Reproductive hormone sensitivity and risk for depression across the female life cycle: A continuum of vulnerability?

Claudio N. Soares, MD, PhD; Brook Zitek, DO

Soares — Women's Health Concerns Clinic, Department of Psychiatry and Behavioral Neurosciences, McMaster University, Hamilton, Ont.; Zitek — Global Medical Affairs, Wyeth Research, Collegeville, Pa.

Throughout most of their lives, women are at greater risk for depression than men. Hormones and neurotransmitters share common pathways and receptor sites in areas of the brain linked to mood, particularly through the hypothalamic-pituitary-gonadal axis. It has been hypothesized that women presenting with episodes of depression associated with reproductive events (i.e., premenstrual, postpartum, menopausal transition) may be particularly prone to experiencing depression, in part because of a heightened sensitivity to intense hormonal fluctuations. The menopausal transition, for example, appears to represent a window during which some women might be more vulnerable to the development of first onset or recurrent depressive symptoms and major depressive episodes. In this review, we examine the association between hormone changes and increased risk of developing depression. Some of the underlying mechanisms that may contribute to such an increased risk are discussed critically, with a special emphasis on the events occurring during the menopausal transition. Last, we explore some of the clinical and therapeutic implications of hormone-modulated depression in women.

Durant la majeure partie de leur vie, les femmes sont plus vulnérables à la dépression que les hommes. Les hormones et les neurotransmetteurs ont des voies et des récepteurs communs dans des régions du cerveau reliées à l'humeur, en particulier l'axe hypothalamus-hypophyse-gonades. On a posé en hypothèse que les femmes qui vivent des épisodes de dépression associés à des événements génésiques (c.-à-d. prémenstruels, postnataux, transition vers la ménopause) peuvent être particulièrement vulnérables à la dépression, en partie parce qu'elles sont plus sensibles aux fluctuations hormonales intenses. La transition vers la ménopause, p. ex., semble représenter une période pendant laquelle des femmes peuvent être plus vulnérables à l'apparition de symptômes dépressifs nouveaux ou répétitifs et à des épisodes dépressifs majeurs. Dans cette synthèse, nous analysons le lien entre les changements hormonaux et le risque accru d'apparition de la dépression. Nous analysons d'un œil critique certains des mécanismes sous-jacents qui peuvent contribuer à l'augmentation de ce risque et nous accordons une attention spéciale aux événements qui se produisent pendant la transition vers la ménopause. Enfin, nous explorons certaines des répercussions cliniques et thérapeutiques de la dépression d'origine hormonale chez les femmes.

Introduction

Epidemiologic studies suggest that an increased risk for major depressive disorder (MDD) exists in women, compared with men[1,2]; such increased risk appears to become more evident after puberty and continues throughout the reproductive life cycle. The National Comorbidity Survey (NCS) found that, between the ages of 15 and 54 years, the lifetime prevalence of MDD is 12.7% for men and 21.3% for women.[3] More recent NCS data corroborated these earlier findings, showing a nearly 2-fold greater lifetime risk of developing MDD in women (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.5–2.0).[1] It has been postulated that this increased prevalence is somewhat associated with female-specific reproductive events such as perimenstrual changes, pregnancy, the postpartum period and menopause.[4–6]

The hypothesis that fluctuations in sex hormones marking female reproductive events could influence neurochemical

Correspondence to: Dr. C.N. Soares, Department of Psychiatry and Behavioral Neurosciences, McMaster University, 301 James St. S, FB#638, Hamilton ON L8P 3B6; fax 905 521-6098; csoares@mcmaster.ca

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pathways linked to depression is extensively supported by animal and human studies and existing clinical data (Table 1).[61,62] The gonadal steroids estrogen and progesterone have been shown to affect brain regions known to be involved in the modulation of mood and behaviour. Receptor sites for these hormones have been identified in the prefrontal cortex, hippocampus, thalamus and brain stem.[63,64]

Other data support the association between changes in the hormone milieu and the occurrence of depressive symptoms, suggesting a potential window of vulnerability during times of hormone instability. In a community-based study, rapidly increasing levels of follicle-stimulating hormone (FSH) were associated with an increased risk of experiencing depressive symptoms among menopausal women.[65] The effects of hormonal interventions, however, indicate a potential window of opportunity to modulate the risk for mood symptoms by stabilizing the hormone environment. In a clinical trial of midlife (45–65 y) men and women with minor and major depression, significant improvements ($p < 0.01$ v. placebo) on the Hamilton Depression Rating Scale and Center for Epidemiologic Studies Depression Scale (CES-D) were observed in patients who received 6 weeks of dehydroepiandrosterone (DHEA) treatment (weeks 1–3, 90 mg/d; weeks 3–6, 450 mg/d).[66] The antidepressant effect associated with DHEA treatment was not the result of ameliorating a deficiency of DHEA because no correlation between DHEA levels and therapeutic response was observed.[66]

Hormonal changes may also play a role in the development of somatic symptoms and may contribute to the exacerbation of medical disorders. For example, the occurrence of vasomotor symptoms (e.g., hot flashes and night sweats) during the menopausal transition and early postmenopausal years is thought to be directly associated with the hormonal fluctuations that occur during this period. These hormonal changes not only adversely affect the hypothalamic thermoregulatory centre[67,68] but also contribute to dysregulation of the serotonergic and noradrenergic systems involved in mood and behaviour.[5,69] Studies of premenstrual asthma[70] and perimenstrual migraines[71] also suggest that progesterone- and estrogen-driven modulation, respectively, play a role in the occurrence of other clinical conditions.

The hypothesis that mood changes are related to a heightened vulnerability to hormonal fluctuations experienced during reproductive life events does not, however, preclude the role of psychosocial stressors. In fact, several psychosocial factors have been associated with mood changes during puberty (e.g., sexual maturity, increased social pressures and obligations),[6] premenstrual dysphoria (e.g., past trauma, lower education)[72,73] and childbirth (e.g., lower income, stressful life events, medical complications).[74,75] Similarly, the menopausal transition and postmenopausal years may be accompanied by health problems, inadequate social support, marital/sexual issues and other stressful events (e.g., divorce, death of a spouse, children leaving home) that could increase the risk for depression.[76]

In this review, we mainly focus on the available evidence linking female reproductive life events and the occurrence of depressive symptoms and disorders. A special emphasis is given to the events occurring during the menopausal transition. Last, we review some common clinical scenarios that could eventually help physicians to improve their ability both to identify patients at risk for developing mood disturbances during reproductive events and to tailor their treatment strategies for these conditions.

Depression across the reproductive life cycle

Premenstrual period

Different hypotheses involving the ovarian steroid hormones have been postulated to explain the occurrence of severe premenstrual symptoms. Hormone fluctuations are particularly intense in the late luteal phase of the menstrual cycle and early days of menses.[5,77] Although differences in the concentrations of the ovarian steroids may underlie the occurrence of mood symptoms in this disorder, the evidence that support this hypothesis remains limited.

Within the patient population that frequently reports physical and psychological complaints during the premenstrual period, a subgroup appears to be particularly affected by dysphoric symptoms of mood lability, depressed mood, increased irritability and tension. These symptoms characterize the core of premenstrual dysphoric disorder (PMDD).[78] These symptoms generally begin to occur during the late luteal phase of the menstrual cycle (i.e., the last 7–10 d) and continue until the first few days of the subsequent follicular phase. Although restricted to a short period of time, symptoms of PMDD adversely affect psychosocial functioning and quality of life.[78]

PMDD occurs during periods of progesterone and estrogen instability.[43] More recently, some investigators examined the concentration of ovarian steroid hormones across the menstrual cycle in women with and without PMDD, using a cross-sectional and prospective experimental design.

Across the menstrual cycle, the overall percentage of free estradiol was significantly lower, while the percentage of sex hormone binding globulin (SHBG) was significantly greater in the PMDD group when compared with control subjects. Moreover, during the luteal phase, free estradiol was significantly lower in the PMDD group when compared with control subjects. The authors speculate that high concentrations of SHBG in subjects with PMDD could limit the bioavailability of estradiol and ultimately affect mood in these individuals.[79]

The use of hormonal interventions for the treatment of PMDD seems intuitive; however, data supporting the efficacy of hormone-based treatments have been inconsistent,[80–82] and only recently have a few controlled clinical trials demonstrated that improvements in hormonal stability (e.g., with the use of continuous oral contraceptives) could prevent or alleviate the occurrence and severity of premenstrual symptoms.[83–85] Contrary to the scarce data on hormone-based interventions for PMDD, abundant evidence does support the role of changes in serotonin-mediated systems in the occurrence of premenstrual syndrome (PMS)[86,87] and PMDD.[88] Moreover, serotonergic antidepressants have been shown to effectively treat PMDD.[89–91]

Prevalence of perimenstrual-related depressive symptoms: PMDD and premenstrual exacerbation

Community-based studies indicate a 3%–9% prevalence of PMDD in the general population.[92,93] A study of 1488 women who were prospectively followed for 48 months found a 12-month prevalence of 5.8% and a cumulative lifetime incidence of 7.4%. This same study found that women with PMDD were likely to develop psychiatric comorbidities. Rates of comorbid anxiety, affective and somatoform disorders were 47%, 30% and 28%, respectively. Only 27% of participants with PMDD had no other psychiatric diagnosis.[94] In a survey of 206 women seeking treatment for PMS, 39% screened positively for a psychiatric disorder. Dysthymia and depression were most commonly comorbid with PMDD.[95] Thus a most probable clinical scenario is the occurrence of premenstrual exacerbation of an underlying (sometimes undiagnosed) mood or anxiety disorder. Its recognition is a fundamental step toward the formulation of a more accurate diagnosis and effective treatment strategies.[96]

Risk factors

Prior psychiatric disorders, especially anxiety disorders, have been found to be significant risk factors for PMDD.[73] In addition, a history of depression[72] and posttraumatic stress disorder,[94] smoking[72] and nicotine dependence[94] and lower educational status were also more common in patients with PMDD.[72]

Pregnancy

Estrogen and progesterone levels steadily increase throughout pregnancy until just before birth, and serotonergic activity follows a corresponding pattern. Results from animal models suggest that a lower baseline level of serotonergic activity may lead to a greater risk for developing depressive symptoms during times when these neuroendocrine networks are challenged.[97]

It was once believed that for most women pregnancy could provide protection against psychiatric disorders. Unfortunately, accumulating evidence has demonstrated the contrary. In fact, for some women, pregnancy can be a time of elevated risk for psychiatric morbidity, particularly depressive and anxiety disorders.[98,99]

Prevalence of depression

In a wide-ranging review of the published literature, rates of depression during the first, second and third trimesters were found to be 7.4%, 12.8% and 12.0%, respectively, suggesting a substantial risk for pregnant women, especially in the second and third trimesters.[98] Notably, a recent naturalistic study conducted in patients with a history of recurrent depression who were followed throughout pregnancy found that 51% of the women who experienced a return of their MDD did so during the first trimester. The overall rate of relapse for this population was 43%.[99]

Risk factors

Women who experience a major depressive episode during pregnancy are more likely to be younger, in a lower socioeconomic stratum,[74,98] not married[74] and to have less education than women who do not experience such an episode.[74] Cohen and colleagues[99] conducted a naturalistic study in pregnant women who had been euthymic since at least 3 months before their last menstrual period but who had a history of MDD and were currently receiving or had recently received antidepressant treatment. When followed throughout pregnancy, women who discontinued their antidepressant treatment were 5 times more likely to experience a depressive relapse than those who maintained treatment (hazard ratio 5.0, 95% CI 2.8–9.1).

Clinicians and patients frequently raise concerns regarding the putative teratogenic risks of antidepressant use during pregnancy. Other concerns include the risk of the newborn developing withdrawal symptoms attributed to prenatal exposure to antidepressants and the relative increased risk for persistent pulmonary hypertension in the neonate.[100,101] Conversely, evidence suggests that untreated depression has negative consequences for both mother and child. Depression in late pregnancy has been associated with poorer obstetric and neonatal outcomes, including increased risk for cesarean sections and instrumental vaginal deliveries, growth retardation and premature delivery.[102,103] The impact of untreated depression during pregnancy is not limited to immediate adverse outcomes. A prospective study of depressed and nondepressed mother–child pairs found that a mother's depression during pregnancy can adversely affect a child's development of language skills and overall cognitive development. This negative impact was not associated with antidepressant use.[104]

Overall, most physicians and patients remain extremely reluctant to use antidepressants during pregnancy. Such reluctance could be explained, at least in part, by the existing confusion and complexity of evaluating absolute and relative risks and by the difficulty in balancing these risks for both the infant and the mother.[105] As a general rule, a risk–benefit consideration must be made concerning pharmacologic treatments during pregnancy (for more details, see[106–108]). The severity of maternal depressive symptoms is a key factor in the decision-making process.

Postpartum

The postpartum period is a time of abrupt decreases in the amounts of circulating estrogen and progesterone. The relative contribution of these hormonal changes to the occurrence of depressive episodes during the postpartum period is a subject of controversy. For example, there have been some attempts to link the vulnerability of specific subgroups (e.g., patients with a diagnosis of bipolar disorder) to susceptibility genes that could predispose women to puerperal psychosis.[109] Nonetheless, clinical experiments support the hypothesis that the abrupt changes in the hormonal milieu associated with the immediate postpartum period may exert a key role in the heightened risk for depression during this period.[62] Bloch and

Table 1: Hormonal effects on neurotransmitters and mood

Hormone; study	Model	Study design	Effect
Estrogen			
Robichaud et al.[7]	A	Male and female rats received ICV 17 β-estradiol for 7 d.	Increased activity of 5-HT neurons v. controls.
Bethea et al.[8] Pecins-Thompson et al.[9]	A	Ovariectomized monkeys treated with estradiol for 28 d or estradiol and progesterone for the last 14 d.	Increased expression of enzyme involved in the synthesis of 5-HT (i.e., TPH) in the dorsal raphe v. controls.
Smith et al.[10]	A	Ovariectomized monkeys treated with estrogen, estrogen + progesterone or raloxifene for 5 mo.	All 3 treatment arms increased TPH in the dorsal raphe v. controls.
Mize et al.[11]	A	Hippocampal and frontal cortex cells of ovariectomized rats incubated with 17 β-estradiol, BSA-estradiol or tamoxifen.	All 3 treatment arms desensitized 5-HT_{1A} autoreceptors.
Sumner et al.[12]	A	Castrated male and ovariectomized female rats treated with estradiol benzoate.	Castration significantly reduced 5-HT_{2A} receptor binding in the frontal, cingulate and piriform cortices, olfactory tubercle and nucleus accumbens. Estradiol increased receptor density in both sexes.
Raap et al.[13]	A	Recently ovariectomized rats treated with estradiol benzoate or vehicle for 2, 4 or 14 d.	Estradiol was found to desensitize 5-HT_{1A} autoreceptors.
Pau et al.[14]	A	Ovariectomized monkeys treated with intravenous estrogen.	Stimulated noradrenaline activity in the hypothalamus v. controls.
Panek and Dixon[15]	A	Female ovariectomized rats treated with 17 β-estradiol or saline for 7 d.	Estradiol exposure increased availability and synthesis of norepinephrine in the hypothalamus and cerebral cortex.
Petitti et al.[16]	A	Ovariectomized rats treated with estradiol benzoate at 24 and 48 h before death.	Estradiol effects α1- and β-adrenoreceptor activity in the hypothalamus.
Karkanias et al.[17]	A	Ovariectomized rats treated with estradiol benzoate at 24 and 48 h before death.	Estrogen controls norepinephrine activity in the hypothalamus through α2-adrenoreceptors.
Ansonoff et al.[18]	A	Ovariectomized rats treated with oestradiol benzoate or vehicle.	Estrogen treatment reduced β-adrenoreceptor activity in the hypothalamus and preoptic area.
Karkanias et al.[19]	A	Ovariectomized rats treated with estradiol benzoate (24 or 24 and 48 h) and untreated controls.	Estradiol exposure for 24 and 48 h produced increases in α1b-adrenoreceptor mRNA in the preoptic areas of the hypothalamus.
Clarke et al.[20]	A	Ovariectomized ewes treated with estradiol benzoate.	An estradiol-related release of norepinephrine in the preoptic area was observed that coincided with luteinizing hormone secretion.
Velisek et al.[21]	A	Ovariectomized rats treated with 17 β-estradiol or vehicle for 6 d had a seizure induced then continued treatment.	Estrogen treatment impacted $GABA_B$ receptor–mediated inhibition in the dentate gyrus, protecting them from seizure related damage.
Schumacher et al.[22]	A	Ovariectomized and adrenalectomized rats were treated with estradiol benzoate alone or concomitantly with progesterone or vehicle.	Estrogen increased $GABA_A$ receptor binding in hippocampal structures rich in ERs.
Jussofie et al.[23]	A	Rats ovariectomized or ovariectomized and adrenalectomized to assess the effect of a decline in estrogen and progesterone on $GABA_A$ receptors.	Ovariectomy alone and ovariectomy + adrenalectomy had region-specific effects on the affinity of $GABA_A$ receptor binding that coincided with decreases in estradiol and progesterone.
OConnor et al.[24]	A	Ovariectomized rats treated with 17 β-estradiol or vehicle.	No effect of estradiol on glutamic acid decarboxylase but significant effect on $GABA_A$ receptor binding in brain areas rich/deficient in ERs.
Murphy et al.[25]	A	Hippocampal cells from rat embryos treated with 17 β-estradiol.	Estradiol was found to indirectly decrease inhibition of GABAergic activity and branching in the hippocampus.
Bazzett et al.[26]	A	Castrated male and ovariectomized female rats treated with estradiol benzoate (d 1–3) and progesterone (d 4), vehicle (d 1–3) and progesterone (d 4), or vehicle (d 1–4).	Estrogen's effect on dopamine receptor activity is regional- and sex-specific. Females experienced an increase in D_2 activity in the caudal striatum, and males experienced a decrease in the rostral striatum.
Tinkler et al.[27]	A	Ovariectomized monkeys treated with estrogen for 24 mo or were untreated controls.	Ovariectomy associated with decrease in cholinergic fibre length and density in prefrontal cortex; estrogen prevented those changes.
Shughrue et al.[28]	A	Ovariectomized rats subcutaneously injected with colchicine followed by estrogen.	Active ERs were found in forebrain cholinergic neurons.
Nilsen et al.[29]	A	Hippocampal neurons collected from rat fetuses treated with conjugated equine estrogen.	Estrogen's regulation of NMDA receptor activity associated with toxic levels of glutamate occurs via intracellular calcium. These results may indicate the ways in which estrogen provides neuroprotection.
Wihlback et al.[30]	H	Symptomatic postmenopausal women received continuous treatment with estradiol valerate then during 3–28 d periods either MPA, norethindrone acetate or placebo.	Significant improvements in depressed mood, irritability and tension in postmenopausal women during estrogen treatment.
Gregoire et al.[31]	H	Women with postnatal depression received double-blind treatment with transdermal 17 β-estradiol or placebo for 12 wk; cyclical dydrogesterone (12 d/mo) was added for 12 wk.	Estradiol treatment improved depressive symptoms to a greater degree than placebo.
Hlatky et al.[32]	H	Postmenopausal women with history of CAD received double-blind equine estrogen + MPA or placebo for 36 mo.	Among patients experiencing hot flushes, hormone treatment was associated with improvements in depressive symptoms.
Halbreich et al.[33]	H	Postmenopausal women given 30 d transdermal estradiol.	Treatment with estradiol increased serotonergic responsivity.
Soares et al.[34]	H	Depressed perimenopausal women randomized to double-blind transdermal 17 β-estradiol or placebo for 12 wk.	Significantly greater improvements in depressive symptoms were seen in the active treatment group v. placebo.
Morrison et al.[35]	H	Depressed postmenopausal women randomized to transdermal estradiol or placebo for 8 wk. Estradiol patients also received 2 wk of medroxyprogesterone treatment.	Similar changes in depressive symptom improvement with estradiol and placebo. Added progesterone produced a significantly greater decrease in positive affect compared with estradiol monotherapy.

continued

Table 1 continued

Hormone; study	Model	Study design	Effect
Schmidt et al.[36]	H	Perimenopausal women with depression randomized to 6 wk of treatment with 17 β-estradiol or 3 wk of placebo lead-in phase followed by 3 wk active 17 β-estradiol treatment.	Significant improvements in depressive symptoms after 3 and 6 wk of continuous 17 β-estradiol treatment v. placebo. Patients who crossed over from placebo to 17 β-estradiol also saw improvements in depressive symptoms after 3 wk of active treatment.
Kugaya et al.[37]	H	Postmenopausal women receiving transdermal 17 β-estradiol were observed for 10 wk.	5-HT_{2A} receptor binding increased in the right prefrontal cortex.
Progesterone			
Gundlah et al.[38]	A	Ovariectomized monkeys treated with progesterone for 28 d.	Decreased levels of monoamine oxidase-A in dorsal raphe v. controls.
Kaura et al.[39]	A	5-HT neurons collected from the dorsal raphe nucleus of rats were treated with allopregnanolone.	Allopregnanolone attenuates the response of serotonin neurons to $GABA_A$ activation.
Karkanias et al.[40]	A	Ovariectomized rats treated with estradiol benzoate and progesterone or vehicle.	Progesterone suppressed activity of α1-adrenoreceptors in the hypothalamus and preoptic area.
Bitran et al.[41]	A	Ovariectomized rats participated in 2 animal models of anxiety while being treated with progesterone.	Treatment with progesterone produced an anxiolytic effect, which was related to its effect on $GABA_A$ receptors.
Weiland et al.[42]	A	Ovariectomized and adrenalectomized rats were treated with estrogen and progesterone or either treatment alone.	Progesterone alone and with the addition of estradiol had an effect on the activity of $GABA_A$ receptors.
Rapkin et al.[43] Monteleone et al.[44]	H	Women with PMS and control women were compared during the luteal phases of their menstrual cycles.	Lower allopregnanolone levels were observed in patients with PMS when compared with control women.
Bicikova et al.[45]	H	Several hormones known to be $GABA_A$ modulators were assessed in women with mixed anxiety-depressive disorder and healthy control women.	During the follicular and luteal phases significantly higher levels of pregnelone-sulfate were observed when compared with healthy control women.
Baker et al.[46]	H	Women with PMS received double-blind treatment with vaginal progesterone suppository or placebo.	Progesterone treatment had no effect on depressive symptoms.
Freeman et al.[47]	H	Healthy women administered oral progesterone in a double-blind, placebo-controlled manner.	Progesterone and allopregnanolone levels correlated with improvements in anxiety symptoms.
Testosterone			
Robichaud et al.[7]	A	Male and female rats received ICV testosterone for 7 d.	An increased activity of 5-HT neurons was observed.
Zhang et al.[48]	A	Male rats that were controls, vehicle controls, castrated, castrated and treated with testosterone, and sham castrated rats were assessed on expression of 5-HT_{1A} and 5-HT_{2A} receptor mRNA expression.	Castrated rats had significantly higher activity of 5-HT_{1A} mRNA than controls, which was prevented by administration of testosterone.
Sumner et al.[12]	A	Castrated male rats treated with testosterone or 5-α dihydrotestosterone.	Castration significantly reduced 5-HT_{2A} receptor binding in the frontal, cingulate, and piriform cortices, olfactory tubercle and nucleus accumbens, which was reversed by testosterone treatment.
Shifren et al.[49]	H	Oopherectomized women aged 31–56 y currently receiving orally administered estrogen were administered 150 or 300 μg of transdermal testosterone.	An improvement in depressive symptoms was seen with the higher dose of testosterone.
Barret-Connor et al.[50]	H	Community-dwelling men aged 50–89 y and suffering from depression were assessed.	Decreases in bioavailable testosterone levels were associated with increases in depressed mood.
Weber et al.[51]	H	Pre- and postmenopausal women with severe depression and elevated cortisol levels and nondepressed control women not receiving hormonal therapy were enrolled.	Levels of circulating androstenedione, testosterone and dihydrotestosterone were significantly elevated in women with depression, compared with nondepressed women.
Santoro et al.[52]	H	Community-dwelling women aged 40–55 y.	Decreases in circulating testosterone levels were associated with higher depressive symptom levels.
DHEA/S			
Robichaud et al.[7]	A	Male rats received ICV administration of DHEA for 7 d.	No effect on 5-HT firing.
Robichaud et al.[53]	A	Female rats were administered ICV DHEA for 21 d.	Greater increases in 5-HT firing in DHEA-treated rats v. controls on days 7, 14 and 21.
Majewska et al.[54]	A	Assessed DHEAS binding using nerve cells from rat brains and barbiturates as a biochemical assay.	DHEAS acts as a $GABA_A$ allosteric antagonist.
Demirgoren et al.[55]	A	The forebrain of rats treated with DHEAS.	DHEAS served as a negative modulator of $GABA_A$ activity.
Yaffe et al.[56]	H	Community-dwelling women aged ≥ 65 y assessed with a depression ratings scale and circulating hormone levels.	Women with DHEAS levels > 2.0 μg/dL had higher depression ratings than women with detectable DHEAS levels.
Wolkowitz et al.[57]	H	Depression patients randomly assigned to double-blind treatment with DHEA or placebo for 6 wk.	DHEA-treated patients had a significantly greater antidepressant response than those receiving placebo.
Bloch et al.[58]	H	Double-blind, randomized clinical trial comparing DHEA and placebo for the treatment of midlife dysthymia.	6 wk of DHEA treatment improved depression ratings to a significantly greater degree than placebo.
Barrett-Connor et al.[59]	H	Postmenopausal women with depression not taking estrogen provided plasma to assess hormone assays.	DHEAS levels were significantly and inversely related to depressive symptoms.
Wolkowitz et al.[60]	H	Men and women aged 51–72 y with depression and low plasma DHEA and DHEAS levels treated with DHEA for 4 wk	Significant improvements in mood related to increases in DHEA and DHEAS.

5-HT = serotonin; A = animal; BSA = bovine serum albumin; CAD = coronary artery disease; DHEA = dehydroepiandrosterone; DHEA/S = dehydroepiandrosterone sulfate; ER = estrogen receptor; GABA = γ-aminobutyric acid; H = human; ICV = intracerebroventricular; MPA = medroxyprogesterone acetate; mRNA = messenger ribonucleic acid; NMDA = *N*-methyl-D-aspartic acid; PMS = premenstrual syndrome; TPH = tryptophan hydroxylase.

colleagues[62] induced a hypogonadal state in women with and without a history of postpartum depression. First, they used the gonadotropin-releasing hormone agonist leuprolide acetate followed by 8 weeks of estrogen and progesterone treatment. At the end of this 8-week add-back period, both hormones were withdrawn in a double-blind manner. Sixty-three percent of the women with a history of postpartum depression and none from the comparison group developed significant depressive symptoms, suggesting that hormonal changes associated with the postpartum period may trigger a depressive episode in at-risk women. A potential window of opportunity for hormonal interventions in postpartum depression was further explored in studies demonstrating the efficacy of estrogen-based treatments for severe postpartum depression.[31,110]

Prevalence and risk factors

A longitudinal study of 1558 pregnant women conducted in Sweden found a prevalence of 13% to 18% for postpartum depressive symptoms during the 6 months after delivery.[111] Worldwide rates of postpartum major depression have been found to range from 4.4% to 9%.[112–115] It appears that depressive symptoms before and concurrent with pregnancy are reliable predictors of postpartum mood disturbances. In a large study (n = 1622) of midpregnancy and 6-month postpartum women, the postpartum women who experienced depressive symptoms before becoming pregnant (OR 3.82, 95% CI 2.31–6.31) and during pregnancy (OR 6.78, 95% CI 4.07–11.31) had an increased risk for postpartum depressive symptoms.[114] These results are supported by a longitudinal study that followed pregnant women until they were 8 months postpartum. The results showed a significant association between antenatal anxiety symptoms and postpartum depressive episodes, even after controlling for prior depressive episodes (OR 3.22, 95% CI 2.28–4.55; $p < 0.001$).[116] Additionally, early postpartum depressive symptoms, a history of PMDD and depression related to the use of oral contraceptives have been identified as risk factors for postpartum depressive symptoms and episodes.[115,117]

The menopausal transition

The onset of the perimenopause or the menopausal transition is marked by the end of menstrual cycle regularity and is associated with decreases in the production of ovarian inhibiting hormones, which leads to increases in FSH and estrogen and increased activity of the hypothalamus and pituitary.[63,118,119] Initially, menstrual cycles become slightly irregular in their length and/or flow. As women continue to advance toward the late perimenopausal period, menstrual cycles become increasingly irregular (i.e., occurrence of 2 or more skipped menstrual periods with gaps of more than 60 days between menstrual periods).

From a hormonal perspective, in the perimenopausal years slightly elevated but highly fluctuating FSH levels may be observed during the early follicular phase of the menstrual cycle. These levels gradually become consistently elevated into the late perimenopause and postmenopausal years, while estrogen and progesterone levels decrease and luteinizing hormone levels increase as the woman approaches menopause.[119]

Recent studies have examined the patterns of change in FSH and estradiol levels in different subpopulations across the menopausal transition and early postmenopausal years. Data from the Study of Women's Health Across the Nation revealed that serum concentrations of estradiol and FSH may vary by race or ethnicity. For example, Chinese and Japanese women had consistently lower (20%) estradiol concentrations when compared with women of European ethnicity, with no comparable differences seen in serum FSH concentrations. This finding suggests either a difference in the feedback regulation of the pituitary or an ethnospecific difference in pituitary sensitivity to gonadal-negative feedback.[120] The same investigators revealed that FSH measures may be a better independent predictor of vasomotor symptom prevalence than serum estradiol levels: higher FSH concentrations were associated with a greater risk of reporting more frequent symptoms even among regularly cycling women, whereas estradiol concentrations did not show an independent effect. They therefore proposed that an annual serum FSH concentration of 40 IU/L could be incorporated, in conjunction with bleeding markers, into the Stages of Reproductive Aging Workshop (STRAW) paradigm for markers of the late menopausal transition.[121]

Figure 1 illustrates the stages of menopause based on a consensus statement developed by 27 invited professionals to the STRAW. The final menstrual period (FMP) serves as the anchor point of this staging system, which describes the components of each menopausal phase (i.e., menstrual cycle regularity, endocrine and biochemical changes, fertility, other organ system changes and uterine/ovarian anatomy).[119]

Clinically, symptoms such as breast tenderness, insomnia, migraines, vasomotor symptoms and dysphoria may be reported with the onset of the perimenopause. In the late perimenopausal years, women also experience significant increases in the intensity of vasomotor symptoms as estrogen levels fluctuate widely and unpredictably and menstrual cycles become increasingly irregular.[119,122] Recent evidence also suggests an increased risk for developing depressive symptoms during this period even in the absence of a history of depression.[76,99,123] Thus, for some women, the perimenopause and early postmenopausal years may constitute a window of vulnerability wherein the occurrence of challenging physical and emotional discomforts could result in significantly impaired functioning and poorer quality of life.[124,125]

Postmenopause

Menopause begins following the FMP and is confirmed only after 12 months of amenorrhea. The postmenopausal period is divided into an early (i.e., 5 years since the FMP) and late phase and is marked by significant decreases in estrogen production, an overall state of hypogonadism, stability in the hypothalamic-pituitary-gonadal axis and elevated FSH levels.[119] The decreased circulating androgen levels associated

with menopause have been linked to loss of libido, fatigue and an increase in depressive symptoms.[126,127] Some data suggest that the significant hormone changes and the related physical and emotional symptoms associated with menopause may differ depending on whether a woman experiences menopause naturally or through surgical means (i.e., resulting from bilateral oophorectomy).[126,128] In a cross-sectional study of postmenopausal women, those experiencing menopause naturally were found to have fewer hot flashes than those with surgically induced menopausal status.[129]

Prevalence of depression

Notably, most women have a positive attitude toward approaching menopause and proceed through the menopausal transition without experiencing significant depressive symptoms or a major depressive episode.[130] However, recent epidemiologic studies suggest an increased risk for the development of psychiatric morbidity even among those who never experienced depression during the premenopausal years. In an 8-year longitudinal study of women with no history of depression (n = 224), Freeman and colleagues[123] found that 50% experienced an increase in depressive symptoms (CES-D ≥ 16) during the perimenopausal transition and 26% met formal MDD diagnostic criteria as assessed with the Primary Care Evaluation of Mental Disorders measure. Perimenopausal women were more than 4 times more likely (OR 4.29, 95% CI 2.39–7.72) to experience clinically significant depressive symptoms and 2.5 times more likely (OR 2.50, 95% CI 1.25–5.02) to be diagnosed with MDD than when they were premenopausal.[123] Another community-based, prospective study, the Harvard Study of Moods and Cycles, also identified a 2-fold greater risk of developing significant depressive symptoms during the perimenopause in women who had never reported prior depression. Interestingly, this increased risk remained significant after adjusting for common confounding factors (e.g., cigarette smoking, socioeconomic status).[72] Moreover, the risk for a new onset of depression was accentuated by the presence of significant vasomotor symptoms.[99] In subjects with a lifetime history of depression, the risk of developing a depressive episode during the late perimenopause is 14 times greater than during the 31-year period preceding perimenopause, compared with a 3-fold increase in risk associated with the early perimenopause.[131]

Risk factors

As in the other reproductive life events discussed, a history of previous depressive symptoms or episodes is a significant risk factor for developing menopausal depression.[65,132] Freeman and colleagues[65] reported a nearly 5-fold increase in the risk of experiencing a major depressive episode during the menopausal transition in women with a history of depression. A similar increased risk was observed in data derived from the Moods and Cycles Study (Dr. Bernard Harlow, University of Minnesota, Division of Epidemiology, personal communication, December 2006). Additional risk factors included a history of severe PMS or PMDD,[133] poor sleep patterns[65] and hot flashes.[134]

Accumulating evidence suggests a link between the presence of vasomotor symptoms and the occurrence of menopause-related depression. For example, in a study of 476 women aged 40 to 60 seeking primary care treatment, perimenopausal women with depression were significantly more

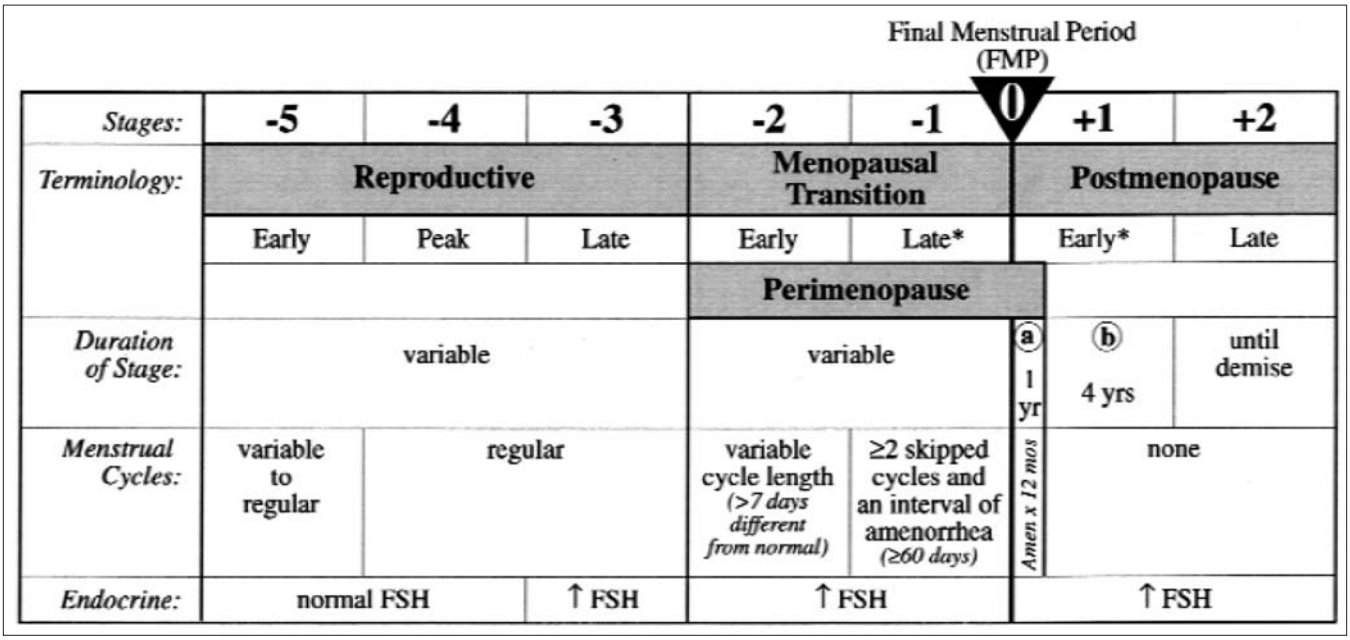

Fig. 1: Stages and nomenclature of normal reproductive aging in women. *Stages most likely to be characterized by vasomotor symptoms. FSH = follicle-stimulating hormone. Reproduced with permission from Soules et al.[119]

likely to report experiencing vasomotor symptoms than those who were perimenopausal and not suffering from depression. Perimenopausal women with vasomotor symptoms were more than 4 times more likely to meet criteria for depression (CES-D ≥ 25) than those who did not have vasomotor symptoms (4.39 95% CI 1.40–13.83).[135] No significant increase in the risk for depression was noted for older premenopausal and postmenopausal women who were also experiencing hot flashes, reinforcing the concept that the perimenopausal period may represent a time of unique vulnerability.[135]

Androgen levels may also play some role in menopause-related depression. Barret-Connor and colleagues[59] found a significant relation between decreased dehydroepiandrosterone sulfate (DHEAS) levels and depressed mood assessed with the Beck Depression Inventory. Another group of investigators found a weak inverse relation between depressive symptoms (according to CES-D scores) and DHEAS levels in women aged 42–52 years. Even after controlling for factors such as waist circumference, ethnicity and age, levels of testosterone and free androgen index levels remained inversely associated with depressed mood.[52]

Reproductive-related depressive disorders: diagnosis and clinical considerations

The occurrence of a similar symptom profile (e.g., increased irritability, disturbed sleep, depressed mood, cognitive dysfunction) associated with the various reproductive life events already discussed has led some to speculate that a continuum of reproductive depressive disorders exists. It has been postulated, for instance, that the hypoestrogenism associated with each of these phases in a woman's life could lead to an increased risk for depression.[4] In addition, some suggest the hypothesis of a kindling effect; women who experience a depressive episode during one reproductive phase (e.g., during the premenstrual period) could be at a greater risk for developing future depressive episodes when facing hormonally challenging situations (e.g., during the postpartum period).[117,136] A preliminary study of 72 women with depression found significant correlations between premenstrual ($r = 0.41$; $p = 0.04$) and postpartum ($r = 0.64$; $p = 0.001$) depression ratings and the presence of perimenopausal depression.[137] Other studies also point to the higher occurrence of lifetime depressive events related to the reproductive cycle.[138] Nonetheless, larger prospective studies confirming these associations are lacking.

The major caveat of the hypoestrogenic state theory is that the hormonal milieu differs with each reproductive event, so the relation between depressed mood and reproductive hormones may not be direct. The occurrence of mood disturbances during separate reproductive events and the wide variations in hormone levels observed during such events suggest that absolute hormone levels do not cause reproductive-related mood disorders. Rather, it is the dramatic — sometimes chaotic — hormone fluctuations that contribute to the increased risk for depression. As discussed above, premenstrual depressive symptoms occur during the luteal phase and continue through the first few days of the follicular phase, when dramatic fluctuations of progesterone and estrogen levels are most prevalent.[5,77] Similarly, estrogen levels in perimenopausal women fluctuate widely as menstrual cycles become increasingly erratic.[119] Conversely, the late postmenopausal years, clearly marked by a constant hypoestrogenic state, are not generally characterized by an increase in depressive episodes (either first onset or reemergent).

The complexity of the interactions between hormone changes and mood is corroborated by the different responses to hormonal fluctuations observed in women going through reproductive events and by different therapeutic responses obtained after the administration of exogenous hormones. For example, the antidepressant properties of estrogen therapy appear to vary according to the population treated. Most clinical trials have shown the positive effects of estrogen treatment for depression in perimenopausal but not postmenopausal women.[34,35,139] Moreover, the formulation and pathways used (e.g., transdermal estradiol as opposed to oral conjugated estrogen) may also affect estrogen's antidepressant effect, with more robust response observed with the use of transdermal estradiol[34,36] and limited antidepressant response with oral preparations.[140]

The response to antidepressants for the management of reproductive-related mood symptoms has also been a point of some controversy. Serotonergic antidepressants are quite efficacious for the treatment of PMDD.[141–143] However, the consistent efficacy of these agents in treating depression in women has been questioned, particularly with regard to women who have entered the postmenopausal years.[144–146]

From the therapeutic point of view, it is plausible that the use of hormonal interventions could have an impact on the presence and severity of mood symptoms when used either alone or in combination with antidepressants. Bloch and colleagues[117] found a significant association between subjects' mood symptoms while taking oral contraceptives and the experiencing of postpartum depressive symptoms and episodes ($p = 0.007$). In the Harvard Study of Moods and Cycles, women receiving hormone therapy to ease the symptoms associated with the perimenopause were less likely to experience a severe depressive episode, compared with those who entered the perimenopause without any hormonal intervention.[134] Last, some but not all depression studies suggest that estrogen-based therapies may constitute a valid treatment strategy (either as monotherapy or an augmenting tool) for the improvement of depression during menopause or for premenstrual exacerbation of depression.[34–36,140,147]

When the treatment of mood disorders in women is being considered, assessment of reproductive history and inquiry about menstrual history or somatic symptoms are important to the decision-making process. Incorporating appropriate questions into psychiatric assessments may improve the ability to identify women vulnerable to experiencing depressive episodes during reproductive events and to effectively manage depression in these women. For example, the decision to use long-term maintenance treatment could be affected by the recognition that a woman at midlife with a history of MDD who is currently in remission could be at an increased risk for recurrence when approaching menopause.

Given the complex overlap between menopause-related

symptoms and some of the somatic and psychological complaints commonly seen in depression, the diagnostic process becomes more difficult and requires different strategies. The domino theory suggests that the sheer increase in the number of symptoms is responsible for more menopausal women meeting the criteria for MDD.[148] However, depression may occur even in the absence of one or more of these symptoms. Use of more specific instruments or scales may help physicians make this delineation. For example, the Edinburgh Postnatal Depression Scale[149] has been successfully used to screen for and monitor the occurrence and severity of MDD during pregnancy and the postpartum period. Similarly, instruments such as the Greene Climacteric Scale,[150] the Menopause-Specific Quality of Life Questionnaire[151] and the Utian Menopause Quality of Life Score[152] could be used to assess and monitor menopause-related physical and psychological symptoms, as well as to assess the impact of these symptoms on functioning and overall well-being. Clinical assessments of menopausal women presenting with symptoms of depression should determine the presence of comorbidities, explore the course of illness (i.e., chronic or recurrent) and identify triggers (i.e., reproductive events, life events, seasonal patterns) and psychosocial contributors to depression.[153] Box 1 highlights some of the most common clinical scenarios seen when depression is diagnosed during the menopausal transition and also includes practical guidelines for addressing them.

Box 1: Common clinical scenarios and treatment strategies for the management of symptomatic perimenopausal and postmenopausal women

Clinical scenario	Treatment strategies / points to consider
1. First onset of depression occurring during the menopausal transition, along with significant vasomotor symptoms. Depressive symptoms are mild to moderate, with no suicidal ideations or thoughts.	1. Antidepressants appear to be a valid option for the management of both depressive and somatic symptoms. 2. If hormone therapy is not contraindicated, a trial with estrogen therapy is also a valid option — preferably transdermal estradiol (50–100 μg/d). If efficacious, response should be observed with 4–8 weeks of treatment. 3. If ET is initiated, periodic reassessments of risks and benefits are needed, particularly after 3–5 years of use. 4. When needed, the use of concomitant progestins should be kept to the minimum necessary for endometrial protection (e.g., micronized progesterone 100–200 mg/d for 12–14 days, either monthly or every 3 months). 5. Patients may benefit from the use of both interventions (antidepressants and ET) concomitantly.
2. Patient with history of several depressive episodes, who had remained stable for many years while taking antidepressants (SSRIs); currently in the menopausal transition, experiencing worsening of depressive symptoms along with hot flushes.	1. Patient may need an adjustment in antidepressant dosing. 2. Hormone therapy should be considered as an option to promote alleviation of hot flushes and owing to potential synergistic effect with antidepressants. 3. If nonresponsive to higher doses of antidepressants and ET, consider switching to a different antidepressant (e.g., SNRI).
3. Patient has been postmenopausal for several years and reports sporadic vasomotor symptoms; significant sexual dysfunction, mainly low libido and dryness; has depressed mood, decreased energy and lack of motivation; sleep problems became more severe after menopause.	1. Consider the use of antidepressants with a more favourable profile with respect to sexual adverse events. 2. ET will have little impact on mood symptoms; consider the possibility of using hormone treatments to improve the existing sexual dysfunction. The initial approach of sexual dysfunction with hormone therapies could increase the adherence to treatment with antidepressants. 3. Consider sleep hygiene measures and behavioural techniques to address sleep problems.

ET = estrogen therapy; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor.

Conclusion

Despite the mounting evidence of an association between reproductive life events and the development of depressive episodes, further research is needed to more clearly identify the driving factors of this association. A better understanding of both systemic and brain-specific biological changes experienced during different reproductive phases may provide the keys to developing better treatment options for these cases and effectively reducing the disease burden and risk for recurrence. Future research should also assess the efficacy and safety of hormonal and nonhormonal strategies to modulate the occurrence of these disturbances or to alleviate their symptoms. With regard to managing menopause-related symptoms, a particular emphasis has been put on identifying safer and more effective treatments such as selective estrogen receptor modulators and serotonergic, noradrenergic and γ-aminobutyric acid–ergic psychoactive agents. In addition, accurate and effective screening strategies and updated treatment guidelines are necessary to provide physicians and patients with the necessary tools to meet the needs of this population.

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Correction

Short telomeres in patients with chronic schizophrenia who show a poor response to treatment

In the print and online versions of the article by Wu-Yang Yu, Hsueh-Wen Chang, Ching-Hua Lin and Chung-Lung Cho (*JPN* 2008;33[3]:244-7]), the contributors' information stated in error that Drs. Yu and Cho contributed equally to the work. The correct information is that Drs. Yu and Chang contributed equally to the work.

We apologize to the authors and our readers for this error.