The Effect of Trauma History on Mood Sensitivity to Perimenopausal Estradiol Fluctuation

Honours Thesis

Submitted in Partial Fulfillment of the Requirements

For the Degree of

Bachelor Arts (Honours)

in Psychology

Supervised by Dr. Jennifer L. Gordon

University of Regina

by

Rashell Wozniak

Regina, Saskatchewan

April, 2017
Abstract

A woman’s risk of depression increases 2-3 times during the menopause transition (i.e., ‘perimenopause’), which constitutes the five or so years leading up the last menstrual period. It is hypothesized that the increased estradiol fluctuation, which accompanies the menopause transition, may play a role. Women who display an increased sensitivity to such fluctuations may be particularly vulnerable to developing depression during this time. A history of abuse has been found to predict increased sensitivity to hormonal fluctuation across the menstrual cycle; however, it has never been examined as a predictor of mood sensitivity to the hormonal fluctuations associated with the menopause transition. The purpose of this study was, therefore, to examine perimenopausal estradiol fluctuation in relation to weekly mood in women with and without a history of sexual or physical abuse. Fifteen perimenopausal women were recruited, 9 with a history of sexual or physical abuse, and 6 without. Participants provided twelve weekly urine samples for the measurement of a metabolite of estradiol, and completed two scales to measure mood and depressive symptoms. Results suggested a nonsignificant interaction between trauma history, absolute change of E1G, and the direction of change on CES-D and PANAS-X scores. After further examination, there was a significant interaction when examining those with a history of early abuse (before age 13), on CES-D and PANAS-X scales. Therefore, women with a history of early abuse, during perimenopause, may be at greater risk of depressed mood due to E1G fluctuation.

*Key words:* estradiol, hormonal fluctuation, menopause transition
The Effect of Trauma History on Mood Sensitivity to Perimenopausal Estradiol Fluctuation

The menopause transition, or perimenopause, describes the phase that all women experience in the years leading up to the cessation of menstruation (Harlow et al., 2012). The menopause transition typically begins in a woman’s mid-40s (Burger, Hale, Robertson, & Dennerstein, 2007) and lasts approximately five years (Burger, et al., 2007). The classification of the menopause transition is based on menstrual bleeding patterns according to the Stages of Reproductive Aging Workshop criteria (Harlow et al., 2012). Based on these criteria, a woman is categorized as being in the early menopause transition if she experiences persistent variability in menstrual cycle length, specifically a difference of seven days or more in the length of consecutive cycles and is categorized as being in the late menopause transition if she has gone at least 60 days (but not more than one year) without a menstrual period.

The menopause transition is triggered by a decrease in the number of follicles in a woman’s ovaries as a result of advancing age (O’Connor et al., 2009). Briefly, this drop in the number of ovarian follicles triggers dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis, which controls a woman’s production of estradiol and progesterone. As a result, the menopause transition is accompanied by important hormonal changes. Progesterone levels stabilize because ovulation becomes increasingly rare; however, estradiol fluctuation increases considerably. At times, a small number of estradiol-producing ovarian follicles simply results in low estradiol levels; at other times, due to decreased negative feedback to “upstream” components of the HPG axis, a small number of ovarian follicles triggers excess stimulation of the few existing follicles, resulting in exceedingly high levels of estradiol. A perimenopausal woman, therefore, experiences considerable fluctuation from low to high estradiol levels.

**Estradiol Fluctuation and Depression in the Menopause Transition**
The risk of depression increases 2-3 times the normal rate during the menopause transition (see Gordon et al., 2015 for review), with 26-33% of perimenopausal women experiencing clinically significant depressive symptoms (Bromberger et al., 2007; Freeman et al., 2004; Woods et al., 2008). The reasons behind this increase in risk are uncertain; but, it is hypothesized that excessive estradiol fluctuation in the menopause transition may be a contributing factor. Some studies concurrently assessing hormones and depressive symptoms infrequently (i.e., less than once per year) have obtained null findings (Bromberger et al., 2011; Woods et al., 2008); however, four studies using more frequent measurements (Freeman, Sammel, Lin, & Nelson, 2006; Gordon, Rubinow, Eisenlohr-Moul, Leserman, & Girdler, 2016b; Gordon, Eisenlohr-Moul, Rubinow, Schrubbe, & Girdler, 2016a; Schmidt et al., 2015) suggest that excessive fluctuation in estradiol may contribute to depressive symptoms in the menopause transition.

Freeman and colleagues (2006) recruited 231 women without current or past depression. At enrolment, they were between 35-47 years of age and had regular menstrual cycles. Ten estradiol assessment periods occurred over eight years, each consisting of two blood draws taken one month apart. Furthermore, the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) and the Primary Care Evaluation of Mental Disorders (PRIME-MD; Spitzer et al., 1994) were used to assess depressive symptoms and clinical depression, respectively, during each assessment period. Estradiol variability at each assessment was calculated as the standard deviation across the two estradiol levels obtained during each assessment period. It was found that over the eight-year study, clinical elevations in depressive symptoms and major depressive disorder were more likely to occur at times when estradiol variability was highest. Gordon and associates (2016b) measured depressive symptoms and hormone levels four times over the
course of 14 months. This study included 52 euthymic women in perimenopause, or early postmenopause, and the CES-D was used to measure depressive symptoms throughout. They found that estradiol fluctuation, calculated as the standard deviation in estradiol across the four measurements, predicted depressive symptoms at month 14; however, this effect was only present among women who had recently experienced a very stressful life event, such as divorce or the death of a loved one. Among women who had not experienced a recent stressful life event, estradiol fluctuation was not associated with depressive symptoms. Gordon and colleagues (2016a) examined the relationship between weekly changes in salivary estradiol, and weekly mood in 30 perimenopausal women, including 10 who met criteria for current major depression, 10 without current depression but with a history of past depression, and 10 with no history of depression. The CES-D was administered weekly to measure depressive symptoms. They found a greater change in estradiol from one week to the next predicted negative mood only in the currently depressed group, suggesting that their depressive symptoms had perhaps arisen due to an increased sensitivity to hormonal fluctuations.

A fourth study by Schmidt and colleagues (2015) examined the effect of estradiol change on mood in the menopause transition by pharmacologically manipulating estradiol levels. In this study, hormone therapy was used to precipitate a large drop in estradiol among 26 asymptomatic postmenopausal women who had a history of perimenopausal depression (i.e., depression with onset in the menopause transition), and 30 asymptomatic postmenopausal women without a history of depression. Both groups were matched for age, body mass index, and reproductive status. For three weeks, all women received open-label transdermal estradiol, after which participants were randomized to either continue receiving estradiol, or to switch to a matched placebo skin patch. Both the CES-D and the 17-item Hamilton Depression Rating Scale (HDRS;
Hamilton, 1960) were used to measure depressive symptom ratings. During the open-label use of estradiol, no women reported depressive symptoms; however, women with past perimenopausal depression who were randomized to the placebo patch experienced a significant increase in depression symptoms. The other women with past perimenopausal depression, who continued with estradiol administration, and all women in the control group, remained asymptomatic. This study provides strong evidence that an increased sensitivity to estradiol fluctuation, particularly a decrease in estradiol, plays an important role in the etiology of perimenopausal depression.

Trauma History and Mood Sensitivity to Estradiol Fluctuation

Taken together, the above research suggests that, within the context of the menopause transition, estradiol fluctuation can trigger an increase in depressive symptoms; however, not all women are uniformly sensitive to such fluctuations, and not all become depressed. Moderating factors, such as recent stressful life events and current depression, may predict greater sensitivity to perimenopausal hormone fluctuations (Freeman et al., 2006). For the purposes of early detection and prevention, it may be clinically useful to identify factors that predict greater sensitivity to estradiol fluctuation and, therefore, greater risk for perimenopausal depression. A recent study by Eisenlohr-Moul and colleagues (2016) suggests that a history of abuse may be another factor that is predictive of increased mood sensitivity to fluctuations in estradiol. In this study, 66 premenopausal women underwent a validated interview assessing abuse history at baseline, after which they completed a mood scale each day throughout an entire menstrual cycle. Blood samples were collected on five occasions for the measurement of reproductive hormones. Women with a history of abuse exhibited greater mood sensitivity to cyclical elevations in estrogen and progesterone. These results suggest that a history of abuse may trigger neurobiological changes that increase a woman’s sensitivity to reproductive hormone
fluctuations within the context of the menstrual cycle; however, no study has yet to examine a history of abuse as a predictor of hormonal sensitivity within the context of the menopause transition.

**Purpose**

The current study aimed to compare the relationship between week-to-week hormone fluctuations and weekly mood in perimenopausal women with and without a history of sexual or physical abuse. The previous research suggests that women with a history of abuse are more sensitive to hormonal fluctuations within the context of the menstrual cycle. Based on this finding, we hypothesized that women with a history of abuse would display greater mood sensitivity to week-to-week estradiol fluctuation within the menopause transition.

**Method**

**Participants**

This research project was reviewed and approved by the University of Regina Ethics Board. Fifteen women between the ages of 45 to 55 years were recruited who were within the menopause transition according to the Stages of Reproductive Aging Workshop (Harlow et al., 2012). A sample size of 15 was chosen based on the practicality of completing a three-month study in a short time frame; however, pilot data from our laboratory using identical methods to those described here suggests that a statistically significant effect of E1G fluctuation on weekly mood is detectible in 15 participants. Nine of the 15 women had a history of physical or sexual abuse as determined by their responses on the unwanted physical and sexual experience subscale of the Trauma History Questionnaire (THQ; Green, 1996), with 6 of these women reporting abuse that occurred before the age of 13. Participants were excluded based on current diagnoses of a psychotic disorder, bipolar disorder, major depressive disorder, or any other psychiatric
disorders, as determined by self-report. Women who were pregnant or nursing, or taking mood-altering medications were also excluded. The study was advertised through ads on Kijiji, UsedRegina, and Facebook, as well as flyers posted throughout the Regina area. Participants were compensated $250 for completing the study in full compliance.

Procedure

**Enrolment Session.** After completing a phone screen to determine their eligibility, participants were asked to come to the laboratory for an enrolment session with one of the research assistants. Once eligibility was confirmed, and consent obtained, the participants were given instructions on how to collect and store urine samples in their homes for the purposes of hormone measurement. For participants located outside of Regina, the enrolment session took place over the phone, after which the urine sample kit was mailed to the participant. Lastly, participants completed a number of online surveys using Qualtrics, including the THQ, and one assessing general demographic information.

**Weekly assessments.** Each week for a 12-week period, participants were reminded by text, email, or phone to fill out mood questionnaires and a questionnaire based on vasomotor symptoms (described below). They were sent a message containing a Qualtrics survey link and a reminder to collect urine the following morning. The survey contained the Positive and Negative Affective Schedule (Expanded Form; PANAS-X; Watson & Clark, 1999) and the CES-D for the assessment of positive and negative affect and depressive symptoms, respectively. Furthermore, participants were asked to report on the number and severity of vasomotor symptoms experienced the day of their mood assessment. Hot flashes and these vasomotor symptoms were measured due to the possibility that these factors may be confounding variables in the association between hormone variability and mood.
The following morning, participants collected a sample of their first-morning voided urine using a provided specimen collection kit. The kit included 12 polypropylene tubes that were labeled for each week, disposable plastic cups, syringes, and a small storage box. Specifically, women collected their first-morning voided urine into a cup using a syringe to fill the polypropylene tube up to the indicated fill line (2 ml), and placed each tube in the supplied box. They then stored the specimen collection kit in their home freezer within two hours of collection. Once all samples were collected we arranged for the samples to be shipped to our laboratory. Once obtained, samples were frozen at -40°C until the samples were assayed for levels of estrone-3-glucuronide (E1G), a urinary metabolite of estradiol. It should be noted that urinary E1G levels were measured the day after participants assessed their mood because first-morning urine levels of E1G have been highly correlated with serum levels of estrogen measured the day prior to urine collection (O’Connor et al., 2003). In other words, first-morning urine levels of E1G reflect an integrated measure of the overall hormone levels from the previous day.

Measures

Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a 20-item self-report scale that is designed to measure depressive symptoms during the previous week, in the general population (Radloff, 1977). Each item on the scale is related to a symptom of depression using a 4-point scale of 0 (rarely) to 3 (most or all the time). A score of ≥ 16 is commonly used as a cutoff for identifying potential clinical depression (Boyd, Weissman, Thompson, & Myers, 1982) and is predictive of major depression (Thomas, Jones, Scarinci, Mehan, & Brantley, 2001). The CES-D was shown to have an acceptable test-retest reliability ($r = .5$), good internal consistency ($\alpha = .80$) (Lewinsohn, Seeley, Roberts, & Allen, 1997), and good concurrent validity with a CES-D score ≥16 associated with a hit rate of 82% (Murrell,
In other words, by using a CES-D score of ≥16, it accurately categorizes participants as being clinically depressed or not, based on a clinical interview in 82% of cases. The CES-D is the most frequently used depression questionnaire in studies of perimenopausal depression (Avis, Crawford, Stellato, & Longcope, 2001; Bromberger et al., 2011; Daly, Danaceau, Rubinow, & Schmidt, 2003; Freeman et al., 2006; Schmidt et al., 2015).

For further detail, refer to Appendix A.

Demographics and medical history. Basic demographic information was collected from each participant. This included their age, ethnicity, marital status, and socioeconomic status. Furthermore, we collected information about any current medications, and their self-reported history of medical diagnoses.

Hormone assays. E1G was assayed using an enzyme immunoassay (Arbor Assays, Ann Arbor, MI), with sensitivity at < 22.5 pg/ml. The specificity is high, showing ≥0.1% cross-reactivity with similarly structured compound. Its cross-reactivity with estradiol is somewhat higher, however, at 5%. The intra-assay variability is 4-6% and the inter-assay variability is 4-7% as advertised by Arbor Assays.

Greene Climacteric Scale (Greene, 1998). Hot flashes, and night sweats were considered as a potential covariate as it may be a confounder in the relationship between hormonal changes and mood. Hot flashes are a known symptom associated with perimenopause and have been linked to symptoms in perimenopause and was, therefore, important to measure (Freeman & Sherif, 2007). Therefore, the climacteric scale was used, specifically the vasomotor symptoms subscale, which examined both hot flashes and night sweats experienced. This was measured through using a rating scale (not at all, a little, quite a bit, extremely), which was
scored from 0-3, allowing us to quantify any possible confounds these symptoms may have had on mood.

Positive and Negative Affect Schedule (Expanded Version; PANAS-X; Watson & Clark, 1999). The PANAS-X, one of the most widely used instruments in mood research, which consists of a number of positive and negative emotions with a rating scale (very slightly or not at all, a little, moderately, quite a bit, and to extremely) (Watson & Clark, 1993). Through this questionnaire they rated 60 emotions on a 5-point scale to measure general negative affects, in addition to 11 other affects. The emotions and feelings assessed for general positive emotion were active, alert, attentive, determined, enthusiastic, excited, inspired, interested, proud, and strong. The emotions and feelings evaluated for general negative emotion were afraid, scared, nervous, jittery, irritable, hostile, guilty, ashamed, upset, and distressed. The internal consistency for two higher order scales are high, ranging from .83 to .90 for positive affect, and from .85 to .90 for negative affect using Cronbach’s coefficient alpha. Its validity and reliability as a measure of positive and negative affect have been well established (Bagozzi, 1993). For further detail, refer to Appendix B.

Trauma History Questionnaire (THQ; Green, 1996). The THQ is a self-report questionnaire that was developed to measure a history of exposure to potentially traumatic events (Hooper, Stockton, Krupnick, & Green, 2011). It consists of 24 yes/no questions, with sections focusing on different possible traumas (Green, 1996). The range of trauma events include crime related events, general disaster and trauma, and unwanted physical and sexual experience. For the purpose of this study, any affirmative answer on the unwanted physical and sexual experience subscale they were classified as having a history of sexual or physical abuse. These questions asked about specific sexual abuse, with an open-ended question at the end to
encompass any missed events (e.g., “Have there been any other situations in which another person tried to force you to have an unwanted sexual contact?”). For physical abuse history, there was also an open-ended question incase (e.g., “Have you experienced any other extraordinarily stressful situation or event that is not covered above? (If yes, please specify)”). All of the other seven questions require a yes/no answer, and if any were answered yes, participants were asked whether it was repeated and to give their approximate age and frequency of the abuse. For further detail, refer to Appendix C.

**Statistical Analysis**

Linear mixed models (PROC MIXED in SAS 4.3) will be used to examine the within-subjects effect of past-week E1G change on mood in women with versus without a history of abuse. This has been used in previous work examining weekly hormonal fluctuation on mood (Gordon et al., 2016a). The predictive models will include the absolute change in E1G since the previous week, the direction of the change in E1G, and the interaction between these two variables. These will be included as independent variables predicting weekly depressive symptoms (CES-D score) as well as positive and negative affect (PANAS-X); however, because we are interested in comparing women with and without a history of abuse with regards to their mood sensitivity to E1G fluctuation, abuse history will be added as a third independent variable. The results of a three-way interaction between absolute change in E1G since the previous week, the direction of the change in E1G, and the presence or absence of a history of abuse will determine whether women with a history of abuse exhibit greater mood sensitivity to weekly fluctuations in E1G levels. A woman’s average E1G level over the entire study as well as weekly vasomotor symptoms will be included as covariates in all analyses to ensure that any
effect of E1G change is not, in fact, reflective of an effect of E1G level or due to its accompanying bothersome physical symptoms.

A sample size of 15 was chosen based on the practicality of completing a three-month study in a short time frame; however, pilot data from our laboratory using identical methods to those described here suggests that a statistically significant effect of E1G fluctuation on weekly mood is detectible in ten participants. Therefore, we are confident that recruiting 15 women – 7 with and 8 without a history of abuse – should provide sufficient statistical power to detect any existing group difference in mood sensitivity to E1G fluctuation.

Results

Participant Demographics

The demographics of the study participants are presented in Table 1. The sample included 15 women who met the STRAW +10 criteria for perimenopause (Harlow et al., 2012), with 12 women being in the late menopause transition and 3 being in the early menopause transition. The number of months since the last menstrual period ranged from 0 to 10 (M = 2.7). All but one woman was Caucasian. Out of all the participants, 9 had reported a history of abuse, 6 of which had a history of early abuse (abuse occurring before the age of 13). Participants’ ages ranged from 44-54 years (M = 48.3). All participants scored below 16 on the CES-D, with scores ranging from 2-13. For further detail, refer to Table 1.

Women with and without a history of any abuse did not differ with regards to gross family income t(13) = 0.5, p = .613, age t(13) = 0.9, p = .342, years in school t(13) = 1.2, p = 0.260, baseline CES-D scores t(13) = 0.1, p = .952, or mean E1G levels t(13) = 1.3, p = 0.223. Similarly, women with and without a history of early abuse did not differ with regards to gross
family income $t(13) = 0.3, p = .737$, age $t(13) = .16, p = 0.167$, years in school $t(13) = 1.1, p = 0.312$, baseline CES-D scores $t(13) = 0.9, p = 0.395$, or mean E1G levels $t(13) = 1.27, p = 0.226$.

**Within-Woman Effect of E1G Change on Mood in Women With or Without a History of Abuse**

**CES-D.** The effect of E1G change on weekly CES-D score was not significantly different among women with versus without a history of abuse, as suggested by a non-significant three-way interaction between abuse history, week-to-week absolute change in E1G, and week-to-week direction of E1G change $F(1,95) = 3.0, p = 0.087$. Similarly, there was a non-significant three way interaction in terms of three subscales of the CES-D; negative affect $F(1, 114) = 0.2, p = .69$, anhedonia, $F(1, 114) = 2.8, p = .10$, and somatic $F(1, 88) = 1.9, p = .18$.

**PANAS-X.** The effect of E1G change on weekly positive emotion, determined by the PANAS-X positive emotion subscale, was not significantly different among women with versus without a history of abuse. This was suggested by a non-statistically significant three-way interaction between abuse history, week-to-week absolute change in E1G, and week-to-week direction of E1G change $F(1, 93) = 0.1, p = 0.751$. Results were also non-significant when examining this three-way interaction on overall negative emotion $F(1, 89) = 1.9, p = 0.175$, sadness $F(1, 115) = 0.6, p = 0.451$, joviality $F(1, 114) = 0.1, p = 0.803$, serenity $F(1, 114) = 0.2, p = 0.684$, self-assurance $F(1, 114) = 0.3, p = 0.581$, fear $F(1, 113) = 0.6, p = 0.427$, and fatigue $F(1, 115) = 0.2, p = 0.661$. Finally, although there was a statistically significant three-way interaction between abuse history, week-to-week absolute change in E1G, and week-to-week direction of E1G change on guilt ratings $F(1, 93) = 4.6, p = 0.037$ (see Figure 1), post hoc tests revealed no significant effects ($ps > .05$).
Within-Women Effect of E1G Change on Mood in Women With or Without a History of Early Abuse

**CES-D.** A statistically significant three-way interaction between early abuse history, week-to-week absolute change in E1G, and week-to-week direction of E1G change $F(1, 113) = 7.3, p = 0.008$ was found such that a large increase in E1G from one week to the next was accompanied by an increase in CES-D score among the women with a history of early abuse but not among those without such a history (see Figures 1 and 2). A similar three-way interaction was found for the anhedonia ($F(1, 100) = 5.0, p = .028$), somatic ($F(1, 99) = 5.2, p = .025$) and, to a lesser extent, negative mood ($F(1, 123) = 3.1, p = .083$), subscales of the CES-D.

**PANAS-X.** A statistically significant three-way interaction between abuse history, week-to-week absolute change in E1G, and week-to-week direction of E1G change was found for both overall negative emotion $F(1, 92) = 5.2, p = 0.025$ (see Figures 3 and 4) and guilt $F(1, 117) = 21.1, p < 0.001$ (see Figures 5 and 6) such that a large increase in E1G from one week to the next was accompanied by an increase in negative mood. A similar three-way interaction effect was seen for sadness scores, but it did not reach significance $F(1, 121) = 5.1, p = 0.079$. However, the effect of week-to-week E1G change was not significantly different among those with versus without a history of early abuse with regards to overall negative affect $F(1, 99) = 1.09, p = .300$, joviality $F(1, 117) = 0.5, p = 0.476$, serenity $F(1, 116) = 0.04, p = 0.844$, self-assurance $F(1, 115) = 0.02, p = 0.889$, fear $F(1, 115) = 1.5, p = 0.218$, or fatigue $F(1, 119) = 0.9, p = 0.328$.

**Discussion**

The findings of the current study suggest that women with a history of early abuse (before the age of 13) are more sensitive to perimenopausal increases in estradiol compared to women without such a history. In these women, week-to-week increases in estradiol were
accompanied by an increase in overall CES-D scores and the anhedonia and somatic subscales of the CES-D. When examining the PANAS-X subscales, increases in estradiol were predictive of negative mood and guilt. These findings emerged despite no group differences in gross family income, years in school, age, baseline CES-D scores, or baseline E1G levels. Having a positive history of physical or sexual abuse over one’s lifetime was not predictive of emotional sensitivity to estradiol changes, suggesting that exposure to physical or sexual abuse prior to the onset of puberty, in particular, may result in neurobiological changes that contribute to increased emotional sensitivity to elevations in estradiol.

The current study, therefore, emphasizes the effects of estradiol change on mood, independent of estradiol levels, which is a finding consistent to previous research (Freeman et al., 2006; Gordon et al., 2016a; Schmidt et al., 2015). The importance of estradiol change has been shown to be important for risk of depression being higher in the menopause transition, and early postmenopause, with the risk decreasing in later postmenopausal years, which is characterized by low but stable estradiol levels.

Although the exact mechanisms by which a history of early abuse would sensitize women to acute increases in estradiol are unknown, it has been proposed that severe stress early in life permanently changes the way that the biological stress systems – particularly the hypothalamic pituitary adrenal (HPA) axis – respond to reproductive hormone changes. Multiple studies suggest that women with a history of trauma exhibit altered reactivity of the HPA axis in adulthood (Heim et al., 2000; Girdler et al., 2007). There have also been a number of animal studies suggesting that severe or repeated stress-exposure early in life changes the neurobiology of the animal, which is reflected in alterations in stress response systems that remain persistent throughout life (Bremner & Vermetten, 2001). The HPA axis is extremely important in
regulating both the physiological and psychological response to stress and dysregulation of the HPA axis has been shown to predict the onset of depression (Harris et al., 2000).

Furthermore, in a previous study by Gordon and colleagues (2016a), week-to-week increases in estradiol were accompanied by elevations in both depressive symptoms and the cortisol awakening response in a sample of depressed perimenopausal women. This suggests that for some women, acute increases in estradiol may trigger activation of the HPA axis and, in turn, increase vulnerability to depressive symptoms. Other findings that support the idea that the HPA axis may be involved in explaining why some women exhibit an increased mood sensitivity to reproductive hormone changes are studies observing HPA axis dysregulation in postpartum depression (Bloch, Daly, & Rubinow, 2003; Bloch et al., 2005; Greenwood & Parker, 1984; Jolley, Elmore, Barnard, & Carr, 2007; Magiakou et al., 1996; Wisner & Stowe, 1997) and premenstrual dysphoric disorder (Bancroft, Cook, Davidson, Bennie, & Goodwin, 1991; Girdler et al., 1998; Roca et al., 2003; Su, Schmidt, Danaceau, Murphy, & Rubinow, 1997), two reproductive mood disorders believed to result from an increased sensitivity to reproductive hormone changes. Furthermore, our findings are in line with previous research, specifically, evidence in support that a history of abuse may predict the strength of association between the fluctuation of E1G and the emergence of symptoms in menstrually-related mood disorders (Eisenlouhr-Moul and colleagues, 2016). This finding supports the importance of a multilevel interaction between abuse history, and cyclical changes in predicting psychiatric symptoms. Fitting to our findings, having a history of abuse, as shown by Eisenlouhr-Moul and associates (2016), may leave these women to be more sensitive to cyclical hormonal changes due to the psychosocial vulnerability that leads to physiological and psychological disturbances.
The importance of early life abuse, in particular, in predicting mood sensitivity to the hormonal changes accompanying the menopause transition is consistent with a large body of literature linking early life abuse with later risk for mental illness. There has been considerable evidence suggesting a strong role between adverse childhood experiences and late development of mood and anxiety disorders (Heim et al., 2000). McCauley and colleagues (1997) examined close to 2000 women, and revealed that women with a history of child sexual or physical abuse exhibited more symptoms of depression and anxiety than those without. Furthermore, women who experienced abuse in their childhood are also four times more likely to develop major depression in adulthood than those not abused (Mullen, Martin, Anderson, Romans, & Herbison, 1996). The severity and frequency of the abuse was also found to positively correlate with the severity of depression, suggesting that examining the effect of early abuse on perimenopausal hormone changes is worthwhile. Child abuse has also been shown to be associated with long-lasting changes in the reproductive axis. For example, childhood abuse is predictive of early menarche (Boynton-Jarrett et al., 2013; Foster, Hagan, & Brooks-Gunn, 2008; Herman-Giddens, Sandler, & Friedman, 1988; Romans, Martin, Gendall, & Herbison, 2003; Wise, Palmer, Rothman, & Rosenberg, 2009). Childhood abuse has also been shown to lead to neuroendocrine disruption, which later affects ovarian function, which may lead to altered age of onset for perimenopause (Allsworth, Zierler, Krieger, & Harlow, 2001), although more research is needed to determine the change in perimenopause onset.

Despite the strength of weekly mood and hormone assessments, and the measurement of hot flashes and night sweats as possible confounds, this study had limitations. First, the sample size was small, potentially limiting the generalizability of our findings. A small sample size also limits our capacity to examine the importance of various abuse characteristics, such as age of
first abuse, the severity, or chronicity of abuse. These findings are still important for further research so we can better understand risk factors, and the underlying mechanism of perimenopausal depression. The consistent weekly measurements used, allows for a better look into hormonal changes on a week-to-week basis, and how the direction of the fluctuation may relate to mood. Second, because there are so many measurements throughout the study, we run the risk of missing data, or participants completing these later than the assigned date or time. Lastly, due to Eisenlohr-Moul and colleagues (2016) finding that progesterone may play a role in the sensitivity to hormonal fluctuations for women with a history of abuse, it may have been beneficial to measure progesterone levels as well. We were able to make up for this, however, by frequently measuring estradiol and, due to the leveling of progesterone during perimenopause, measuring estradiol levels was a good starting point.

Despite these limitations, this study has several notable strengths. It was the first study of its kind to look at trauma effects on mood sensitivity in the menopause transition. The results of this study may allow us to identify women who are at greatest risk for developing depression in the menopause transition, allowing health care professionals to take steps towards preventing the development of depression in these women, either by stabilizing estradiol levels with the use of hormone therapy or by increasing psychological resilience with the use of stress management strategies or by increasing social support. If our hypotheses are confirmed, future research will be needed to investigate the neurobiological mechanisms by which a history of abuse may increase sensitivity to changes in estradiol. Furthermore, with a larger sample size we could examine different severities, or the frequencies, of abuse to see if these play a role in sensitivity to changes in estrogen. This would also allow us to see whether women are more at risk of
depressive symptoms during perimenopause, and if other factors like age of abuse affect sensitivity as well.

According to MacMillan and colleagues (1997) a population-based, national survey, indicated that 13-27% of women were sexual abused as children. Based on this finding alone, it highlights the importance of examining these women, specifically during this transition. Further studies are needed, especially if these women with a history of abuse are more sensitive to increases in estradiol during perimenopause, to determine preventative measures to help those more at risk. Therefore, one implication is that women with a history of abuse may be especially sensitive during the early menopause transition, when increases in estradiol are more frequent (due to ovulation). Therefore, the clinical significance of this study will allow for future developments of hormonal therapy and preventative measures for women that have had early life abuse. Furthermore, due to this study highlighting the estradiol change, rather than levels as an explanation for this increased risk of depression, women with a history of early life abuse may benefit from the use of transdermal estradiol, which helps stabilize estradiol levels.
Reference


immunoassays for population research. *Clinical chemistry, 49*, 1139-1148.
doi:10.1373/49.7.1139


doi:10.1177/014662167700100306


doi:10.1017/s0033291703007530


doi:10.1001/jama.272.22.1749


Table 1

Participant Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.3 (3.2)</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>90%</td>
</tr>
<tr>
<td>Gross Household Income</td>
<td>$70,000 – 89,999</td>
</tr>
<tr>
<td>Years of Education</td>
<td>15.0 (6.4)</td>
</tr>
<tr>
<td>Works Full Time (%)</td>
<td>70%</td>
</tr>
<tr>
<td>Baseline CES-D Score</td>
<td>8.1 (3.3)</td>
</tr>
<tr>
<td>E1G Level</td>
<td>21427.7 (17519.2)</td>
</tr>
</tbody>
</table>
Figure Caption

*Figure 1.* Effect of weekly E1G change on CES-D score among early abuse victims

*Figure 2.* Effect of weekly E1G change on CES-D score among controls

*Figure 3.* Effect of weekly E1G change on negative emotion among early abuse victims

*Figure 4.* Effect of weekly E1G change on negative emotion among controls

*Figure 5.* Effect of weekly E1G change on guilt among early abuse victims

*Figure 6.* Effect of weekly E1G change on guilt among controls
Figure 1

Effect of weekly E1G change on CES-D score among early abuse victims
Figure 2

Effect of weekly E1G change on CES-D score among controls

![Weekly E2 Change on CES-D Score Among Controls](image)

- Decreasing
- Increasing

Weekly CES-D Score

Absolute E1G Change From Last Week
Figure 3

Effect of weekly E1G change on negative emotion among early abuse victims
Figure 4

Effect of weekly E1G change on negative emotion among controls

![Graph showing the effect of weekly E1G change on negative emotion among controls. The graph plots weekly negative emotion against absolute E1G change from last week. Two lines are shown: one for decreasing E2 and one for increasing E2. The y-axis represents weekly negative emotion (0-16), and the x-axis represents absolute E1G change from last week, with categories for no change and change (+/- 1.5 SD).]
Figure 5

Effect of E1G change on guilt among early abuse victims

![Diagram](image_url)
Figure 6

Effect of E1G change on guilt score among controls

Weekly Guilt

No Change

Large Change

Absolute E1G Change From Last Week

- Decreasing
- Increasing
Appendix A: CES-D

Below is a list of some ways you may have felt or behaved. Please indicate how often you have felt this way during the past week:  (circle one number on each line)

<table>
<thead>
<tr>
<th>During the past week…</th>
<th>Rarely or none of the time (less than 1 day)</th>
<th>Some or a little of the time (1-2 days)</th>
<th>Occasionally or a moderate amount of time (3-4 days)</th>
<th>All of the time (5-7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I was bothered by things that usually don’t bother me…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. I did not feel like eating; my appetite was poor…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. I felt that I could not shake off the blues even with help from my family…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. I felt that I was just as good as other people…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. I had trouble keeping my mind on what I was doing…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. I felt depressed…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. I felt that everything I did was an effort…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. I felt hopeful about the future…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. I thought my life had been a failure…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. I felt fearful…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11. My sleep was restless…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12. I was happy…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13. I talked less than usual…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14. I felt lonely…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15. People were unfriendly…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16. I enjoyed life…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>17. I had crying spells…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>18. I felt sad…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>19. I felt that people disliked me…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>20. I could not get “going”…</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Appendix B: PANAS-X

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you have felt this way during the past week. Use the following scale to record your answers:

<table>
<thead>
<tr>
<th>1 (very slightly or not at all)</th>
<th>2 (a little)</th>
<th>3 (moderately)</th>
<th>4 (quite a bit)</th>
<th>5 (extremely)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cheerful</td>
<td>sad</td>
<td>active</td>
<td>angry at self</td>
<td></td>
</tr>
<tr>
<td>disgusted</td>
<td>calm</td>
<td>guilty</td>
<td>enthusiastic</td>
<td></td>
</tr>
<tr>
<td>attentive</td>
<td>afraid</td>
<td>joyful</td>
<td>downhearted</td>
<td></td>
</tr>
<tr>
<td>bashful</td>
<td>tired</td>
<td>nervous</td>
<td>sheepish</td>
<td></td>
</tr>
<tr>
<td>sluggish</td>
<td>amazed</td>
<td>lonely</td>
<td>distressed</td>
<td></td>
</tr>
<tr>
<td>daring</td>
<td>shaky</td>
<td>sleepy</td>
<td>blameworthy</td>
<td></td>
</tr>
<tr>
<td>surprised</td>
<td>happy</td>
<td>excited</td>
<td>determined</td>
<td></td>
</tr>
<tr>
<td>strong</td>
<td>timid</td>
<td>hostile</td>
<td>frightened</td>
<td></td>
</tr>
<tr>
<td>scornful</td>
<td>alone</td>
<td>proud</td>
<td>astonished</td>
<td></td>
</tr>
<tr>
<td>relaxed</td>
<td>alert</td>
<td>jittery</td>
<td>interested</td>
<td></td>
</tr>
<tr>
<td>irritable</td>
<td>upset</td>
<td>lively</td>
<td>loathing</td>
<td></td>
</tr>
<tr>
<td>delighted</td>
<td>angry</td>
<td>ashamed</td>
<td>confident</td>
<td></td>
</tr>
<tr>
<td>inspired</td>
<td>bold</td>
<td>at ease</td>
<td>energetic</td>
<td></td>
</tr>
<tr>
<td>fearless</td>
<td>blue</td>
<td>scared</td>
<td>concentrating</td>
<td></td>
</tr>
<tr>
<td>disgusted with self</td>
<td>shy</td>
<td>drowsy</td>
<td>dissatisfied</td>
<td></td>
</tr>
</tbody>
</table>
Appendix C: THQ Sexual and Physical Abuse Subscale

For each event, please indicate (circle) whether it happened, and if it did, the number of times and your approximate age when it happened (give your best guess if you are not sure). Also note the nature of your relationship to the person involved, and the specific nature of the event, if appropriate.

<table>
<thead>
<tr>
<th>Physical and Sexual Experiences</th>
<th>Circle one</th>
<th>If you circled yes, please indicate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Repeated?</td>
</tr>
<tr>
<td>18 Has anyone ever made you have intercourse or oral or anal sex against your will? (If yes, please indicate nature of relationship with person [e.g., stranger, friend, relative, parent, sibling] below)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>19 Has anyone ever touched private parts of your body, or made you touch theirs, under force or threat? (If yes, please indicate nature of relationship with person [e.g., stranger, friend, relative, parent, sibling]</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>20 Other than incidents mentioned in Questions 18 and 19, have there been any other situations in which another person tried to force you to have an unwanted sexual</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>21 Has anyone, including family members or friends, ever attacked you with a gun, knife, or some other weapon?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>22 Has anyone, including family members or friends, ever attacked you without a weapon and seriously injured you?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>23 Has anyone in your family ever beaten, spanked, or pushed you hard enough to cause injury?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>24 Have you experienced any other extraordinarily stressful situation or event that is not covered above? (If yes, please specify below)</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>