increase the likelihood that a woman will experience other types of reproductive depressions. A prospective study of women with prospectively defined PMDD who are followed through pregnancy and the perimenopause is required to solidify this association. While these findings indicate that different types of reproductive depression are associated with each other, they do not indicate that reproductive depression is necessarily distinct from nonreproductive depression.

## Genetic Studies

Though relatively few genetic studies have been conducted on reproductive depression, current data support the idea that reproductive depression has a distinct biological vulnerability from that of nonreproductive MDD.

Several studies have found that PPD exhibits familial aggregation25,26 in families with MDD, thus suggesting a genetic basis for the disorder. These studies indicate that in families with MDD, PPD clusters in some, but not all families, thus supporting the idea that the vulnerability to PPD is separate from the vulnerability to MDD. Individuals participating in these studies met criteria for DSMdefined MDD and also had a history of non-reproductive depressions. Notably, familial aggregation among women with PPD was seen only when PPD was defined as developing within four weeks of delivery and not when PPD was

defined broadly as onset within six months.25 thus linking the onset more closely to the hormonal changes associated with labor and delivery.

Several analyses of the heritability of premenstrual symptoms, as well as several twin studies, suggest that premenstrual depression may have a genetic basis,27-33 though not all these studies are positive.34,35 A preliminary association between the risk of prospectively confirmed PMDD and genetic variation in the ESR1 estrogen receptor alpha gene36 suggests that specific genetic variants may predispose to the development of PMDD. While the results are preliminary, familial aggregation, genetic association, and heritability studies of the reproductive subtype of depression support the idea that the reproductive subtype may have a unique and distinct biological basis from MDD.

### Decreased Risk During Hormonal Stability

One additional line of evidence supporting reproductive depression is the observation that when hormone levels in women are not fluctuating, such as during pregnancy and the postmenopause, the risk for depression does not appear to be elevated. Although estradiol and progesterone levels do increase steadily during pregnancy, they do not decline rapidly or fluctuate erratically as they do during the postpartum and perimenopausal phases. It is the effects of rapidly changing levels of estradiol and progesterone in brain regions involved in mood regulation that are thought to contribute to the risk of reproductive depression.13,37,38

A recent study conducted as part of the 2002 National Epidemiologic Survey on Alcohol and Related Conditions interviewed 14,549 women with a known past-year pregnancy status, and compared rates of major psychiatric illness during pregnancy and postpartum, and in the non-pregnant female population.39 No increase in risk for MDD was found during pregnancy as compared to the non-pregnant population, though the risk for MDD postpartum was elevated, with an adjusted odds ratio of 1.52.39 Similarly, recent studies have demonstrated an increased risk of MDD during perimenopause.13,40,41 Further, while the rate of MDD in women is well known to be double the rate in men during the reproductive years, when hormone levels fluctuate,1 depression rates are similar in older postmenopausal women and men, supporting the idea that exposure to fluctuations in reproductive hormones may increase the rate of MDD in women.42

In summary, correlation studies indicate that women with one type of reproductive depression are at an elevated risk for other types of reproductive depression. The fact that not all depressive episodes that occur at times of hormonal change meet the definition for reproductive depression, and may instead be due to a coincidence of timing, may explain why this correlation is not one to one. Genetic studies support the idea that the biological vulnerability to reproductive depression is separate and distinct from the vulnerability to nonreproductive depression. Finally, the observation that there is a decreased vulnerability to, but not zero risk of, MDD in women during times of reproductive hormone stability also supports the idea that vulnerability to reproductive depression is separate from nonreproductive depression. Thus, two subgroups of women with MDD appear to exist: those with nonreproductive depression and those with depression that occurs both during times of hormonal change and during nonreproductive times.

## POTENTIAL MECHANISMS OF “REPRODUCTIVE” DEPRESSION

It has been hypothesized that women with reproductive-related depressive disorders have abnormalities within the gonadal steroid system. Multiple studies43-49 have shown that hormone levels of estrogen and progesterone are normal in women with PMDD, PPD, and perimenopausal depression. A series of other studies, however, has provided evidence that

reproductive depressions occur in women with a specific sensitivity to hormonal change.[38,50,51] These studies have taken women with a history of reproductive depression; in a blinded fashion, exposed them to hormonal change; and, in that setting, induced depressive symptoms. For example, 10 women with PMDD experienced a recurrence of their mood symptoms when estrogen or progesterone was added back after symptoms were stabilized by the gonadotropin-releasing hormone analog, leuprolide.[50] In contrast, none of 15 women without PMDD experienced mood symptoms with the same protocol, and none of 5 women with PMDD experienced mood symptoms when a placebo was added.[50] Similarly, in another study focused on PPD, 8 women with a history of PPD had a recurrence of depressive symptoms when high doses of estrogen and progesterone were withdrawn precipitously, modeling the hormonal pattern of PPD.[38] In contrast, using the same protocol, none of 8 women without a history of PPD experienced mood symptoms.[38] Finally, 18 women with perimenopausal depression experienced spontaneous improvements in their symptoms in conjunction with a decline in plasma FSH levels (indicating a restoration of ovarian function).[51] Thus, in studies modeling the hormonal changes occurring in reproductive depression episodes, depressive symptoms were seen in women with a history of reproductive depression but not in women without a history of reproductive depression. Results of such studies have led to the conceptualization of a specific biological vulnerability to fluctuating hormone levels underlying reproductive depression.

One hypothesis explaining the vulnerability to mood disorders in some women during stages of hormone change proposes that the neuromodulating effects of estrogen via the serotonergic system triggers MDD episodes in susceptible women.[7] Although the exact vulnerability remains to be defined, it has been hypothesized that a reduced capacity to adapt to changing levels of estradiol or progesterone may predispose some women to depression.[52] In the next two sections we will review clinical evidence and studies in animals that support this hypothesis.

## Clinical Studies

Sex differences in serotonergic function provide indirect evidence of female-specific hormonal influence on the serotonergic system. Studies of tryptophan (serotonergic) and catecholamine (noradrenergic) depletion indicate that there are sex differences in the serotonergic system. Euthymic women without a history of MDD appear to be at higher risk than men for developing depressive symptoms in response to low levels of serotonin following tryptophan depletion,[52-55] whereas the response to catecholamine depletion appears to be similar for both sexes.[55] These findings suggest that female-specific factors such as estrogen influence the serotonergic system.

Several tryptophan infusion and depletion studies have also been conducted in women with reproductive subtypes of depression. Tryptophan infusion normally results in an increase in circulating prolactin and growth hormone,[56] but this response is known to be blunted in both male and female depressed patients relative to nondepressed controls. Interestingly, the response of prolactin and growth hormone appears to be blunted for all women when they are premenstrual compared to postmenstrual, and this finding is exaggerated in women with "premenstrual depression."[56] Similarly, tryptophan depletion has been shown to increase irritability premenstrually in healthy women[57] and to worsen symptoms of documented premenstrual syndrome.[58] Preliminary tryptophan studies in peri- and postmenopausal women suggest that serotonin may not play as critical a role in perimenopausal depression.[59]

Results from radiolabeling and positron emission tomography (PET) studies in women suggest that serotonin receptors implicated in depression are affected by female gonadal hormones and cycles.[60,61] Preliminary studies in women with prospectively confirmed

PMDD demonstrate a reduction in 5HT1A receptor binding in the dorsal raphe nucleus between the follicular and luteal phase relative to female controls without PMDD.60 Another study found that the administration of estrogen and progesterone in postmenopausal women increased the density of 5HT2A receptors in the cerebral cortex, showing that hormonal treatments influence the serotonergic system in the central nervous system.61

### Animal Studies

Studies in animals have shown that estradiol acts on neurotransmitter systems thought to be involved in the pathophysiology of mood disorders. These estrogenic effects result in effects on neuroregulation and behavior similar to those exerted by serotonergic antidepressants in animal models of depression. For example, estrogen has been shown in animal models to increase the levels or activity of critical neural-signaling systems that have been implicated in mood regulation, including brain-derived neurotrophic factor, cAMP response element-binding protein, and tyrosine kinase A.62 In other models, estradiol has been shown to inhibit mRNA expression of the serotonin transporter 63 and to decrease activity of 5HT1A receptors.64 Rats who become estrogen deficient through ovariectomy demonstrate increased immobility (or more depressed-like behavior) in the forced swim test, a model for MDD.65 Treatment with estradiol reverses the increased immobility.65 A recent study has further linked the serotonergic system to maternal behavior. Mouse mothers who were genetically engineered to have disrupted serotonin neuron development fail to display critical postpartum mothering behaviors.66

Taken together, the clinical and animal data support the hypothesis that reproductive depression may stem from a vulnerability within the serotonergic system triggered by changes in the reproductive hormones estradiol or progesterone. It is important to note that some evidence supports a specific role for estrogen, whereas with other evidence it is difficult to discern whether changes in estrogen, progesterone, or the combination triggers the underlying vulnerability.

## HORMONAL TREATMENTS FOR “REPRODUCTIVE” DEPRESSION

If the reproductive subtype of MDD is triggered by fluctuations in hormone levels, particularly estradiol, one would postulate that the use of hormonal treatments might be effective specifically for women with reproductive depression. Providing support for this hypothesis is evidence that estrogen and other hormonal treatments are effective in premenstrual, postpartum, and perimenopausal episodes of MDD but not in nonreproductive MDD episodes. Table 267-83 details studies using hormonal treatments (alone, not in conjunction with antidepressants) used for premenstrual, postpartum, and perimenopausal depression.

### Premenstrual Symptoms and PMDD

Both estrogen monotherapy and oral contraceptive pills (OCPs) containing a combination of estrogen and progesterone have been used to treat premenstrual mood disturbances. Recent placebo-controlled trials have reported benefit of the OCPs formulated with the novel progestin drospirenone in women with PMS and PMDD. Benefits are seen both as singular73,84 therapy in PMS and PMDD, and as adjunctive75,85 treatment in premenopausal women with treated MDD and premenstrual breakthrough of symptoms.86 It is unknown whether these benefits are specific to the OCP that contains drospirenone. Preliminary evidence also suggests that the OCP containing the progestin levonorgestrel suppresses PMS symptoms,87 but the results of the placebo-controlled trial are pending.

A recent comprehensive review88 suggests that drospirenone itself may play an important role in the treatment of PMDD because it is long acting and may have some unique

neuroactive properties. Moreover, other progestins used alone or as part of an OCP failed to show a clear benefit, consistent with earlier evidence that older progestin preparations are ineffective in PMDD.70,89 Although it is plausible that drospirenone may have unique therapeutic effects in women with PMDD, another factor that may play an important role in the efficacy of OCPs containing drospirenone is that they have shorter hormone-free intervals compared to older OCP preparations. Specifically, the drospirenone-based OCP has a four-day hormone-free interval, in contrast to a typical seven-day hormone-free interval. The truncated hormone-free interval in the newer OCPs results in greater suppression of pituitary and ovarian hormone levels than with the standard OCPs with their seven-day hormone-free interval.90

In an effort to maximally suppress follicular activity, some newer OCP preparations have been administered continuously for 3 to 12 months, thereby eliminating the hormone-free interval. Use of such extended regimens, in contrast to those with seven-day hormone-free intervals, may have additional benefits for women with PMDD.91 This evidence supports the principle that OCPs treat PMDD by suppressing hormonal fluctuation and that PMDD is a reproductive depression. Other studies have found that another hormonal intervention involving ovulation suppression by the GnRH agonist leuprolide also appears to improve premenstrual depressive symptoms.88

Several studies have investigated the use of estrogen therapy alone for severe premenstrual mood complaints in young women. Continuous use of estrogen therapy throughout the menstrual cycle67,69,71—but not luteal phase–only estradiol therapy68—reduced premenstrual dysphoria.

## Postpartum Depression

Several clinical trials have examined the effectiveness of estrogen in the prevention and treatment of PPD. A randomized, double-blind, placebo-controlled trial of 61 women with postpartum depression that developed within three months of delivery found that 80% of patients receiving an estrogen patch (200 mcg/day) had a significant reduction in their depressive symptoms compared to 31% of patients receiving placebo.78 In another open-label trial of sublingual 17$\beta$-estradiol (1 mg; 3–8 times daily, depending on serum estradiol), symptoms of severe postpartum depression remitted in 23 women after two weeks of treatment.80 However, nearly half of the estrogen-treated patients were also receiving antidepressants, making it difficult to determine if the estrogen or the antidepressant improved depressive symptoms. In a study of 10 women with postpartum psychosis, sublingual 17$\beta$-estradiol (1–6 mg, dosed to achieve 400 pmol/L serum estradiol) significantly reduced psychotic symptoms in all participants, all of whom had extremely low serum estradiol levels at baseline.79 Finally, high-dose estrogen (begun at 10 mg/day, tapered over 28 days to 0.625 mg/day) following delivery in 4 women with a history of postpartum depression prevented the expected relapse rate of 35%–60% of depressive symptoms within the first postpartum year.77 Although the lack of a pure control group limits these studies, their findings suggest that estrogen treatment may be helpful in preventing or treating postpartum depression.

## Perimenopausal Depression

A number of studies have demonstrated that estrogen therapy is effective for perimenopausal depression but not for depression in older, postmenopausal women. In studies of perimenopausal women, estradiol (50–100 mcg/day) administered both as monotherapy82,83 and in combination with antidepressants improved depressive symptoms when hormone replacement alone was only partially effective.92-94 In contrast, a randomized, placebo-controlled trial of estrogen (100 mcg/day) in older, postmenopausal

women with depressive disorders but no vasomotor symptoms demonstrated no improvement in mood symptoms.95 Further, results from the Heart and Estrogen/Progestin Replacement Study (HERS)96 trial of postmenopausal hormone therapy showed that combination therapy with estrogen and progestin (0.625 mg/day and 2.5 mg/day, respectively) improved depressive symptoms in postmenopausal women only if they were experiencing vasomotor symptoms. It remains unclear whether the result in the HERS study is due to the combination of estrogen and progestin or, instead, whether the presence of vasomotor symptoms contributes to depressive symptoms in this population, thus allowing for improvement when vasomotor symptoms are decreased. In either case, available data suggests that estrogen treatment during perimenopause, a time of hormonal fluctuation, may be helpful in treating depressive symptoms. In contrast, estrogen postmenopause, when hormone levels stabilize, does not appear to treat depression unless vasomotor symptoms are present.

### Nonreproductive Depression

Few studies have examined whether estrogen and other hormonal treatments are effective in nonreproductive depression in women. As noted, estrogen does not appear to be effective in treating depression in older, postmenopausal women.95 There have been no clinical trials reporting the efficacy of estrogen to treat depression in younger, premenopausal women. One observational study examined whether hormonal contraception influenced the severity of depressive symptoms in 1320 premenopausal women.76 The study concluded that women on nonrandomly assigned birth control pills were significantly less depressed than women not taking hormonal treatments. In this large sample, however, the difference in the average depression score between women who were on hormonal contraception and those who were not was only one point, indicating that this difference may not be clinically significant. In addition, there was no assessment for a history of premenstrual symptoms, which could have influenced the results.

## ANTIDEPRESSANT TREATMENT OF “REPRODUCTIVE” DEPRESSION: CLUES REGARDING PATHOPHYSIOLOGY

A number of studies suggest that reproductive depression may be specifically responsive to SSRIs. Gonadal steroids may at least partially explain these observations, with endogenous estrogen levels playing a permissive or augmentation role in the setting of an SSRI.97 Our review of the evidence supporting the role of gonadal steroids in response to SSRIs begins with the evidence that premenopausal women, who have significant estradiol levels, may respond preferentially to SSRIs as compared both to postmenopausal women, who have undetectable estradiol levels, and to men. We will then review the evidence for the use of SSRIs in reproductive depression and end with a discussion of potential mechanisms underlying this differential response.

Several authors have noted differential responses to SSRIs and other classes of antidepressants between preand postmenopausal women (Table 3).98-102

One such study found that women with MDD who were over age 40 responded better to the tricyclic antidepressant (TCA) imipramine than did women who were under 40.98 This study was limited by the use of age as a proxy for menopausal status. Because the mean age for menopause is 51, it is unlikely that the age cutoff used in this study accurately divides the group into pre- and postmenopausal status. Another study reported that postmenopausal women with MDD responded less well to SSRI therapy than premenopausal women.102 A meta-analysis of eight randomized, controlled trials of patients with MDD found an inferior SSRI response rate among women over age 50 compared to women under age 50, whereas

there was no such difference among men.101 Interestingly, nonrandomized hormone therapy improved the response rate in women over age 50.101 In a multicenter, randomized, open-label trial, sertraline was found to be a more effective treatment of depression than imipramine in women, whereas men responded similarly to both medications.100 Finally, another study99 showed differential effectiveness of SSRIs and TCAs in premenopausal women compared to men and postmenopausal women, with premenopausal women showing a significantly higher response rate to sertraline as compared to imipramine. Furthermore, postmenopausal women showed equal response rates to sertraline and imipramine.99 These data provide indirect evidence that SSRIs may be more effective in women who have significant estradiol levels.

Evidence from PMDD trials reveals that SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) treat PMDD within the first menstrual cycle and are also effective with intermittent luteal-phase treatment.86, 103-109 This rapid response is in contrast to the minimum of 4–8 weeks110, 111 required for the treatment of MDD. Furthermore, SSRIs and SNRIs are effective for PMDD, whereas non-serotonergic antidepressants are not.112, 113 In contrast, nonreproductive depression can be treated effectively with SSRIs, SNRIs, and nonserotonergic antidepressants. These observations argue for a specific mechanism involving serotonergic pathways underlying the pathophysiology of PMDD that is distinct from the mechanisms underlying MDD that is unrelated to the reproductive cycle.

In studies of women with PPD, preliminary evidence suggests that women with PPD may respond preferentially and more rapidly to SSRIs than to TCAs. There have been two small, randomized clinical trials of PPD recurrence prevention and one randomized trial in the treatment of current PPD. The SSRI sertraline prevented recurrence in significantly more women than did placebo,114 whereas in a separate study, the TCA nortriptyline failed to improve recurrence rates compared to placebo.115 In the randomized trial for treatment of current PPD, no difference between sertraline and nortriptyline was observed, but the response to sertraline was significant within the first week of treatment, whereas the response to nortriptyline was not significant until the second week,97 suggesting that in women who respond to sertraline, the onset of action was more rapid. A one-week difference is small, but these observations suggest that “reproductive” depression may respond more rapidly to SSRIs that to TCAs.

The superior responsiveness of reproductive depression to SSRIs raises the question about the serotonergic mechanism of action underlying reproductive episodes of MDD. A uniquely serotonergic mechanism is not supported, because TCAs also exert their effects on the serotonergic system, albeit via a less direct mechanism. Thus, another mechanism of action unique to selective serotonergic medications is needed.

One potential explanation for the rapid response to SSRIs by women with reproductive depression is the action of SSRIs on neurosteroids. These steroids, synthesized in the central nervous system, control glial and neuronal cell responses through genomic mechanisms and membrane-receptor modulation.116 While a complete review of the various neurosteroids and their actions is beyond the scope of this review, we will focus on allopregnanolone (ALLOP), a potent modulator of GABA-A receptors and a metabolite of progesterone that is synthesized in the brain, ovary, and adrenal glands. ALLOP has been shown to be decreased in plasma and cerebrospinal fluid of patients with MDD, and to normalize with successful treatment.117-120 In reproductive-related depression, there are conflicting results regarding ALLOP levels in women with PMDD,121 potentially reflecting the presence or absence of a history of nonreproductive MDD. However, a recent study using proton magnetic resonance spectroscopy found evidence that cortical GABA and plasma ALLOP were reduced in the postpartum period, although there was no direct correlation with the diagnosis of PPD.122

SSRIs, including fluoxetine,123 appear to have a specific, nonserotonergic-based action on neurosteroids that is not seen with some tricyclic antidepressants.124,125 SSRIs, but not imipramine, have been shown to decrease the activity of a crucial enzyme leading to an increase in ALLOP.124, 125 Thus, one potential explanation for a selective and rapid response to SSRIs in reproductive depression is that the pathophysiology of reproductive depression reflects a specific abnormality within the neurosteroid system that is not be seen in nonreproductive MDD. Supporting this hypothesis is a recent animal study that found that the absence of a specific subunit ($\delta$) of the GABA receptor—one that is normally regulated by progesterone-derived neurosteroids throughout pregnancy and during the postpartum period—is associated with depression-like and abnormal maternal behaviors, resulting in decreased pup survival.126

## DISCUSSION

In summary, reproductive depression episodes commonly occur in women with nonreproductive MDD episodes. Having one type of reproductive depression is predictive of experiencing other types of reproductive depression, and preliminary family and twin studies suggest that PMDD and PPD may have a genetic basis. These findings, in turn, support the hypothesis that reproductive depression stems from a specific biological vulnerability to normal fluctuation in reproductive hormones during reproductive life events in women. This biological vulnerability is likely to result from the interactions between estrogen and the serotonergic system, although other hormones and brain systems, including neurosteroids, may also be involved. Observations that SSRIs may be uniquely and more rapidly effective in treating reproductive depressive episodes, along with the observation that hormonal treatments are also uniquely effective in reproductive depression, may provide a clue regarding the underlying biology. The literature suggests a pathophysiologic link between premenstrual, postpartum, and perimenopausal depression, likely involving the interplay of female gonadal steroids and neurotransmitter systems, along with a possible role for neurosteroids.

Large, prospective studies both of the differential effects of serotonergic versus noradrenergic antidepressants and of the rapidity of onset of action need to be conducted in order to further elucidate the mechanism of reproductive depression. Future studies should take into account a positive or absent history of reproductive depression and should track carefully the onset of action of antidepressant action. Careful examination of these details may help to decide not only whether reproductive depression is a useful clinical subtype, but whether women suffering from this type of depression preferentially and quickly respond to SSRIs or hormonal treatments.

One other important issue warranting further investigation is that not every depressive episode that occurs in conjunction with a reproductive event necessarily meets the definition of reproductive depression. If one defines reproductive depression as a major depressive episode that occurs specifically as a biological response to hormonal change, then it likely that the current literature includes samples of women that are heterogeneous, including both women who have an underlying biological vulnerability to hormonal fluctuation and women whose MDD episode presents during a reproductive life event because of psychosocial factors or merely by coincidence. Genetic studies indicating that PPD has a genetic basis—but only if the depressive episode developed rapidly within the first four weeks postpartum—suggest that not every episode of depression associated with a reproductive event is a reproductive subtype of depression. This factor should be considered when designing research studies and reviewing treatment options for this population. Clinical clues that a particular major depressive episode may be a “reproductive” depression remain to be defined but may include a clear correlation between the timing of the onset of the MDD

episode and the timing of hormonal change, a history of previous reproductive depressions, and a history of a preferential, quick response to SSRIs.

In conclusion, reproductive depression is an important clinical subtype of MDD. It may predict future clinical course during reproductive life events and may also imply specific treatment options/algorithms. Available evidence suggests that antidepressants targeting the serotonergic system, as well as hormonal treatments, should be considered. As this field develops, it is expected that biological markers, whether genetic, hormonal, or via neuroimaging, will differentiate the reproductive subtype of depression from nonreproductive MDD episodes. These markers will inform the development of more targeted and successful treatments for women with reproductive depression.

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**TABLE 1**

Correlational Studies of Reproductive Depression at Different Reproductive Life Stages

| Study Number | Author/year | *n* | Population | Was an association found between | | |
|---|---|---|---|---|---|---|
| | | | | PMS & PPD? | PMS & PMD? | PPD & PMD? |
| 1 | Stewart & Boydell (1993)8 | 44 | Women w/ “high psychological distress” attending menopause clinic | Yes | Yes | Yes |
| 2 | Chuong & Burgos (1995)9 | 190 | Women seeking gynecologic care with PMS but no psychiatric history | Yes | N/A | N/A |
| 3 | Morse et al. (1998)10 | 291 | Community sample of urban Australian women 45–55 with PMS; psychiatric history unknown | N/A | Yes (difficult transition) | N/A |
| 4 | Gregory et al. (2000)11 | 72 | Women 19–75 with history of major depressive or bipolar disorder | No | Yes | Yes |
| 5 | Binfa et al. (2004)12 | 300 | Chilean women 50–59 w/ history of PMD; psychiatric history unknown | N/A | Yes | N/A |
| 6 | Freeman EW et al. (2004)13 | 436 | Population-based cohort of women in their 40s | N/A | Yes | N/A |
| 7 | Aydin et al. (2005)14 | 728 | Turkish women within the first postnatal year | Yes | N/A | N/A |
| 8 | Bloch et al. (2005, 2006)15,16 | 1800 | Israeli women in a general hospital maternity ward postpartum | Yes | N/A | N/A |
| 9 | Richards et al. (2006)17 | 70 | Depressed perimenopausal women 40–55 attending menopause clinic | N/A | Trend only | N/A |
| 10 | Haywood et al. (2007)18 | 63 | Community sample of 63 English women who had given birth in past three years | No | N/A | N/A |
| 11 | Payne et al. (2007)19 | 509 | Postmenopausal women with major depressive disorder & prior pregnancy | Yes | Yes | Yes |
| 12 | Steinberg et al. (2008)20 | 116 | Women 40–55 seen at NIMH midlife mood disorders clinic meeting criteria for PMD | N/A | No, but 55% positive | No |

PMD, perimenopausal depressive symptoms; PMS, premenstrual symptoms; PPD, postpartum depressive symptoms.

## TABLE 2

Hormone Therapies for Reproductive Depression

| Disorder/study | *n* | Population | Hormone treatment | Result |
|---|---|---|---|---|
| PMS/PMDD | | | | |
| Watson et al. (1989)67 | 40 | Women w/ PMS | Estrogen patches (2 × 100 mcg) for 3 months (placebo crossover 6-month trial) | Both groups showed improvement in PMS symptoms (at end of study); those switched to placebo from estrogen deteriorated; those switched to estrogen from placebo improved further |
| Dhar et al. (1990)68 | 11 | Women w/ PMS | Conjugated estrogens (Premarin) for luteal phase for 2 cycles vs. placebo for 2 cycles | Placebo > conjugated estrogens |
| Watson et al. (1990)69 | 50 | Women w/ severe PMS | Estradiol implants, varying doses | 96% improved in depressive symptoms |
| Freeman et al. (1995)70 | 170 | University hospital gynecology outpatients meeting criteria for PMS | 300 mg oral micronized progesterone vs. 0.25 mg alprazolam vs. placebo | Alprazolam > placebo > progesterone |
| Smith et al. (1995)71 | 20 | Women w/ prospectively confirmed severe PMS | Estradiol patches, 100 mcg vs. 200 mcg twice weekly | 100 mcg = 200 mcg, w/ 45%–57% improved; 100 mcg better tolerated |
| Freeman et al. (2001)72 | 82 | Women w/ PMDD | EE/DRSP vs. placebo for 3 cycles | EE/DRSP > placebo for luteal symptoms on BDI, POMS, & COPE; significant ($p > 0.027$) only on appetite, acne, & food-craving measure |
| Pearlstein et al. (2005)73 | 64 | Women w/ PMDD | EE/DRSP vs. placebo for 3 cycles | Mean DRSP decrease of 12.47 w/ EE/DRSP vs. 6.66 w/ placebo ($p < 0.001$); 61.7 % of EE/DRSP vs. 31.8% of placebo ($p = 0.009$) had good response (CGI-I score of 1 or 2) |
| Yonkers et al. (2005)74 | 450 | Women w/ PMDD | EE/DRSP vs. placebo 3 cycles | DRSP scores decreased by 37.49 w/ EE/DRSP vs. 29.99 w/ placebo ($p < 0.001$); 48% EE/DRSP vs. 36% placebo ($p = 0.015$) responded (50% score decrease) |
| Joffe et al. (2007)75 | 21 | Women w/ AD-treated MDD & luteal-phase breakthrough symptoms | EE/DRSP (open) for 21 days, then EE vs. placebo (blind) for 7 days, for 2 cycles | MADRS ($p = 0.0019$) & DRS ($p = 0.0001$) scores improved in both groups |
| Young et al. (2007)76 | 1238 | Female outpatients <40 yrs w/ nonpsychotic MDD participating in STAR*D | Estrogen/progestin vs. progestin-only OCP vs. no OCP | Progestin-only group had worse function than other 2 groups; estrogen/progestin group had fewer depression symptoms than no OCP & better function than other 2 groups |
| PPD | | | | |
| Sichel et al. (1995)77 | 4 | Newly postpartum women w/ history of PPD | 10 mg conjugated estrogens daily | 0% relapse (vs. 35%–60% expected) after 1 year |
| Gregoire et al. (1996)78 | 61 | Women w/ PPD w/in 3 months of delivery | Estrogen patch vs. placebo | 80% had significant decrease in symptoms vs. 31% of placebo controls |
| Ahokas et al. (2000)79 | 10 | Women w/ low estradiol levels meeting ICD-10 criteria for postpartum psychosis | 1–6 mg 17$\beta$-estradiol (to serum level 400 pmol/L) | 100% had significant reduction in symptoms on BPRS |
| Ahokas et al. (2001)80 | 23 | Women w/ severe PPD | Open-label 17$\beta$-estradiol | 83% had full remission after 2 weeks |
| PMD | | | | |

| Disorder/study | *n* | Population | Hormone treatment | Result |
|---|---|---|---|---|
| Amsterdam et al. (1999)81 | 568 | Women aged >45 on ERT (40) vs. not on ERT (132) vs. women aged <45 (396) vs. men (262) w/ MDD | FLX ± ERT for 8 weeks, then remitters for 1 year | No difference in antidepressant effects by HAM-D w/ FLX vs. FLX + ERT, regardless of age or sex; greater relapse rate in women >45 on ERT ($p < 0.06$) |
| Schmidt et al. (2000)82 | 34 | Perimenopausal women aged >45 w/ depression ± hot flashes | ERT (17-$\beta$ estradiol) vs. placebo for 3 weeks, then continuing ERT vs. placebo group (converted to ERT) for 3 more weeks | At least partial remission of symptoms seen w/ ERT (80%) vs. placebo (22%) ($p < 0.01$); hot flashes and duration of ERT treatment did not affect outcome |
| Soares et al. (2001)83 | 50 | Perimenopausal women aged 40–55 w/ depression | 17-$\beta$ estradiol patch (100 mcg) vs. placebo for 12 weeks after 4-week washout | Remission by MADRS was observed in 68% on estradiol patch vs. 20% on placebo ($p = 0.001$). |

AD, antidepressant; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impressions–Improvement; COPE, Calendar of Premenstrual Experiences; DRS, Daily Record of Severity of Problems; DRSP, drospirenone (Yasmin); EE, ethinyl estradiol; ERT, estrogen replacement therapy; FLX, fluoxetine; HAM-D, Hamilton Depression Rating Scale; HRT, hormone replacement therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MPA, medroxyprogesterone acetate; OCP, oral contraceptive pill; PMD, perimenopausal depression; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome; POMS, Profile of Mood States; PPD, postpartum depression; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

## TABLE 3

Differential Responses to SSRIs by Menopausal Status and Gender

| Study | Population | *n* | Agents | Outcome |
|---|---|---|---|---|
| Raskin et al. (1974)98 | Women >40 vs. women <40 | 555 women | Imipramine | Women >40 responded better to imipramine |
| Kornstein et al. (2000)99 | Premenopausal women vs. postmenopausal women vs. men | 400 women (264 on sertraline, 136 on imipramine); 235 men (162 on sertraline, 73 on imipramine) | Sertraline vs. imipramine | Premenopausal women responded better to sertraline; postmenopausal women and men responded equally to both agents |
| Baca et al. (2004)100 | Women vs. men | 184 women (90 on sertraline, 94 on imipramine); 50 men (23 on sertraline, 27 on imipramine) | Sertraline vs. imipramine | Women responded better to sertraline; men responded equally to both agents |
| Thase et al. (2005)101 | Women >50 vs. women <50 vs. men (meta-analysis of 8 studies) | 2045 overall (851 on venlafaxine, 748 on SSRI, 446 on placebo) 1312 women (955 <50, 357 ≥50) | Venlafaxine, SSRI, placebo | Women <50 responded better to SSRI than women >50; no difference for men by age; no difference for venlefaxine by age |
| Pinto-Meza et al. (2006)102 | Postmenopausal women vs. premenopausal women | 242 women (95 menopausal, 147 premenopausal) | SSRI | Premenopausal women responded better to SSRI |

SSRI, selective serotonin reuptake inhibitor.