Published in final edited form as:

Menopause. 2016 March ; 23(3): 257–266. doi:10.1097/GME.0000000000000528.

Estradiol Variability, Stressful Life Events and the Emergence of Depressive Symptomatology during the Menopause Transition

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Abstract

Objective—To examine the role of estradiol fluctuation in triggering depressive symptoms in the menopause transition and assess the role of recent very stressful life events (VSLEs) as a moderating factor in this relationship.

Methods—52 euthymic women in the menopause transition or early postmenopause (age 45–60) who were assigned to the placebo arm of a randomized controlled trial of hormone therapy provided the data for this report. At enrollment, women's experience of recent VSLEs, depressive symptoms, serum estradiol and progesterone were assessed. At months 1, 8 and 14, depressive symptoms and hormones were re-assessed and participants underwent a stressor battery involving a speech and a mental arithmetic task. Participants rated their feelings of anxiety, fear, anger and rejection. The standard deviation of estradiol provided an index of hormone variability over the entire 14 months.

Results—Greater estradiol variability across the 14 months predicted greater depressive symptoms at month 14, though only in women reporting a higher number of VSLEs at baseline (39% of women reported ≤1 recent event). Greater estradiol variability also predicted greater feelings of rejection to the laboratory stressor at months 8 and 14. Furthermore, among women reporting higher VSLEs at baseline, feelings of rejection in response to the laboratory stressor at month 8 predicted depressive symptoms at month 14.

Conclusion—These data suggest estradiol variability may enhance emotional sensitivity to psychosocial stress, particularly sensitivity to social rejection. Combined with VSLEs proximate to the menopause transition, this increased sensitivity may contribute to the development of depressed mood.

Keywords

Estradiol fluctuation; menopause transition; perimenopausal depression; stressful life events; stress sensitivity; rejection sensitivity

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Conflicts of Interest/ Financial Disclosures: For the remaining authors, none were declared.

Women's lifetime prevalence of major depressive disorder (MDD) is double that of men's[1]. Depressive episodes tied to reproductive events, including perinatal depression, premenstrual dysphoric disorder (PMDD), and depression with onset in the menopause transition (i.e. perimenopausal depression) may contribute in a substantial way to the gender disparity that exists in rates of MDD. Studies in women with PMDD and those with a history of postpartum depression that pharmacologically manipulate the hypothalamic-pituitary-gonadal axis suggest that sensitivity to reproductive hormonal change, and not absolute levels of hormones, is pathophysiologically relevant to these disorders[2, 3]. The menopause transition and early postmenopausal period provides an ideal model in which to examine the influence of hormonal flux on mood destabilization and the development of depression in women[4] for the following reasons: 1) the day-to-day variability in reproductive hormones can be significant during this period[5] and 2) the menopause transition and early postmenopausal period is a time of particularly increased vulnerability to depression for women, with rates of MDD[6] and clinical elevations in depressive symptoms[7–9] roughly doubling to tripling compared to pre- and late postmenopausal rates.

Extreme variability in estradiol concentrations is particularly characteristic of the menopause transition, whereas progesterone fluctuation progressively declines over the menopause transition as women experience an increasing number of anovulatory cycles. Consequently, the role of estradiol fluctuation in the etiology of perimenopausal depression has been of particular interest. To our knowledge, five studies to date have evaluated the hormone variability hypothesis of perimenopausal depression by examining naturally occurring fluctuations in ovarian hormones in relation to depressive symptoms among perimenopausal women, with three of these studies[6, 9, 10] obtaining null findings and two studies observing an association between hormonal fluctuation and depressive symptoms[11, 12]. The two positive studies differed from the negative studies in ensuring that they included exclusively women with depression onset in the menopause transition rather than women whose symptoms began prior to, and continued into, the menopause transition. Second, the negative studies assessed hormone levels at most once annually, while the positive studies used more frequent hormonal assessments. Specifically, in one[11], ten assessment periods occurred over 8 years, each consisting of two blood draws taken one month apart. Estradiol variability at each assessment was calculated as the standard deviation across the two levels obtained during each assessment period and was found to predict both increased depressive symptoms (Center for Epidemiologic Studies Depression Scale - CES-D > 16) (OR = 1.30) and DSM-IV diagnosed depressive disorders (OR = 2.22). In the other positive study[12], follicle stimulating hormone (FSH) was measured once weekly for six weeks and hormonal change was calculated as the difference between week six and baseline FSH levels. This study found that those women who experienced a 50% drop in FSH over six weeks, indicative of a return to premenopausal ovarian function, experienced a significant decline in depressive symptoms (five-point decline on the CES-D). Taken together, these results suggest that studies employing more frequent assessment of ovarian hormone variability and studying exclusively depression with onset in the menopause transition may advance our understanding of the role of hormonal variability in the etiology of perimenopausal depression.

A substantial proportion of women, 26–33%,[6–9, 13] will develop clinically significant depressive symptoms within the context of perimenopausal hormonal flux. However, because the majority will not develop depression symptomatology, identification of potential moderators of the relationship between hormonal flux and the emergence of affective symptomatology may inform preventative intervention efforts. In a recent conceptual review[4], we have proposed a model of perimenopausal depression development whereby estradiol fluctuation increases sensitivity to stress such that in the context of stressful life events proximate to the menopause transition, clinical elevations in depressive symptoms may ensue. Such a model would be consistent with the observation that while hormonal influences are believed to play a role in perimenopausal depression development, psychosocial stress, including unemployment[8], financial strain[7], lack of social support[7] and recent stressful life events[6, 7] also predict increased risk for both depressive symptoms and syndromal MDD during the menopause transition. Notably, in a large scale, prospective epidemiologic study of women's health across the nation (the SWAN study), very stressful life events were found to be the strongest predictor of elevated depressive symptoms in the menopause transition[7].

The goals of the current preliminary report were therefore threefold: 1) To examine the relationship between estradiol variability and depressive symptomatology with onset in the menopause transition using more frequent hormone assessments than in previous studies; 2) To explore stressful life events proximate to the menopause transition as a candidate moderator of this relationship; and 3) To investigate increased sensitivity to psychosocial stress as a mechanism underlying any relationship observed between estradiol variability and perimenopausal depressive symptoms.

Methods

Participants

The women included in this report were recruited from the community to participate in the Perimenopausal Estrogen Replacement Therapy (PERT) Study, a 12-month placebo-controlled randomized trial evaluating the mood and cardiovascular benefits of transdermal estradiol in perimenopausal women. Women were recruited who were aged 45–60 years, medically healthy and perimenopausal or early postmenopausal according to the Stages of Reproductive Aging Workshop (STRAW+10) criteria (early perimenopause, defined as menstrual cycle length 7+ days longer than usual; late perimenopause, defined as ≥ 2 skipped cycles and an interval of amenorrhea ≥ 60 days but within one year of the last menstrual period and early postmenopause defined as an interval of amenorrhea between one and two years). Women who had partial hysterectomies (at least one ovary retained) for whom menstrual bleeding patterns could not be assessed were included in the study if: 1) they were experiencing vasomotor symptoms and their baseline estradiol levels were above postmenopausal concentrations (> 40 pg/ml) (n = 8) or, 2) they were not experiencing vasomotor symptoms but had baseline estradiol > 40 pg/ml and baseline FSH levels > 14 pg/ml (n=0) (a cutoff of two standard deviations above the mean level obtained from a sample of premenopausal women, consistent with STRAW guidelines[14].

Exclusion criteria included the following: current psychiatric diagnosis of MDD or any other current psychiatric diagnosis with severity greater than mild, a history of severe substance use within the past 10 years, a history of suicide attempts, use of psychotropic medication, hormonal preparations, or herbal compounds indicated for menopausal symptoms (e.g. Black Cohosh) or mood (e.g., St. John's Wort), use of statins or antihypertensive agents other than diuretics, regular over-the-counter medication use (e.g., non-steroidal anti-inflammatory agents), or blood pressure >160/90 mmHg. Multiple exclusion criteria aimed at minimizing risk related to hormone therapy also applied and included the following: endometrial hyperplasia, abnormal uterine anatomy, history of thrombophlebitis or thromboembolic disorders, history of estrogen-dependent neoplasias, body mass index > 35. To be eligible for the study, women also must have had a normal mammogram within one year of study enrollment. The study protocol was approved by the institution's Institutional Review Board. All participants provided informed, written consent prior to participating and received up to $1525 in compensation for participating in full compliance.

The data reported herein are derived from 52 women who were randomized to the placebo arm of the trial. These women wore a placebo patch in place of a transdermal estradiol patch (0.1 mg) and took placebo pills every other month in place of micronized progesterone pills (200 mg/day). It should be noted that the analyses for this report were conducted by the first author who was unblinded to treatment assignment but had no interaction with the research participants and no access to identifiable data. The participants remained blinded throughout the protocol. While this study was not specifically designed to examine the association of hormone variability and the onset of depressive symptoms in the menopause transition, the multiple assessments of ovarian hormones, stress responses to a standardized psychosocial laboratory stressor and depressive symptoms nonetheless makes it uniquely suited to do so. Although the entire trial will be completed in March 2016, early dissemination of the present results is intended to serve a heuristic purpose in informing both the design and analyses of other studies investigating the etiology and treatment of perimenopausal depression, which is currently gaining much attention[15–18].

Study Overview

Figure 1 depicts the overall study design. Participants first underwent an enrollment visit during which their study eligibility was determined and informed written consent was obtained. At this time, participants completed questionnaires pertaining to their demographic characteristics, medical history and current menopausal symptoms; participants' experience of stressful life events in the past six months was also assessed. One month following the enrollment session, those women who were determined to be eligible completed the first laboratory stress testing session, which included the Trier Social Stress Test (TSST). They were subsequently randomized to the active estradiol patch and micronized progesterone pills or the placebo patch and pills, though only women randomized to placebo are included in this manuscript. Six and twelve months later (months 8 and 14), participants repeated the stress testing protocol. This schedule was determined by the protocol of the RCT from which this study was derived; consequently, this was a convenience sampling protocol. At all four time points, serum estradiol and progesterone and depressive symptoms were

measured. At baseline, estradiol and progesterone were measured between 8:00 and 10:00 a.m. while at months 1, 8 and 14, they were measured between 1:00 and 2:00 p.m.

The Trier Social Stress Test (TSST)

All laboratory sessions began at 1:00 p.m. and involved a 40-minute quiet rest period, the last 10 minutes of which served as the pre-stress baseline, the administration of the TSST, and a 60-minute recovery period.

The TSST, which has been shown to induce a reliable stress response[19], involved four components: 1) Pre-task instructions (1 minute) during which participants were introduced to the committee who later listened to their job talk and were given instructions for the mental arithmetic task; 2) Speech preparation period (5 minutes) during which participants prepared their job talk while the selection committee stood in the room; 3) Job speech (5 minutes) - immediately following the preparation period, the selection committee asked the participant to deliver his/her job talk. The exact topic of the job talk was different at each of the three laboratory sessions to minimize habituation. If the participant ended their talk before 5 minutes, the selection committee questioned the participant in a systematic fashion to ensure the participant would speak the entire 5 minutes. 4) Serial subtraction task, which involved subtracting a 1-digit number from a 4-digit number as fast and as accurately as possible for 5 minutes. The numbers differed at each test session. For each mistake, the participant was instructed by a member of the selection committee to restart from the beginning. Participants were video-recorded throughout their performance.

Following the recovery period, participants were asked to rate on a scale from 0 to 10 the extent to which the job speech and the arithmetic task caused them anxiety, fear, anger/hostility and feelings of rejection. Using a similar scale, participants also rated how difficult the tasks were and how much effort they exerted in completing the tasks. However, because we have found the speech to be a more potent stressor inducing greater negative affective responses, we have only analyzed emotional responses to the speech task in the current manuscript.

Estradiol and Progesterone Assays

Serum estradiol and progesterone were determined using radioimmunoassay (RIA) techniques (MP Biomedicals). Intra-assay coefficients of variation were 5.5% for estradiol and 5.1% for progesterone, while inter-assay coefficients were 7.6% for estradiol and 8.5% for progesterone.

Measures

Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression Scale (CES-D), a 20-item self-report form that asks about the frequency of depressive symptoms during the previous week on a 4-point scale of 0 (rarely) to 3 (most or all of the time)[20]. A score of 16 or above is commonly used as a cutoff for identifying potential clinical depression[21] and is predictive of major depression[22]. The CES-D has been frequently used in perimenopausal samples[6, 9–12].

Recent total and very stressful life events were measured using a modified version of the Life Events Survey (LES)[23, 24] that assesses the presence of stressful events during the 6 months before the baseline assessment. The list had been modified to include only those events that are considered moderate to severely stressful based on previous studies with interviewer-based objectively rated stresses[25–27]. This interviewer-based objective rating has been shown to be consistently related to immune decline and HIV disease progression[25–27]. More recently, the modified LES questionnaire has been shown to predict non-adherence[27] and worse physical functioning and pain[28] in HIV infected men and women.

Using the LES, the distinction can be made between total stressful life events and very stressful life events, which includes only divorce or separation from a partner, serious illness or death of a close family member or close friend, a major worsening in one's financial status or major chronic financial problems (e.g. months behind in bills, foreclosure on a mortgage), being physically attacked or having one's life threatened, being sexually abused or assaulted, being arrested for a serious crime or having a mate or close relative arrested for a serious crime. The selection of these six specific events is based on the research of Leserman and colleagues finding that these events are experienced as very stressful in a particularly high proportion of participants and are uniquely predictive of negative health outcomes in chronically ill populations[26, 29]. Stressful life events not considered "very stressful" included such things as getting married or engaged, working long hours or changing residences more than once. In the current study, we examined both the number of total stressful life events and the number of very stressful life events an individual experienced in the last 6 months in relation to depressive symptoms.

Vasomotor symptoms were measured using the Greene Climacteric Scale (GCS)[30], a self-report form that asks the participant to rate the extent to which they currently suffer from 21 menopausal symptoms on a 4-point scale from 'not at all' to 'extremely' The Vasomotor Subscale of the GCS consists of two items: "hot flashes" and "sweating at night". Construct validity of this scale has been established in multiple studies[31–33].

Statistical Analyses

As recommended by Warner (2012)[34], sensitivity analyses were used to identify extreme outliers prior to data analysis, defined as values 3 or more interquartile ranges below the first quartile or above the third quartile (SAS Institute Inc., 2011). This resulted in the removal of two extreme estradiol variability scores. Although the analyses presented are those with the outliers removed, analyses with the outliers retained yielded an identical pattern of results.

The standard deviation in estradiol and progesterone across all four measurements was used as respective indicators of estradiol and progesterone variability and used to predict outcomes at month 14. In three cases in which only the baseline hormone levels were missing, the standard deviation in estradiol and progesterone was calculated across the three existing levels (months 1, 8 and 14) to predict outcomes at month 14. For analyses predicting outcomes assessed at month 8, the standard deviation in estradiol and progesterone across only the first three assessments was used. As such, the three participants with missing baseline hormone levels were excluded from this analysis.

Separate regression models were used to examine the main effects of estradiol variability and the number of baseline total and very stressful life events on CES-D score at months 8 and 14. All analyses included baseline CES-D score as a covariate. This approach was chosen over a repeated measures analysis to examine the effect of estradiol variability on CES-D score at months 0, 1, 8 and 14 because it was reasoned that CES-D score at months 8 and 14 should have two different predictors: estradiol variability measured until month 8 and estradiol variability until month 14, respectively. In a repeated measures analysis, the independent variable (estradiol variability measured across the 14 months) would partially be measured six months after the dependent variable (CES-D score at month 8), which would be inappropriate.

To examine total stressful life events as a potential moderator in the relationship between estradiol variability and depressive symptoms, the interaction between baseline total stressful life events and estradiol variability was examined in relation to CES-D score at months 8 and 14. Baseline CES-D score was included as a covariate. As such, the regression model included the following variables: total stressful life events, estradiol variability, total stressful life events X estradiol variability and baseline CES-D score. A similar regression model was conducted replacing total stressful life events with very stressful life events.

With the goal of exploring the role of increased stress sensitivity in linking estradiol variability and depressive symptoms, the main effect of estradiol variability as well as the interaction between estradiol variability and baseline total stressful life events were examined in relation to emotional responses to the TSST at months 8 and 14. Similar analyses were conducted using very stressful life events in place of total stressful life events. For all of these analyses, ratings of TSST difficulty and effort were included as covariates to account for any menopause transition-related declines in verbal memory[35, 36].

In light of the prominent “domino hypothesis” of perimenopausal depression[37, 38], which posits that vasomotor symptoms are responsible for triggering depressive symptoms through increased sleep disturbance, additional regression analyses examined the relationship between vasomotor symptoms and estradiol variability as well as the relationship between vasomotor symptoms and CES-D score. In addition, all regression models including estradiol variability as a predictor were rerun with the following potential confounders: age, race, body mass index (BMI), progesterone variability and estradiol levels.

All analyses were conducted using SAS v. 9.4.

Results

Participant Characteristics

As reflected in Table 1, the participants were of above-average socioeconomic status and reflected the racial demographics of our region (73% Caucasian, 23% African American, and 4% other). Twenty women (38.5%) endorsed at least one very stressful life event. These included: divorce (5 cases), death of a close friend or family member (5 cases), serious illness of a family member (4 cases), serious financial difficulty (7 cases) and one’s own serious illness or accidental injury (3 cases). Although a similar proportion of women

(30.8%) had a history of major depressive disorder, the overlap between very stressful life events and past depression was small, with only five past-depressed women endorsing at least one very stressful life event.

Depression scores were low at baseline; no participant scored >16 on the CES-D at baseline but roughly 8% did so at month 14. Based on STRAW +10 criteria, most women were in the late menopause transition (STRAW −1) at baseline and the majority remained in the menopause transition by the end of the study. Although 9% of women were postmenopausal at baseline according to STRAW+10 criteria, only one participant had a baseline estradiol level < 40 pg/ml. Repeated measures analyses revealed that post-TSST emotional ratings and ratings of difficulty and effort remained similar across the three administrations of the TSST (ps = .06–.78).

Estradiol Variability and Stressful Life Events Predicting Depressive Symptoms

Estradiol variability—When adjusting for baseline CES-D score, estradiol variability was not associated with CES-D score at either month 8 or 14 (ps >.10).

Total stressful life events—Adjusting for baseline CES-D score, the number of baseline stressful life events positively predicted CES-D score at month 8 (*Mean difference* = 1.9, p < .01) but not at month 14 (*Mean difference* = 1.4, p = .13).

Very stressful life events—Adjusting for baseline CES-D score, the number of baseline very stressful life events positively predicted CES-D score at month 8 (*Mean difference* = 2.2, p = .05), and this relationship became stronger by month 14 (*Mean difference* = 4.1, p = .01).

Estradiol variability by total stressful life events interaction—Adjusting for baseline CES-D score, estradiol variability did not interact with stressful life events at either month 8 (*Mean difference* = 0.03, p = .42) or month 14 (*Mean difference* = 0.03, p = .21)

Estradiol variability by very stressful life events interaction—Adjusting for baseline CES-D score, there was a significant interaction between estradiol variability and the number of very stressful life events such that estradiol variability was associated with higher month 14 CES-D scores, but only in those women reporting a greater number of very stressful life events at baseline (*Mean difference* = 0.1, p = .03). Although estradiol variability and very stressful life events were analyzed as continuous variables, they have been split at the median for illustration purposes in Figure 2, which displays mean CES-D score as a function of high versus low estradiol variability and very stressful life events. An interaction between estradiol variability and very stressful life events was not observed at month 8 (p = .42). It should be noted that this finding was the same when a repeated measures analysis was used to assess the interactive effect of estradiol variability and very stressful life events on CES-D score at months 0, 1, 8 and 14: a significant estradiol variability by life stress by time interaction on CES-D score was found such that the interaction between estradiol variability and life stress was only significant at month 14.

Estradiol Variability and Stressful Life Events Predicting Emotional Responses to the TSST

Estradiol variability—At month 8, higher estradiol variability was associated with greater anger/ hostility (*Mean difference* = 0.02, p < .01) and feelings of rejection (*Mean difference* = 0.05, p < .01) but not anxiety (p = .23) or fear (p = .08) in response to the TSST (Figure 3). This effect continued at month 14 for feelings of rejection (*Mean difference* = 0.02, p < .01) but not anger/ hostility (p = .51).

Total stressful life events—Adjusting for perceived difficulty and effort, the number of stressful life events reported at baseline predicted less anxiety (*Mean difference* = −0.41, p = .01) at month 8 but not at month 14 (p = .76) and did not predict the other emotional responses to the TSST at either time points (ps = .42–.93).

Very stressful life events—Adjusting for perceived difficulty and effort, the number of very stressful life events reported at baseline did not predict any emotional responses to the TSST at either month 8 or 14 (ps > .20).

Estradiol variability by very stressful life events interaction—There was no significant interaction between estradiol variability and very stressful life events in predicting emotional responses to the TSST at either month 8 or 14 (ps > .10).

Emotional Responses to the TSST at Month 8 Predicting Month 14 Depressive Symptoms

To further investigate the role of increased anger and rejection to the TSST as processes involved in estradiol variability's negative mood effects among women experiencing very stressful life events, we investigated the ability of these emotional responses to the TSST at month 8, as well as the interaction between these emotional responses and baseline very stressful life events, to predict CES-D score at month 14. TSST-induced feelings of rejection at month 8 and the number of very stressful life events at baseline were found to interact in predicting month 14 CES-D score such that feelings of rejection at month 8 predicted depressive symptoms at month 14 only within the context of elevated very stressful life events (*Mean difference* = 1.1, p = .02). This was not the case for anger (p = .20). Although feelings of rejection and very stressful life events were examined as continuous variables, they have been split at the median for illustration purposes in Figure 4, which displays mean CES-D score as a function of high versus low feelings of rejection at month 8 and very stressful life events. Neither post-TSST anger (p = .10) nor rejection (p = .17) predicted depressive symptoms at month 14.

Vasomotor Symptoms and Other Potential Confounders

It should be noted that in our sample, vasomotor symptoms were not associated with depressive symptoms at any time point (ps > .39). Furthermore, although estradiol levels tended to be negatively associated with vasomotor symptoms at month 14 (*Mean difference* = −0.004, p = .09), estradiol variability was not associated with vasomotor symptoms at any time point (ps >.19), nor did vasomotor symptoms interact with very stressful life events to predict depressive symptoms (ps > .16).

All analyses involving estradiol variability were rerun including the following potential confounders: age, race, BMI, progesterone variability and estradiol levels. However, all statistically significant results reported above remained statistically significant despite adjustment for these potential confounders.

Discussion

The current study found that estradiol variability predicted the development of depressive symptoms over a 14-month window of the menopause transition/early postmenopause in women who had a recent history of very stressful life events. Furthermore, the association of estradiol variability with depressive symptoms was preceded in time by its relationship with greater anger/ irritability and feelings of rejection to a psychosocial laboratory stressor, and stress-induced feelings of rejection at month 8 predicted depressive symptoms at month 14 in those women with a recent history of very stressful life events. Taken together, these results may suggest that estradiol fluctuation in the menopause transition enhances emotional sensitivity to psychosocial stress, particularly sensitivity to social rejection; and in combination with recent very stressful life events this increased sensitivity may contribute to the development of depressed mood. Importantly, these effects of estradiol fluctuation on stress sensitivity and mood appear to be independent of estradiol levels and vasomotor symptoms that may accompany the menopause transition. However, it is important to stress that these results are preliminary and prone to type I error given the large number of analyses conducted. The current results will require replication.

Of note, the interaction between estradiol variability and *total* stressful life events was not statistically significant. It may be that stressful life events not considered very stressful, such as working long hours, do not have the same long-lasting mood impact that very stressful life events, such as the death of a loved one, might have. The fact that total stressful life events significantly predicted CES-D score at month 8 but not month 14 whereas the negative mood effects of very stressful life events actually increased from month 8 to month 14 is supportive of this. Thus, perhaps only women suffering from very stressful life events at baseline would, fourteen months later, continue to show the emotional scars of those events. While speculative, these long-lasting emotional effects might then combine with prolonged exposure to estradiol variability to negatively impact mood. Another possibility is that the potency of very stressful life events to activate central neuroendocrine pathways that are both stress-responsive and modulated by estradiol is greater than stressful life events not considered very stressful. However, regardless of the underlying reason for which total stressful life events did not interact with estradiol variability, our findings are consistent with the fact that severe life stressors but not total life stressors have been found to predict perimenopausal depression[7]. Importantly, estradiol variability does not lead to significant mood disturbance in the absence of very stressful life events. If estradiol variability increases sensitivity to stress as the current study's results suggest, it may be that within the context of this increased stress sensitivity, significant life stress is a necessary trigger for negative mood induction.

Although a number of studies have shown that stressful life events predict depressive symptomatology during the menopause transition[6–8], this is the first report to identify a

potential mechanism that may contribute to the relationship between stress and depressive symptoms in this reproductive life phase. While our finding that estradiol variability is specifically correlated with rejection sensitivity, and not other emotional responses, may be the result of type I error, it may also suggest the possibility that estradiol fluctuation enhances the perception of negative social cues to impact social cognition. This is consistent with research in premenstrual dysphoric disorder (PMDD), a mood disorder triggered by ovarian hormone changes[3], in which the premenstrual phase is associated with negative bias in the processing of facial expressions[39] as well as altered corticolimbic reactivity in response to negative social pictures (reviewed in[40]). It is also consistent with evidence implicating rejection sensitivity as a transdiagnostic factor across psychological disorders[41]. Even in nonclinical samples, laboratory manipulations of social rejection are powerful, resulting in negative psychosocial effects such as increased aggression[42] and acute depressive symptoms[43]. If estrogen variability indeed increases perceived social rejection, this disturbance may mediate links to other negative interpersonal and affective outcomes in the menopausal transition.

One potential mechanism by which estradiol variability may influence sensitivity to rejection and mood may involve the modulation of hypothalamic oxytocin production by estrogen receptor (ER) activation[44–47]. Mounting evidence suggests that central oxytocin acts on the limbic system to increase the salience of social cues, positive and negative, and enhance affective responses to those cues (reviewed in[48]). Therefore, as discussed by Bartz et al.[49], oxytocin's effect on responses to social cues depends largely on context - enhancing positive responses to pro-social cues and having the opposite effect within the context of social rejection, particularly in women[50–53]. However, it should be noted that these studies are constrained by either the use of plasma oxytocin as an imperfect indicator of central levels or by the use of intranasal administration of oxytocin, which has a short half-life. Nonetheless, we might postulate that prolonged periods of low estradiol concentrations, which are characteristic of the menopause transition[5], could result in hypothalamic ERβ sensitization, thus enhancing estradiol's effect on oxytocin release following a long period of low estradiol. High levels of oxytocin may then increase sensitivity to rejection within the context of the TSST, as is suggested by a previous study examining the effects of intranasal oxytocin on emotional responses to the TSST[51].

An alternative, though not mutually exclusive, possibility that has been recently suggested[4] is that perimenopausal estradiol variability may, via alterations in GABAergic inhibitory control, contribute to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis response to stress and consequently contribute to the development of perimenopausal depression. Both proposed mechanisms are currently speculative, though future research investigating the relationships between changes in estradiol, oxytocin, cortisol and mood in the menopause transition is warranted. It is also possible that other well-known risk factors for perimenopausal depression, such as having a family history of depression[9] may increase the likelihood that a life event would be perceived as very stressful within the context of estradiol variability. Future research should therefore investigate the potential moderating role of other risk factors for depression as well. Other steroid hormones such as androgens may also be relevant to perimenopausal depression. Although not measured in the present study, the investigation of androgens in the etiology of perimenopausal depression is

warranted given that androgens, including dehydroepiandrosterone (DHEAS) and testosterone, rise during the perimenopausal and early postmenopausal years[54] and this rise has been implicated in perimenopausal depression in one previous study[55].

The current study should be interpreted in light of its limitations. First, although the estradiol measurement schedule is substantially more frequent than that of previous studies, it is still imprecise in capturing the true degree of hormonal fluctuation to which a woman is exposed during the menopause transition. Second, it is limited by its single measurement of life stress. Third, unless participants scored >16 on the CES-D during interim study visits, in which case a psychiatric interview was administered to determine the presence or absence of MDD, depressive symptoms used in analyses in this study were solely assessed using a self-report questionnaire. Fourth, due to the current study's small sample size and therefore already limited statistical power, we chose not make any adjustments for multiple comparisons to reduce the family-wise error rate. Finally, because the data presented here are from a randomized controlled trial with many exclusion criteria, including baseline psychopathology, its participants may not be representative of the general population of perimenopausal women and is likely above average in both mental and physical health. We hypothesize that the effects of estradiol fluctuation on mood may have been even more pronounced had this study been more inclusive. The fact that the women in this study were participants in a randomized controlled trial may also have dampened the effect of estradiol variability on mood by creating an expectation that hormone therapy would benefit mood and other perimenopausal symptoms. A placebo effect may have therefore prevented depressive symptoms from becoming as elevated as they otherwise would have.

Despite these limitations, the current study addresses several gaps in the current literature on estradiol variability and perimenopausal depression development. It is the first to examine the relationship between estradiol variability and emotional responses to the TSST, allowing us to examine increased stress sensitivity as a candidate mechanism linking estradiol variability and perimenopausal depression symptomatology. It is also the first study to examine potential moderating variables in linking perimenopausal estradiol variability and depressive symptoms. Furthermore, by excluding depressed women at baseline, the current study also ensured that any clinical elevations in depressive symptoms observed had their onset in the menopause transition.

Conclusions

The current study's findings suggest that perimenopausal estradiol fluctuation may increase women's sensitivity to social rejection, and when this sensitivity is combined with psychosocial stressors such as divorce or bereavement, women are particularly vulnerable to the development of clinically significant depressive symptoms. Should these preliminary findings be confirmed in future research, they may have important clinical implications, suggesting that depressive symptoms might be prevented and/ or treated in at least two ways. First, by implicating estradiol fluctuation in the etiology of perimenopausal depression, the current study provides support for the use of transdermal estradiol as a treatment for perimenopausal depression through the stabilization of estradiol levels. To date, small RCTs find that transdermal estradiol is more effective than placebo at decreasing

depressive symptoms and treating MDD in perimenopausal women[56–58] – the current study provides indirect evidence that estradiol stabilization may be the mechanism underlying these results. Second, because estradiol fluctuation was associated with both increased sensitivity to psychosocial stress and development of depressive symptomatology, the current study's results may also suggest a role for the use of psychosocial interventions aimed at increasing resilience in the face of stress to prevent and/ or treat perimenopausal depression. For example, multiple studies suggest that mindfulness meditation training[59, 60] and mindfulness based cognitive therapy[61] decrease negative emotional responses to psychosocial stress. These interventions are also known to prevent the onset of depression in at-risk populations[62, 63]. However, studies testing the efficacy of these interventions to promote mental health in the menopause transition are needed.

Importantly, if the current study's findings are replicated, they suggest that the effect of estradiol variability on mood is not the same in all women. In fact, unless severe life stress was present, estradiol variability did not predict depressive symptoms in this sample. In clinical practice, an assessment of current life stress may therefore be used to identify women who are most vulnerable to developing perimenopausal depression and perhaps most likely to benefit from the prophylactic interventions. Future research should continue to search for moderators in the relationship between estradiol fluctuation and perimenopausal depression to inform and advance individualized medicine for improving quality of life for women in the menopause transition.

Acknowledgments

Sources of Financial Support: This research was supported by NIH grant RO1-MH087619. Dr. Gordon is also the recipient of a Postdoctoral Fellowship of the Fonds de la Recherche du Québec – Santé (FRQS).

Dr. Rubinow serves on the editorial board of Servier Laboratories, is a consultant for Sage Therapeutics Inc. and has received grant funding from the Foundation of Hope. Both Drs. Rubinow and Girdler have also received grant funding from NIH.

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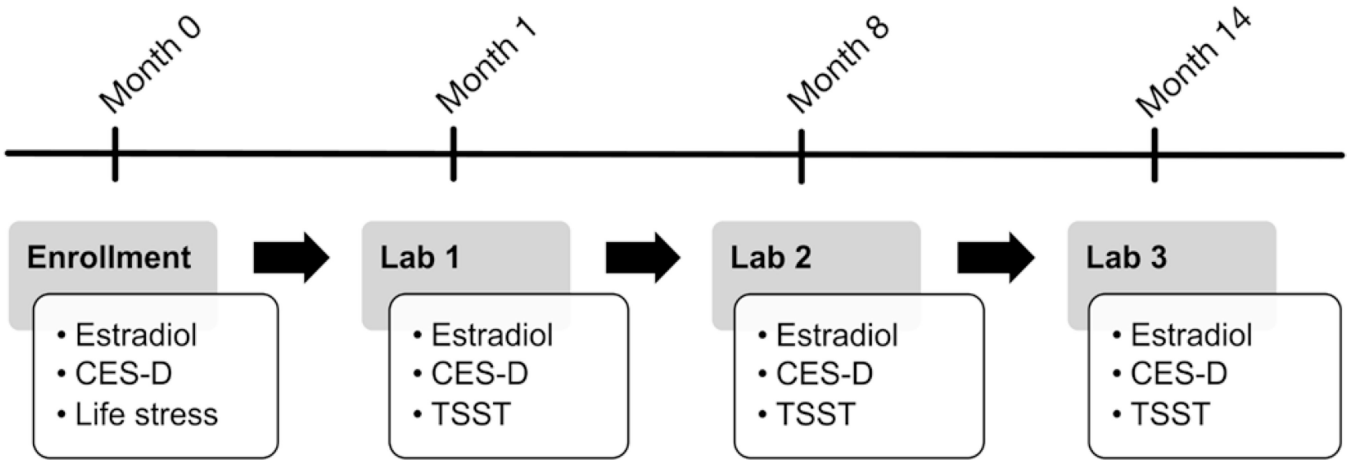

Figure 1.
Study design.

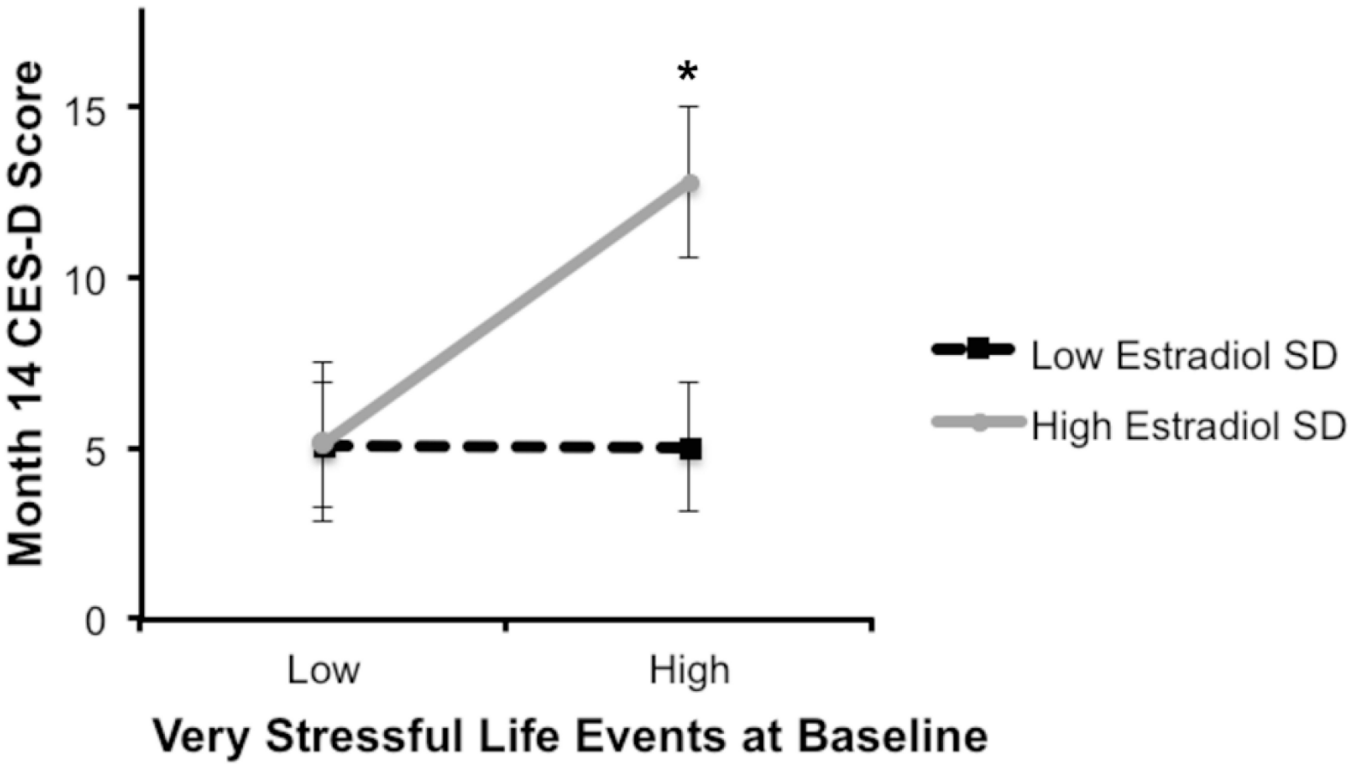

Figure 2.

Mean (+SEM) month 14 CES-D score as a function of low versus high very stressful life events at baseline and E2 variability (both split at the median) adjusting for baseline CES-D score. N = 42; *p<.05

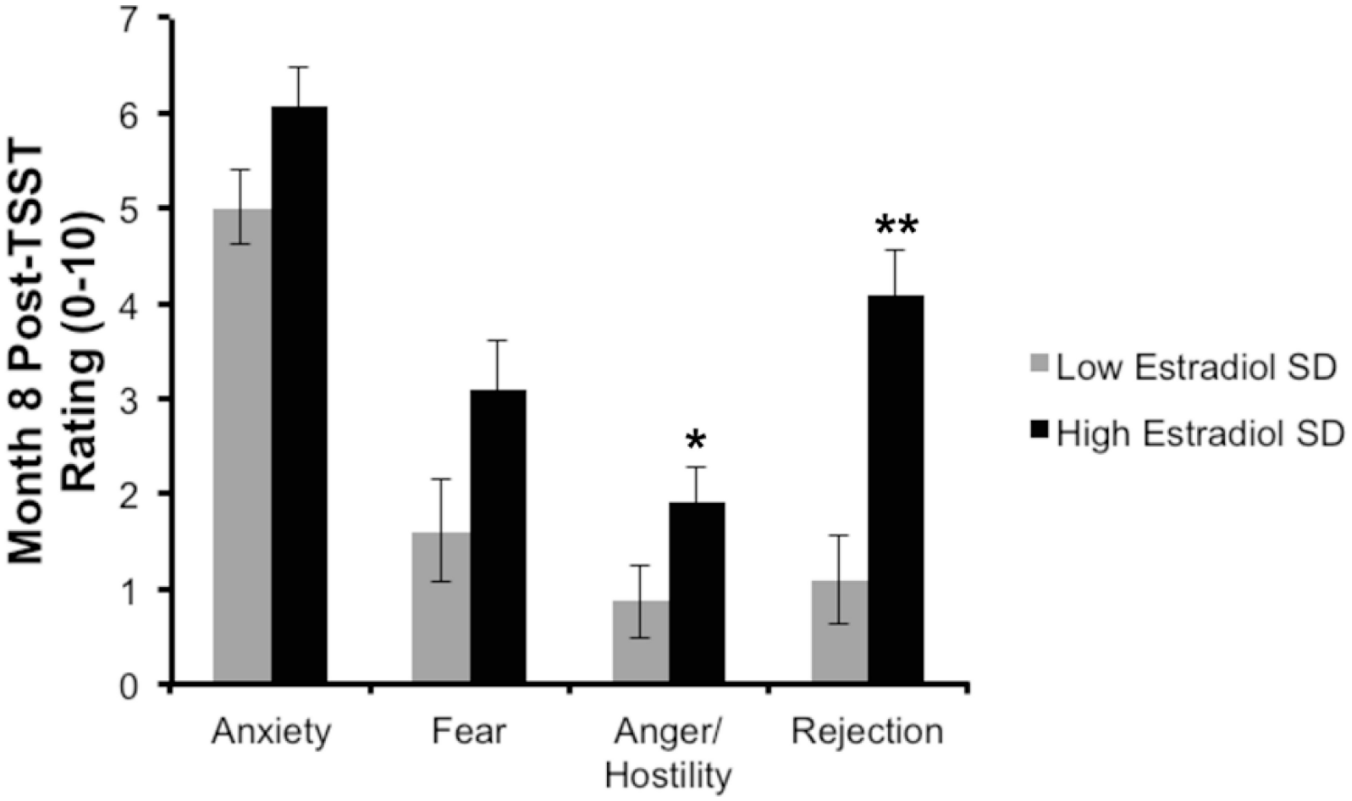

Figure 3.

Mean (+SEM) month 8 post-TSST emotional ratings as a function of low versus high estradiol variability (based on a median split), adjusting for perceived task difficulty and perceived effort. N = 47; *p<.05 **p<.001

Figure 4.
Mean (+SEM) month 14 CES-D score as a function of very stressful life events at baseline and post-TSST feelings of rejection at month 8, adjusting for perceived task difficulty and perceived effort; N = 44 *p<.05

Table 1

Participant characteristics

Variable	Mean (SD) or %
Age	50.9 (3.0)
Household Income	$80 000 – 99 999
Race	
% Caucasian	73.1%
% African American	23.1%
% Other	3.8%
Mean GCS Vasomotor subscale score (/6)	
Baseline	2.1 (1.7)
Month 14	1.4 (1.5)
History of major depressive disorder (%)	30.8%
Mean CES-D score	
Baseline	5.0 (3.8)
Month 14	6.5 (7.3)
Mean CES-D score change (Months 0 to 14)	2.0 (7.0)
% Reporting baseline very stressful life events	38.5%
% CES-D score >16	
Baseline	0%
Month 14	7.7%
Mean estradiol change (pg/ml) (Months 0 to 14)	7.0 (80.0)
Estradiol (pg/ml)	
Baseline	127.5 (102.2)
Month 1	97.4 (54.4)
Month 8	97.3 (56.8)
Month 14	127.2 (100.1)
Mean progesterone change (pgml) (Months 0 to 14)	−0.8 (6.2)
Progesterone (pg/ml)	
Baseline	1.8 (3.9)
Month 1	1.5 (4.4)
Month 8	1.9 (5.9)
Month 14	1.2 (4.3)
Menopausal Status at Baseline	
Early perimenopausal	29.6%
Late perimenopausal	61.4%
Postmenopausal	9.1%
Estradiol < 40 pg/ml	1.9%
Menopausal Status at Month 14	
Early perimenopausal	17.8%
Late perimenopausal	48.9%
Postmenopausal	33.3%

Variable	Mean (SD) or %
Estradiol <40pg/ml	7.1%