Depression in Women: Windows of Vulnerability and New Insights Into the Link Between Estrogen and Serotonin

Sonali Lokuge, MSc; Benicio N. Frey, MD, PhD; Jane A. Foster, PhD;
Claudio N. Soares, MD, PhD, FRCPC; and Meir Steiner, MD, PhD, FRCPC

ABSTRACT

Objective: The purpose of this commentary is to provide an update on the research in both preclinical and clinical models regarding the cross-talk between estrogen and various serotonin molecular markers and the possible implications this may have on female-related mood disorders.

Conclusions: Animal and human studies provide strong and consistent evidence suggesting that estrogen is able to regulate the serotonin pathway at various levels. The general trend that emerges is that estrogen administration increases serotonin availability by altering mRNA and protein levels of various serotonin markers and by decreasing serotonin breakdown. These effects may have direct implications on female mood disorders such as premenstrual disorders and depression during pregnancy, postpartum, and during the menopausal transition.

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Major depressive disorder (MDD) is a chronic and disabling disorder that is characterized by affective, cognitive, behavioral, and somatic symptoms. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*), the essential feature of MDD is a minimum 2-week period in which an individual endorses depressed mood and/or experiences a loss of interest or pleasure from everyday activities. Additional symptoms may include diminished ability to concentrate, changes in sleep/appetite, psychomotor agitation/retardation, and suicidal thoughts.[1] MDD has been found to be associated with significant burden leading to personal, social, and financial costs. In the United States, the annual cost of depression has been estimated to be up to $52.9 billion. This total includes costs directly associated with health care as well as workplace-related losses.[2] Thus, significant functional impairment and high prevalence rates associated with depression ultimately result in increasing financial cost.

By 2030, the World Health Organization has predicted that MDD will be the leading cause of disability-adjusted life-years, an indication of the high burden of disease the illness is associated with worldwide.[3] Prevalence rates and symptoms of MDD are distinct among men and women. As reported by the National Comorbidity Survey, lifetime prevalence of unipolar depression in men is 12.7% versus 21.3% in women.[4] Such heightened risk among women has been documented in many epidemiologic studies, and it is widely accepted that women are twice as likely as men to develop depression during their reproductive years. Women are at a particularly higher risk for depression during periods of hormonal fluctuation, such as during the premenstrual period, pregnancy, the postpartum period, the transition to menopause, and the early postmenopausal years. Here, we will outline these windows of vulnerability across the female life cycle and briefly review preclinical and clinical literature that investigates the biological basis underlying the higher vulnerability for mood disorders observed in women, with a particular focus on the interaction between estrogen and serotonin neurotransmission. Additionally, we propose a possible mechanism of interaction between estrogen and serotonin and discuss the implications that this may have for reproductive-related mood disorders.

WINDOWS OF VULNERABILITY— MENARCHE, PREMENSTRUAL PERIOD, PREGNANCY, POSTPARTUM, AND MENOPAUSAL TRANSITION/EARLY POSTMENOPAUSE

The increased risk for developing depression in women begins at menarche and continues until the early postmenopausal years.[5] Throughout these years, there are specific time points at which risk is heightened for new-onset or recurrent affective disorders. This begins at menarche and continues to include the time prior to menses, during pregnancy, postpartum, and during the menopausal transition/early postmenopause.[6]

Before adolescence, depression rates in males and females are similar. However, at menarche, females undergo a dramatic change in hormonal

Clinical Points

- Women are at higher risk for developing depression compared to men, and such increased risk appears to be associated with reproductive "windows of vulnerability."

- The association between reproductive milestones and depression in women suggests a contributing role of sex hormones (ie, estrogen) to mood regulation.

- Animal data and clinical studies support the notion that estrogen has important modulatory effects on serotonin activity.

milieu with fluctuations affecting reproductive capability. At the same time, depression rates also change: females are twice as likely to develop a depressive episode when compared to males.[7]

Following menarche, some women develop premenstrual syndrome (PMS), which is characterized by a variety of physical and emotional symptoms. Prevalence rates of PMS vary based on the severity. Reports have identified that up to 75% of women experience at least 1 symptom of PMS and approximately 20% have clinically significant moderate to severe PMS.[8] The *DSM-IV-TR* has a category for a severe form of PMS termed *premenstrual dysphoric disorder* (PMDD), which is found in 3%–8% of women within the reproductive age.[9–11] PMDD is considered a clinical entity distinct from MDD and displays a defined "on/off" time course that occurs in the late luteal phase and ceases soon after menses. For PMDD, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are the first line of therapy. However, unlike in MDD, SSRIs appear to exert a rapid effect when used continuously (administration of SSRI once daily throughout the menstrual cycle) or intermittently (treatment during the last 2 weeks of the menstrual cycle).[12]

Pregnancy poses another vulnerable time when women undergo major hormonal and psychological changes. While these hormonal changes are necessary for proper fetal development, they may also be linked to mood changes. A systematic review of depression rates in pregnant women found that occurrence rates during the first, second, and third trimesters are 7.4%, 12.8%, and 12.0%, respectively.[13] During pregnancy, women either are at an increased risk for developing their first depressive episode or, if they have a past history of depression, are at an increased risk of recurrence, continuation, or exacerbation of previous depressive symptoms.[14] Mood disturbances in pregnancy not only affect the mother but also have been associated with numerous obstetric complications such as preterm delivery and low birth weight.[15] Depression risks also extend to the postpartum period, and the prevalence rates for postpartum depression in Western societies range from 12%–16%.[16] According to the *DSM-IV-TR*, depression is classified as having a postpartum onset if it begins within 4 weeks of delivery.[1] However, results from epidemiologic studies and researchers in this field strongly suggest 3 months as the most appropriate time frame for specifying postpartum onset.[17] Like depression during pregnancy, postpartum depression is linked with a change in hormonal levels—the removal of the placenta itself causes a rapid hormonal drop. Furthermore, postpartum depression affects not only the mother but also the newborn/infant. During early development, infants are particularly sensitive to the quality of contact they receive. Thus, the mental state of the mother may have marked effects on that of the child, including sleep disturbances, increased temper tantrums, and cognitive deficits.[18]

Elevated risk of depression in females continues up to the postmenopausal period, when the gap between rates in males and females narrows,[5] although recent data suggest that this elevated risk does not disappear altogether.[19,20] Compelling data from large epidemiologic studies and clinical evidence support the notion of a heightened risk for depression (new onset or recurrent) during the menopausal transition and early postmenopausal years.[21–24] During this period, menstrual cycle length and flow become increasingly irregular[25] and there are wide and erratic fluctuations of sex hormones.[26] At the same time, depressive symptoms and psychological distress appear to increase substantially in this subpopulation.[27]

In summary, relative risks of depression are found throughout the female reproductive life cycle. While the underlying etiologies (biological, psychosocial) of depressive symptoms during each of these "windows of vulnerability" may be different, they all occur at periods of significant hormonal fluctuation.

NEUROBIOLOGICAL ASPECTS OF SEX DIFFERENCES IN DEPRESSION

The underlying mechanisms driving the difference in depression incidence between males and females are still unknown. Some argue that women may have increased vulnerability and/or exposure to stressful life events, resulting in an increase in risk. However, underlying biological predispositions also seem to play a contributing role to this discrepant risk. The serotonergic system has long been implicated in mood disorders. Evidence comes from tryptophan depletion studies where plasma tryptophan, and consequently serotonin synthesis and release, is decreased. After tryptophan depletion challenges, women experience a greater depletion of plasma tryptophan than men.[28] Furthermore, healthy women are likely to develop depressive symptoms during tryptophan depletion compared to men.[29] Positron emission tomography (PET) shows that both baseline rates of serotonin synthesis and effects of tryptophan depletion are more prominent in women than in men throughout various brain regions,[30] supporting the notion that women are more vulnerable to dysregulation of the serotonergic system than men.

The contrasting depression rates between males and females may also be associated with differential exposure to hormonal fluctuations. Differences in serotonin

metabolism, neural activity, and impact of tryptophan depletion challenges all support the idea that women may have a biological predisposition to mood disorders. From the hormone viewpoint, one of the main candidates implicated in mood regulation is estrogen. There is now compelling evidence showing that some women experience an abnormal response to *normal* hormonal cycling rather than having an increased vulnerability to depression due to abnormal (higher, lower) estrogen levels.[31] This model was first tested by giving subjects with PMS and healthy controls an ovarian hormone suppressor, leuprolide; subjects with history of significant PMS had a decrease in PMS symptoms but experienced a recurrence of symptoms once they were reexposed to estradiol and progesterone, ie, during the estrogen and progesterone add-back phase of the study. These mood changes were not seen in healthy controls.[32] Similar findings were seen when women with or without a past history of postpartum depression were submitted to a hormone challenge involving high doses of progesterone followed by an abrupt progesterone withdrawal. Those with a history of postpartum depression experienced an increase of depressive symptoms during hormonal manipulations in comparison to healthy women.[33] High variability of mean estrogen levels over time (ie, within-subject measures) has also been found to be associated with higher depressive scores in midlife women, even after adjusting for risk factors for depression, such as smoking, hot flashes, and body mass index.[34] More recently, women undergoing in vitro fertilization showed an increase in depressive symptoms as they transitioned from a high estradiol level, estradiol-dominant phase into a low estradiol, progesterone-dominant phase.[35] It has been hypothesized that such increased sensitivity to hormone changes may accompany women throughout their reproductive milestones. For instance, some have suggested that women who report PMS earlier in life are at a greater risk for developing menopausal hot flashes, depressed mood, poor sleep, and decreased libido during midlife years.[23]

ESTROGEN AND ITS REGULATORY EFFECT ON MOOD: WHAT IS THE EVIDENCE?

Since the current hypothesis for the role of estrogen in mood regulation suggests that the *absolute* levels of estrogen are not the root cause for mood changes, it is important to further look into the molecular level and explore the changes that occur during hormonal fluctuation. Estrogen has been shown to act through 2 "classical" genomic receptors, estrogen receptors α (ERα) and β (ERβ). Once estrogen binds to its specific receptor, this complex then binds to estrogen response element sequences that are found on regulatory regions of genes and interact with coactivator proteins and an RNA polymerase II transcription initiation complex. Alternatively, the estrogen–estrogen receptor (ER) complex can interact with transcription factors and affect transcription through mechanisms that do not involve direct receptor binding to DNA.[36–38]

More recently, estrogen has been found to act more rapidly through nongenomic pathways. Instead of acting via intracellular ERα and Erβ receptors, it is proposed that these fast effects may be the consequence of membrane-localized ERs.[39] These ERs are able to act through second messenger pathways.[39–47] A novel G protein–coupled receptor named GPR30, which is also localized on the plasma membrane, has also been shown to regulate estrogen and may contribute to its fast-acting effect.[48–52]

At the molecular level, estrogen can regulate serotonin neurotransmission. Estrogen has been implicated with increased serotonin synthesis, decreased serotonin breakdown, and modulation of serotonin receptors.[53] Thus, the close relationship between estrogen and the serotonin system may provide insight as to why some women experience increased susceptibility to mood symptoms during periods of hormonal fluctuation.

Animal Studies

Estrogen has been found to inhibit monoamine oxidases (MAOs), which are enzymes that deaminate serotonin. MAO-A is an isoform of MAO, and rat models show that estrogen administration leads to a decrease in MAO-A activity in the hypothalamus, cerebellum, and amygdala.[54–56] Other studies show that 1 month of estrogen replacement treatment in macaques leads to a decrease in MAO-A mRNA and protein levels in the dorsal raphe and several hypothalamic nuclei.[57,58] Overall, these studies suggest that estrogen is acting as an MAO inhibitor. While MAO is involved in the degradation of serotonin, tryptophan hydroxylase (TPH) is the rate-limiting enzyme in serotonin synthesis. TPH causes the conversion of L-tryptophan to 5-hydroxy-L-tryptophan, which is the immediate precursor to serotonin. Various functional polymorphisms of the TPH gene have been associated with mood and anxiety disorders,[59–61] suggesting that changes in serotonin synthesis may be involved in affective disorders. Estrogen regulation of TPH mRNA has been explored, and it has been demonstrated that estrogen increases TPH mRNA in the dorsal raphe of macaques.[62] TPH has 2 isoforms: TPH1 is predominantly expressed in the periphery, whereas TPH2 is exclusively localized in the brain.[63] Considering the location of TPH2 in the central nervous system and its consequent relationship with brain levels of serotonin, recent studies have explored the relationship between it and estrogen. TPH2 mRNA and protein levels have been shown to increase after chronic estrogen administration in the dorsal raphe nuclei in rats and macaques,[58,64,65] with ERβ playing a particularly relevant role in TPH2 regulation.[66]

Another mechanism by which estrogen may regulate serotonin transmission is via the serotonin transporter (SERT). Acute estrogen administration increases the amount of SERT density in the forebrain and SERT mRNA in the dorsal raphe nuclei in rats. However, after chronic administration, a decrease in SERT mRNA is observed in the dorsal raphe nuclei.[67–70] An increase in levels of the SERT protein has been observed in the raphe nuclei in macaques.[58,71]

Estrogen also has significant effects on serotonin receptor subtypes such as 5-HT$_{1A}$ and 5-HT$_{2A}$. 5-HT$_{1A}$ receptor mRNA has been found in the hippocampus and is particularly abundant in the raphe nuclei.[72,73] One of the hypotheses as to why there is a lag of efficacy in the therapeutic response to SSRIs in depressed patients is the need to desensitize the 5-HT$_{1A}$ autoreceptor so that serotonin levels can increase. Consequently, studying 5-HT$_{1A}$ changes has important clinical implications. Following acute 17β-estradiol administration, decreases in 5-HT$_{1A}$ receptor mRNA were seen in the amygdala and cortex of rats,[74] whereas no changes in mRNA were seen after chronic administration.[75] However, chronic 17β-estradiol administration was associated with a decrease of 5-HT$_{1A}$ mRNA in the raphe nucleus of macaques.[76] Furthermore, estrogen administration has been found to reduce receptor density in the amygdala, hippocampus, and cortex[75] and receptor binding in the dorsal raphe nuclei and hypothalamus.[77] Together, these studies suggest that estrogen can down-regulate 5-HT$_{1A}$ receptor expression and density in brain areas associated with stress response.

Unlike 5-HT$_{1A}$ receptors that are primarily inhibitory, 5-HT$_{2A}$ receptors are involved in neural activation.[78] Acute estradiol treatment increased 5-HT$_{2A}$ receptor mRNA in the dorsal raphe nuclei and density in the forebrain.[79] A study conducted in male rats found that while castration decreased 5-HT$_{2A}$ density in the frontal, cingulate, and piriform cortices, olfactory tubercle and nucleus accumbens, estradiol benzoate increased 5-HT$_{2A}$ density in those areas to the same or even higher levels than in uncastrated animals.[67] This may indicate that the ability of estrogen to modulate serotonin is consistent across discrete brain regions and is independent of sex. Overall, the accumulated evidence from animal studies that investigated the link between estrogen and serotonin provides an interesting hypothesis for the heightened vulnerability to depression in women compared to men.

Clinical Studies

Several human studies have provided further translational confirmation for the estrogen-serotonin link hypothesis. In one study, estrogen replacement therapy (ERT) was administered to postmenopausal and healthy reproductive women for 30 days; after that, the serotonin agonist meta-chlorophenylpiperazine (m-CPP) was given. Menopausal women who did not receive ERT had blunted prolactin and cortisol response to m-CPP, while those given ERT had increased hormonal responses to m-CPP, suggesting that ERT may increase serotonergic activity in postmenopausal women.[80,81]

More recently, PET imaging studies have provided useful insights into the relationship between estrogen and serotonin in humans. Moses et al[82] measured cerebral blood flow using [^{15}O]water and 5-HT$_{2A}$ receptor binding using [^{18}F] altanserin in 5 postmenopausal women (4 of them early postmenopausal) before and after treatment with transdermal estradiol 100 μg for 8 to 14 weeks, followed by transdermal estradiol plus micronized progesterone 100 mg bid for 2

to 6 weeks. They found a 10% increase in 5-HT$_{2A}$ binding with each of these 2 hormonal treatments in all subjects and across all brain structures, including frontal, temporal, and limbic regions. This finding is consistent with a subsequent study[83] that also measured [^{18}F]altanserin binding in 10 postmenopausal women after 10 weeks of treatment with transdermal estradiol 75–150 μg. This study was able to replicate the finding that ERT increases 5-HT$_{2A}$ binding in discrete subregions of the prefrontal cortex. However, these results contrast with a recent single-photon emission computed tomography study[84] that failed to detect significant changes in 5-HT$_{2A}$ binding in 17 oophorectomized women submitted to long-term ERT (most receiving conjugated equine estrogen). Together, these studies suggest that short-term use of transdermal estradiol—but not long-term use of oral conjugated equine estrogen—increases 5-HT$_{2A}$ receptor density in brain regions associated with mood and cognition. These receptor-binding studies are consistent with clinical trials demonstrating that transdermal estradiol, but not oral estrogen, appears to be efficacious in reducing menopause-associated depressive symptoms.[85–87] Moreover, the response to transdermal estradiol might be time-specific (or "window-specific"), as postmenopausal women with MDD did not show a significant antidepressant response to estradiol as observed in perimenopausal, depressed women.[88]

Further evidence of potential interaction between estrogen and serotonin transmission comes from a recent study examining MAO-A binding (an indirect measure of MAO-A activity). Fifteen healthy women who were 4 to 6 days postpartum and 15 controls (women who were not recently postpartum) underwent carbon 11–labeled harmine position emission tomography in several cortical and subcortical areas. Total MAO-A distribution was significantly increased, at a mean level of 43%.[89] Considering that estrogen levels decrease 100- to 1,000-fold during the first 3 to 4 days postpartum, this study suggests that elevated MAO-A activity may be associated with a sudden drop in estrogen levels that occurs at the early postpartum period. Such a significant drop may render some women more vulnerable to develop postpartum blues and, presumably, postpartum depression.[89] Finally, a series of PET imaging studies that measured an index of serotonin synthesis in the human brain using α-[^{11}C]methyl-L-tryptophan showed that healthy women have lower serotonin synthesis as compared to healthy men, whereas women who suffer with MDD have higher serotonin synthesis as compared to healthy men.[30,90,91] These findings are in line with the tryptophan depletion studies[28] and further suggest that predisposed women are more vulnerable than men to develop depression after serotonin challenge.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, animal and human studies provide strong and consistent evidence suggesting that estrogen is able to

Table 1. Effects of Estrogen Administration on Serotonergic Neurons

Serotonergic Molecular Marker	Effects of Estrogen	Significance
MAO-A	↓ In the hypothalamus with acute estrogen (rat)[54,56] ↓ In the hypothalamus with chronic estrogen (macaque)[57] ↓ In raphe nuclei with chronic estrogen (macaque)[57,58]	An overall increase in serotonin availability
TPH1	↑ In raphe nuclei with chronic estrogen (macaques)[62]	An increase in serotonin levels in the periphery
TPH2	↑ In raphe nuclei with chronic estrogen (rat and macaques)[58,64,65]	An increase in serotonin levels in the central nervous system, of particular interest to mood disorders
SERT	↑ In raphe nuclei with acute estrogen (rat)[67,69] ↓ In raphe nuclei with chronic estrogen (macaque)[58,70] ↑ In hypothalamus with acute estrogen (rat)[67]	An increase in SERT, which decreases the amount of serotonin available for neurotransmission
5-HT$_{1A}$	↓ In amygdala with acute estrogen (rat)[74] ↓ In raphe nuclei with chronic estrogen (macaque)[76,77] ↓ In amygdala with chronic estrogen (macaque)[77] ↓ In hypothalamus with chronic estrogen (macaque)[77]	An overall increase in serotonin neurotransmission
5-HT$_{2A}$	↑ In raphe nuclei with acute estrogen (rat)[79] ↑ In forebrain with acute estrogen (rat)[79] ↑ In cerebral regions, prefrontal cortex, frontal gyrus, anterior cingulated cortex with hormone replacement therapy (human PET)[82,83]	An overall increase in serotonin neurotransmission; PET studies give insight to regulation in humans following hormone replacement therapy

Abbreviations: 5-HT$_{1A}$ = serotonin receptor 1A, 5-HT$_{2A}$ = serotonin receptor 2A, MAO-A = monoamine oxidase A, PET = positron emission tomography, SERT = serotonin transporter, TPH1 = tryptophan hydroxylase 1, TPH2 = tryptophan hydroxylase 2.
Symbols: ↓ = decrease, ↑ = increase.

regulate the serotonin pathways at various levels (Table 1). The overall impression is that estrogen administration increases serotonin availability by altering mRNA and protein levels of various serotonin markers and by decreasing serotonin breakdown in brain regions associated with mood regulation, stress response, and memory/cognition. These effects may have direct implications on female, reproductive-related mood disorders such as PMS/PMDD, depression during pregnancy, postpartum depression, and depression during menopause transition—ie, female "windows of vulnerability" for depression. Fluctuating levels of estrogen may cause altered transmission of serotonin, which in turn can affect mood. However, it is noteworthy that mood swings do not seem to be a product of abnormal hormonal levels; instead, they quite likely reflect *an abnormal response (increased sensitivity) to normal hormone fluctuations over time.* If confirmed, this hypothesis suggests that women who experience mood disorders during periods of hormonal fluctuation may constitute a particular subpopulation that could carry this increased vulnerability over time, ie, throughout their reproductive life cycle. Molecular biology can provide more information regarding the underpinnings of this vulnerability, and future studies in this area could lead to the detection of potential biological markers, tools that could greatly aid clinicians for proper diagnosis and clinical management.

To date, there are no evident biological markers that identify vulnerable female populations with depression. Some have argued that such biological markers might be unique for subpopulations susceptible to mood changes premenstrually, during pregnancy/postpartum, or during the perimenopause. Rapid effects of estrogen via nongenomic receptors may be one source of variation in female-specific mood disorders and MDD in general.[52] Additionally, while estrogen appears to play a modulating role in serotonin neurotransmission and this role is sex specific, it is important to understand that estrogen is probably one of multiple factors that affect serotonin. While estrogen levels constantly fluctuate, so do progesterone levels. It has been reported that progesterone can also affect brain functioning and, consequently, mood and behavior.[92] Additionally, norepinephrine and dopamine pathways may also play a role in women's increased susceptibility for depression. Considering the high prevalence rates of depression in women, further animal and human research is encouraged to facilitate the translation of knowledge from the laboratory to the clinical setting.

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