Published in final edited form as:

Ann N Y Acad Sci. 2009 October ; 1179: 70–85. doi:10.1111/j.1749-6632.2009.04982.x.

Sex Hormones and Mood in the Perimenopause

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Abstract

The focus of this chapter is the relationship between the onset of depression in women and the reproductive events of the menopause transition. Epidemiologic studies have documented that the majority of women do not become depressed during the menopause transition. However, recent longitudinal studies suggest that in some women, the reproductive events related to the menopause transition could play a role in the onset of depression. No abnormality of ovarian hormones has been identified that distinguishes women with depression from those who remain asymptomatic during the menopause transition. Nonetheless, several findings suggest a role of ovarian hormones in the onset of these depressions. First, episodes of depression cluster during the stage of the menopause transition that is accompanied by estradiol withdrawal. Second, randomized controlled trials have documented the short-term (3–6 weeks) antidepressant efficacy of estradiol in depressed perimenopausal women. Third, experimentally induced estradiol withdrawal triggers mood symptoms in some women. Thus, although depression is not a uniform accompaniment of the menopause transition, in some women, age-related changes in ovarian estrogen production may alter central nervous system function and predispose them to develop depression.

Keywords

menopause transition; depression; estrogen

Introduction

The focus of this chapter is the potential relationship between the onset of affective disorders in women and the endocrinology of the menopause transition. First, we will review background information that is relevant to this relationship, including the endocrinology of the menopause transition and studies in both lower animals and humans demonstrating the widespread neuroregulatory effects of ovarian steroids. Second, we will review epidemiologic studies reporting the risks of mood disorders occurring during the menopause transition. Finally, we will present studies examining the role of ovarian steroids in the development of depression in women during the natural menopause transition, as well as in those with pharmacologically induced menopause.

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Conflicts of Interest: The authors declare no conflicts of interest.

Endocrinology of the Menopause Transition and the Postmenopause

The menopause is defined by the permanent cessation of menstruation for 12 months secondary to a loss of ovarian activity. The postmenopause is characterized endocrinologically by tonically elevated gonadotropin (follicle stimulating hormone (FSH), luteinizing hormone (LH)) secretion, persistently low levels of ovarian steroids (estradiol, progesterone) and relatively low (50% decrease compared to younger age groups) testosterone secretion.¹ The menopause transition and the perimenopause are the transitional periods from reproductive to nonreproductive life.² The average duration of the menopause transition (defined by menstrual cycle irregularity) is estimated to be approximately 4 years, but there is considerable individual variation in the duration of this phase of reproductive life, ranging from 0 to 11 years.^{3,4} During the early stages of reproductive aging, the length of the follicular phase of the menstrual cycle shortens,^{5,6} early follicular phase plasma FSH levels increase and inhibin B levels decrease.^{7–9} As the menopause transition progresses, ovarian follicular depletion occurs, the ovary becomes less sensitive to gonadotropin stimulation, and a state of relative hypoestrogenism occurs; gonadotropin secretion is elevated across the menstrual cycle; ovulatory cycles are fewer; and menstrual cycle irregularity ensues. However, in contrast to the postmenopause, episodic (not tonic) gonadotropin secretion is present and both ovulation and normal premenopausal (or at times increased) estradiol secretion may occur.^{2,10–12} The late menopause transition is characterized endocrinologically by tonic elevations of plasma FSH and sustained menstrual cycle irregularity with more prolonged periods of amenorrhea and hypoestrogenism. The levels of several other hormones decrease with aging and accompany these changes in reproductive function, including androgens (testosterone, dehydroepiandrosterone (DHEA) and androstenedione), which begin to decline in the 20s and reach peak decline during the late 40s and 50s, as do insulin-like growth factors and binding proteins.^{10,13–16}

Role of Ovarian Steroids in Modulating the Systems Involved in Affective Adaptation

Neuroregulation

Results from animal studies demonstrate that ovarian steroids influence many of the neuroregulatory systems implicated in the pathophysiology of affective disorders.^{17–19} Pre-clinical studies have documented the manifold effects of ovarian steroids on neurotransmitter system activities, including regulation of synthetic and metabolic enzyme production as well as receptor and transporter protein activity. For example, in some, but not all, (reviewed in Ref. 20) experimental paradigms, estradiol has been observed to inhibit serotonin transporter (SERT) mRNA,²¹ alter SERT protein levels and binding,^{20–25} increase 5-HT_{2A} receptor binding²⁶ and mRNA,²⁷ and facilitate imipramine-induced downregulation of 5-HT₂ receptors in the rat frontal cortex, an action seen to accompany antidepressant administration.²⁸ Although, 5HT_{1A} receptor binding is modulated by both estradiol^{29–35} and progesterone,^{25, 36–38} estradiol has been reported to both decrease activity of the 5HT_{1A} receptor (downregulation and uncoupling from its G-protein)^{39,40} and increase the expression of 5HT_{1A} receptors. The latter action occurs by means of an interaction involving nuclear factor- κ B complexes, estrogen-receptor- α and a nonclassical estrogen response element.³⁰

In humans, there are patterns of effects of ovarian steroids on the serotonin system similar to those observed in animals. Menstrual cycle phase effects on the concomitants of serotonergic stimulation include an increased prolactin secretion during the luteal phase after administration of the serotonergic agents m-CPP⁴¹ and buspirone⁴² compared with the early follicular phase and a decreased prolactin response after L-tryptophan⁴³ or d-fenfluramine⁴⁴ during the luteal phase compared with mid-cycle. In asymptomatic women in whom a reversible menopause

was induced by a GnRH-agonist, we observed that m-CPP-induced prolactin secretion was increased during progesterone replacement; however, no differences in any m-CPP-stimulated hormone measures were observed during estradiol replacement.⁴⁵

Recent positron emission tomography (PET) studies in humans employing radioligands for 5HT_{1A} receptors report both decreased^{46–48} and increased⁴⁹ binding in depression. Both sex- and menstrual cycle phase-related differences in 5HT_{1A} binding (C11WAY) have been observed by PET, with women having both greater 5HT_{1A} binding than men (in the anterior cingulate, frontal and temporal cortices, insula, hippocampus and dorsal raphe) and decreased binding (in the dorsal raphe) during the follicular phase compared with the luteal phase of the menstrual cycle.^{50,51} Finally, one uncontrolled study reported an increase in 5-HT_{2A} binding (F18 altanserin) in the anterior cingulate, dorsolateral prefrontal cortex and lateral orbital frontal cortex during combined estrogen and progestin replacement (but not after estradiol alone).⁵² Despite recent evidence suggesting the roles of 5HT_{1B} and 5HT₆ receptors in depression, no studies in either animals or humans have examined the potential role of ovarian steroids in the regulation of these 5HT receptor subtypes.^{53,54}

Several nonclassical neural signaling systems also have been identified as potential mediators of the therapeutic actions of antidepressant agents (e.g., cAMP response element binding protein (CREB) and brain-derived neurotrophic factor (BDNF)).⁵⁵ These cellular systems are modulated by a range of therapies effective in depression (e.g., serotonergic and noradrenergic antidepressants and electroconvulsive therapy (ECT)) and exhibit a pattern of change in keeping with the latency to therapeutic efficacy for most antidepressants.⁵⁶ For example, antidepressants increase the expression and activity of CREB in certain brain regions (e.g., hippocampus)⁵⁷ and regulate activity of genes with a cAMP response element in a brain region-specific manner.⁵⁶ Genes for BDNF and its receptor, trkB, have been proposed as potential targets for antidepressant-related changes in CREB activity.⁵⁶ Estradiol has been reported to influence many of these same cellular processes. Specifically, ovariectomy has been reported to decrease and estradiol increase, BDNF levels in the forebrain and hippocampus.⁵⁸ Estrogen also increases CREB activity⁵⁹ and trkA expression⁶⁰ and decreases glycogen synthase kinase-3 β activity (Wnt pathway)⁶¹ in the rat brain, changes similar to those seen with mood stabilizer drugs. In contrast, an estradiol-induced decrease in BDNF has been reported to mediate estradiol's regulation of dendritic spine formation in hippocampal neurons.⁶² Thus, the therapeutic potential of gonadal steroids in depression is suggested not only by their widespread actions on neurotransmitter systems, but also by certain neuroregulatory actions shared by both ovarian steroids and traditional therapies for depression (i.e., antidepressants, ECT).

Neurocircuitry

Neuroimaging techniques (i.e., PET and functional magnetic resonance imaging (fMRI)) have been employed to examine the effects of ovarian steroids or the normal menstrual cycle on regional cerebral blood flow under conditions of brain activation. First, using PET (H₂O¹⁵), Berman *et al.*⁶³ employed the Wisconsin Card Sort Test, a measure of executive function and cognitive set shifting and observed that during conditions of GnRH agonist-induced ovarian suppression, both estradiol and progesterone upregulated cortical activity in brain regions (prefrontal, parietal, and temporal cortices and hippocampus) that are also reported to be involved in the regulation of mood. Similarly, Shaywitz *et al.*⁶⁴ employed fMRI in women who were several years postmenopause and showed that estrogen therapy (but not placebo) significantly increased activation in the inferior parietal lobule and right superior frontal gyrus during verbal encoding and decreased activation in the inferior parietal lobule during nonverbal coding. These findings are consistent with a recent report by Craig *et al.*,⁶⁵ who observed significantly decreased activation in the left prefrontal cortex, right precentral gyrus, anterior

cingulate and medial frontal gyrus during verbal encoding in a group of women with GnRH agonist-induced “menopause” for the treatment of uterine fibroid tumors. Finally, MRI studies also have documented menstrual cycle phase-related changes in the activities of several brain regions involved in the neurocircuitry of arousal, the stress response and reward processing, including the amygdala, orbitofrontal cortex, and striatum.^{66–68} Thus, although the brain regions potentially regulated by estradiol remain to be fully characterized, the activities in the frontal cortex, amygdala, and hippocampus, areas subserving memory and the regulation of affect, appear to be regulated by ovarian steroids in women.

Stress Axis

Studies in animals demonstrate that reproductive steroids also regulate basal and stimulated hypothalamic-pituitary-adrenal (HPA) axis function. In general, low-dose, short-term administration of estradiol inhibits HPA axis responses in ovariectomized animals,^{69–72} while higher doses and longer treatment regimens enhance HPA axis reactivity to a variety of stressors.^{73–75} Studies also indicate that estrogen administration decreases glucocorticoid receptor mRNA production in the thymus⁷⁶ and the pituitary.^{76–79} Moreover, evidence further suggests that gonadal steroids influence the serotonergic regulation of the HPA axis by altering the function of the 5-HT_{1A} and 5-HT₂ receptor systems in the cortex and hippocampus.^{80–82} Finally, interactions between glucocorticoid and estrogen response elements and their receptors suggest additional ways by which gonadal steroids may modulate stress-related neural activity.⁸³ For example, estrogen and glucocorticoid receptors compete for CREB binding protein (CBP) and glucocorticoid receptor interacting protein (GRIP), with the relative amounts of these receptors increasing (estrogen) or decreasing (glucocorticoid receptor) transcription at the AP-1 site.^{84,85}

In women, the regulatory effects of changes in reproductive steroids on the HPA axis are less well studied. Although some studies using psychological stressors identified increased stimulated cortisol in the luteal phase,^{86,87} others using psychological^{88,89} or physiological (e.g., insulin-induced hypoglycemia, exercise)^{90,91} stressors failed to find changes in HPA axis activity across the menstrual cycle. Altemus *et al.*⁹² demonstrated that exercise-stimulated HPA responses were increased in the mid-luteal compared with the follicular phase. However, in contrast to a large animal literature documenting the ability of estradiol to increase HPA axis secretion, Roca *et al.*⁹³ found that exogenously administered progesterone, but not estradiol, significantly increased exercise-stimulated vasopressin (AVP), adrenocorticotrophic hormone (ACTH), and cortisol secretion compared with a GnRH agonist-induced hypogonadal condition. The mechanism by which progesterone augments stimulated HPA axis activity is currently unknown but could include the following: modulation of cortisol feedback restraint of the axis^{69,94–97}; neurosteroid-related downregulation of GABA receptors⁹⁸; upregulation of AVP (consistent with luteal phase reductions in the threshold for AVP release)⁹⁹; and enhancement of oxytocin-induced corticotropin-releasing hormone (CRH) secretion.¹⁰⁰ Overall, it seems likely that multiple variables (e.g., the nature and intensity of the stressor, the exact phase of the menstrual cycle) influence the detection of reproductive steroid regulation of HPA axis activity.

Behavior

Behavioral studies in lower animals have documented the antidepressant-like effects of estradiol in the forced swim test.^{19,101} Additionally, existing evidence suggests that the antidepressant effects of estradiol in the forced swim test are mediated by estrogen receptor β ^{102–104} and can be reversed by the co-administration of a 5HT_{1A} receptor antagonist.¹⁰⁵ Selective agonists of estrogen receptor β also have anxiolytic effects on behavior tests of anxiety in rodents (e.g., open field or elevated plus maze) and decrease the HPA response to stress.^{104,107} Finally, estrogen receptor β knock-out mice display an anxious phenotype in the

female.^{35,108} Thus, behavioral studies in lower animals confirm that ovarian steroids modulate central nervous system function and behaviors relevant to affective adaptation and stress-responsivity.

Epidemiology of Depression during the Perimenopause

The majority of women do not develop depression during either the perimenopause or the postmenopause. In fact, epidemiologic studies have concluded that postmenopausal women are not at increased risk for developing depression^{109–120}; however, in four studies,^{111,112, 116,117} depressive symptoms were observed more frequently in perimenopausal than postmenopausal women. Indeed, in several other longitudinal, community-based studies, the perimenopause (or the presence of menstrual cycle irregularity and hot flashes) was associated with an increased risk for depression,^{121–126} consistent with studies of women attending gynecology clinics.^{127–129} In the initial cross-sectional survey from the Study of Women's Health Across the Nation (SWAN),¹²³ perimenopausal women reported significantly more “psychological distress” than either pre- or postmenopausal women (defined by self-reported menstrual cycle status).¹²³ In this study, “psychological distress” was employed as a proxy for the syndrome of depression by requiring that core depressive symptoms (sadness, anxiety, and irritability) persist for at least 2 weeks (similar to the duration criterion employed in DSM-IV). The results of several studies published during the last 4 years have found similar results. First, in a longitudinal study, Freeman *et al.*¹²⁶ found an increased risk for clinically significant depression (defined by elevated CES-D scale scores and the Primary Care Evaluation of Mental Disorders (PRIME-MD)¹³⁰) during the perimenopause compared with the pre- or postmenopause. In these studies, the relationship between the menopause transition and the onset of depression could have been confounded by the presence of a past history of depression in the women studied, since a prior episode of depression increases the risk for future recurrences. Thus, two subsequent studies examined the risk of depression in women with no past history of depression. Cohen *et al.*¹³¹ evaluated the risk of depression in 460 women who were followed prospectively for up to 7 years and who had no past history of depression. The risk of new onset depression (defined by Structured Clinical Interview SCID-IV) in the perimenopause was nearly twice that observed in the premenopause (adjusted OR = 1.8). Similarly, Freeman *et al.*¹³² demonstrated a significantly increased (2½ times greater) rate of new onset depression in women with no history of depression during the late perimenopause compared with women who remained premenopausal. Finally, two recent reports by Bromberger *et al.*^{133,134} demonstrate an increased incidence of first-onset and recurrent major and minor depressive episodes during the late menopause transition and early postmenopause. These data notwithstanding, the majority of women in these studies remained asymptomatic throughout the perimenopause. However, these data suggest that events occurring during the menopause transition and early postmenopause may predispose some women to develop clinically significant depressive illness.

Endocrine Studies in Perimenopausal Depression

The stage of the menopause transition during which episodes of depression appear could provide clues to the physiologic events accompanying the onset of depression. We have examined the temporal linkage between the stages of the menopause transition and depression in two studies. First, we prospectively examined asymptomatic premenopausal women with regular menstrual cycles to determine whether the onsets of depression clustered during a specific stage of the menopause transition. Women were followed with behavioral and reproductive measures for an average of 5 years until 6 months to 1 year after the last menstrual period. In a preliminary analysis of 29 women, we documented nine episodes of major or minor depression in eight women, only two of whom had a prior depressive episode. These data documented a clustering of depressive episodes in women during the late menopause transition

relative to the premenopause.¹³⁵ Second, we performed a cross-sectional study of 116 women presenting to the NIMH midlife clinic for evaluation and treatment—all of whom met criteria for perimenopause-onset major or minor depression. The majority of depressive episodes occurred during the late menopause transition regardless of the presence of vasomotor symptoms or a past history of depression.¹³⁶ The late menopause transition is characterized by estradiol “withdrawal” relative to either the postmenopause or the early perimenopause.^{2, 10} Thus, the temporal appearance of the depressions observed suggests an endocrine trigger related to the perimenopause (estradiol withdrawal and/or recent-onset of prolonged hypogonadism) in the onset of perimenopausal depression.

Basal Hormone Studies

Several reports indirectly support a role for abnormalities of reproductive hormones during the perimenopause in depression: (1) lower gonadotropin levels are sometimes observed in postmenopausal depressed women compared with asymptomatic comparison groups^{137–140}; (2) perimenopausal women with depressive symptoms are reported to have lower plasma estrone levels¹⁴¹ than nondepressed perimenopausal women; and (3) an association has been described between increased plasma FSH levels and depression.¹⁴² In contrast, three studies of perimenopausal and postmenopausal women observed either no diagnosis-related differences in plasma estradiol and FSH,¹⁴³ or no correlation between plasma levels of estrogens or androgens and severity of depressive symptoms.^{144,145} Similarly, in a study of 21 women with their first episode of depression occurring during the perimenopause, and 21 asymptomatic perimenopausal controls,¹⁴⁶ we were unable to confirm previous reports of lower basal plasma levels of LH^{137–140} or estrone¹⁴¹ in perimenopausal and postmenopausal women with depression. Additionally, we observed no diagnosis-related differences in basal plasma levels of FSH, estrone, testosterone, or free testosterone.

In addition to ovarian hormones, age-related differences in the function of several other physiologic systems are observed in both animals and humans. Some of these differences may occur coincidentally with the perimenopause and, therefore, may potentially contribute to mood dysregulation at this time.

A role for the adrenal androgen DHEA and its sulfated metabolite (DHEA-S) in the regulation of mood state is suggested by both its effects on neural physiology^{147,148} and its reported antidepressant-like actions in some,^{149–152} but not all, clinical trials.¹⁵³ DHEA's potential role in the onset of depression may be particularly relevant at midlife given the declining levels of DHEA production that occur with aging and the accelerated decrease in DHEA levels reported in women, but not men, during midlife.¹⁵⁴ It is possible, therefore, that declining secretion (or abnormally low secretion) of DHEA may interact with perimenopause-related changes in ovarian function to trigger the onset of depression in some women. Two studies¹⁴⁶ (Rasgon *et al.*, personal communication) measured plasma levels of DHEA and cortisol in samples of women with depression during the perimenopause and in nondepressed women matched for age and reproductive status. Depressed perimenopausal women had significantly lower levels of plasma DHEA, but not cortisol, compared with controls. These findings are consistent with several previous studies suggesting an association between plasma DHEA levels and mood. First, plasma DHEA levels correlated with the severity of depressive symptoms in a group of postmenopausal women, with lower levels of DHEA associated with higher depression scores.¹⁴⁴ In two other studies, a positive correlation between DHEA-S plasma levels and feelings of well-being was observed in groups of peri- and postmenopausal women,¹⁴⁵ as well as elderly depressed men and women.¹⁵⁵ These differences in DHEA levels notwithstanding, there was considerable overlap in plasma DHEA levels between perimenopausal women with and without depression. Thus, at present, in addition to the limitations of basal hormonal measures,

there is no consistent evidence that women who develop depression during the menopause transition have an ovarian or adrenal hormone-deficient state.

Longitudinal Studies

Daly *et al.*¹⁵⁶ evaluated mood scores and plasma FSH levels serially over a 6-week screening phase in women presenting to the NIMH midlife clinic with perimenopausal depression. In the group of women ($n = 18$) whose CES-D scores spontaneously decreased by $\geq 50\%$, we observed an incremental decline in FSH levels at each of the four clinic visits that paralleled the improvements in CES-D scores.¹⁵⁶ Increased plasma FSH levels during the same 6-week period were not consistently associated with worsening CES-D scores, nor were increased CES-D scores associated with corresponding elevations in plasma FSH levels, whereas a more uniform relationship was observed between mood and plasma FSH level when either measure decreased. Thus, we identified a subgroup of women with perimenopausal depression whose mood symptoms remitted spontaneously in association with a significant decline in gonadotropin levels (and a suggested alteration in pituitary-ovarian function). Thus, although cross-sectional studies suggest that perimenopausal depression is not associated with abnormalities of ovarian function, longitudinal studies support a meaningful association between alterations in pituitary-ovarian function and mood symptoms in these women.

Effects of Estradiol “Replacement” Therapy

An association between the endocrine events related to the perimenopause and the onset of depression is also implicated (albeit indirectly) by reports of the mood-enhancing effects of estradiol in depressed hypogonadal women.¹⁵⁷ Recently, three double-blind, placebo-controlled trials, which used similar methodologies and identical preparations of estradiol (i.e., 17 beta estradiol), have examined the efficacy of estradiol in perimenopausal and postmenopausal women with major or minor depressions.^{158–160} First, the therapeutic efficacy of estradiol was examined in a double-blind, placebo-controlled trial in 34 perimenopausal women (late perimenopause by STRAW criteria¹) who also met standardized diagnostic criteria for major and minor depression.¹⁵⁸ After 3 weeks of estradiol, depression rating scale scores were significantly decreased compared with baseline scores and significantly lower than scores in the women receiving placebo. The therapeutic response to estradiol was observed in women regardless of the presence of major or minor depression, a history of non-perimenopause-related depression, or the presence of hot flashes. Finally, neither baseline nor post-treatment plasma estradiol levels predicted the observed therapeutic response. In keeping with recent community-based cross-sectional surveys,¹²³ these data suggest that estrogen's effect on depression is not solely a product of its ability to reduce the distress of hot flashes. These findings also are consistent with data from Montgomery *et al.*¹⁶¹ and Saletu *et al.*¹⁶² which document the beneficial effects of estradiol on mood in perimenopausal women reporting depressive symptoms.

A second randomized, double-blind, placebo-controlled study by Soares *et al.*¹⁵⁹ confirmed the observations of Schmidt *et al.*¹⁵⁸ Soares *et al.* reported a significant and beneficial effect of estradiol replacement compared to placebo in women with perimenopause-related major depression (as defined by the PRIME-MD)¹⁶³ and, additionally, reported that baseline plasma estradiol levels did not predict response to estrogen treatment.¹⁵⁹ In contrast, a recent study using a similar design to that employed in perimenopausal women^{158,159} failed to observe a significant antidepressant effect of estradiol relative to placebo¹⁶⁰ in depressed women who were 5–10 years post natural menopause.

The evidence that younger perimenopausal, but not older postmenopausal, depressed women respond to short-term estradiol therapy suggests that the mood disorders occurring in

perimenopausal women are caused by changes in hormones (e.g., withdrawal or fluctuations) rather than prolonged ovarian steroid deficiency.

Endocrine Manipulations: Induction of Estradiol Withdrawal and Hypogonadism

Several case series describe the onset of depressive symptoms after the induction of hypogonadism by GnRH-agonists in gynecology clinic-based samples of women. For example, both Warnock¹⁶⁴ and Steingold¹⁶⁵ observed that 75% and 80% of women, respectively, experienced clinically significant depressive symptoms during GnRH agonist-induced hypogonadism. These observations provide further support for the potential role of the endocrine events accompanying the menopause transition in the onset of perimenopausal depression.

We have examined the effects of estrogen withdrawal and the recent onset of hypogonadism on mood symptoms using two strategies. First, Harsh *et al.*¹⁶⁶ administered a GnRH agonist for 2–3 months to 53 regular cycling, premenopausal women. In contrast to previous reports from gynecology clinic-based samples, all women had the absence of current or past psychiatric illness confirmed by a structured psychiatric diagnostic interview and completed daily symptom ratings for 2 months prior to the study entry to confirm the absence of significant mood or behavioral symptoms associated with their menstrual cycle. Additionally, all women had normal gynecologic and medical exams. Mood and behavioral symptoms during GnRH-agonist treatment were measured by the Beck Depression Inventory (BDI) and a self-report symptom rating form completed on a daily basis. Plasma hormone measures confirmed that the GnRH agonist suppressed the secretion of both ovarian steroids and gonadotropins. Only three women (5.7% of the sample) reported BDI scores greater than seven (suggestive of clinically significant symptoms of depression) and in only one of these women did the elevated BDI scores persist beyond 2 weeks' duration. In contrast to the relative absence of depressive symptoms in these women, we did observe the significant appearance of several symptoms, including both daytime and nocturnal hot flashes, disturbed sleep, and diminished libido. The latter finding is consistent with a prior study performed in a smaller sub-sample of these women in whom significant reductions in libido (as measured by a modified Derogatis Inventory of Sexual Functioning Scale¹⁶⁷) were observed in approximately 30% of the sample.¹⁶⁸ Thus, in otherwise healthy women, the induction of neither hypogonadism nor hot flashes (with an accompanying sleep disturbance) uniformly precipitated depressive symptoms.

In a second ongoing study, we are evaluating the effects of the acute withdrawal of estradiol therapy in women with and without a past history of perimenopausal depression. In this study, asymptomatic, postmenopausal women with and without a past history of depression during the menopause transition are placed on a standard dose (100 mcg) of estradiol therapy and after 3 weeks are randomly assigned under double-blind conditions to continue to receive estradiol (maintenance of estradiol) or placebo (estradiol withdrawal). Preliminary results suggest that estradiol withdrawal induces depressive symptoms in women with a past history of perimenopausal depression, but not in those without such a history. In women with a past history of depression during the perimenopause, estradiol withdrawal is associated with a significant increase in depressive symptoms (as measured by the CES-D scale¹⁶⁹) compared with those women who were maintained on estradiol therapy under double-blind conditions. Additionally, no significant depressive symptoms emerged in the women lacking a history of a past perimenopausal depression who were either withdrawn or maintained on estradiol therapy. Thus, in contrast to our findings with GnRH agonist-induced hypogonadism in premenopausal women with no past psychiatric history, estradiol withdrawal in women with a past history of perimenopausal depression triggers mood symptoms. Additionally, in those women who developed depression during the perimenopause, preliminary evidence suggests a direct relationship between declining estradiol secretion, the onset of hypogonadism and the

development of clinically significant mood symptoms. These data are consistent with those from epidemiologic studies showing that, for a subgroup of women, the endocrine events of the late menopause transition may represent important triggers for mood destabilization and the onset of depression. Both the markers of this risk and the mechanisms underlying estradiol withdrawal-induced depressive symptoms remain to be identified.

In summary, endocrine studies of depression during the menopause transition suggest the following:

1. Depression during the menopause transition is not associated with a simple deficiency or excess of reproductive hormones, as is the case in other reproductive endocrine-related mood disorders.
2. Pharmacologic induction of hypogonadism and estradiol withdrawal is not uniformly associated with depressive symptoms, but in some women, estradiol withdrawal appears to be an important physiologic trigger for the onset of mood disturbance.
3. Similarly, based on the antidepressant efficacy of estradiol therapy, declining estradiol secretion may play a role in the pathophysiology of depression during the menopause transition (in contrast to depressions in the postmenopause).

Conclusions

Ovarian steroids regulate many of the signaling pathways, neurocircuits and behaviors that are hypothesized to be abnormal in depression. Recent evidence from prospective studies suggests that for a subgroup of women the endocrine events during the menopause transition play a role in the onset of depression. Additionally, although perimenopausal depression is not caused by abnormalities of basal ovarian hormone secretion, this disorder, nonetheless, may be effectively treated with estradiol. The specificity of the relationship between the endocrine events of the menopause transition and depression in these women is further suggested by reports of the lack of antidepressant action of estradiol therapy in postmenopausal depressed women. Nonetheless, studies in which menopause is induced pharmacologically demonstrate that estradiol withdrawal and hypogonadism are sufficient to trigger depression in only a subgroup of women. Future studies need to identify the biochemical factors and markers of risk underlying the differences between those women who remain asymptomatic during the menopause transition and those who develop depression. The biological underpinning of this differential behavioral phenotype also may serve to reconcile and/or predict differences in response to hormone therapies.

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