IMPACT OF REPRODUCTIVE HISTORY ON MOOD SENSITIVITY TO HORMONE FLUCTUATIONS DURING THE MENOPAUSE TRANSITION

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Julie Ziemer

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Abstract

The risk of depression in women increase 2-4 times in the years leading up to the last menstrual period, known as the menopause transition (i.e., 'perimenopause'). Excessive perimenopausal estrogen fluctuation has been hypothesized to play a role, though the factors predicting sensitivity to perimenopausal hormone flux are not well known. Research from animal models suggests that past exposure to pregnancy and childbirth and the immense hormonal flux that accompanies it can lessen mood sensitivity to hormonal fluctuations. The current study aimed to examine whether the number and recency of a woman's past pregnancies would be associated with altered sensitivity to estrogen fluctuation in the context of the menopause transition. To test this, 100 perimenopausal women were recruited for a 12-week study: once a week, participants answered a mood survey and collected their first-morning urine sample to allow for the measurement of urinary metabolites of estrogen and progesterone. Details about their reproductive history, including the number and timing of any previous pregnancies, were assessed. Results revealed a significant interaction between number of pregnancies and weekly estrogen fluctuation on mood, such that women with a greater number of pregnancies were less sensitive to increases in estrogen. Length of time since last pregnancy did not significantly predict sensitivity to hormonal fluctuations. These findings suggest that women with few or no previous pregnancies may be at greater risk for developing depressive mood in the menopause transition.

Keywords: menopause transition, mood regulation, reproductive history

Impact of Reproductive History on Mood Sensitivity to Hormone Fluctuations during the Menopause Transition

As women age, they experience a number of physical and psychological changes connected to reproductive status and entering menopause. The shift from reproductive fertility to senescence is referred to as the menopause transition. Occurring prior to menopause, the menopause transition is based more on reproductive age than chronological age, affecting women within a 42 to 58 year old age range (Soules et al., 2001). There is debate over how long the menopause transition lasts, with claims of anywhere from five to 10 years (Morrison, Brinton, Schmidt, & Gore, 2006; Soules et al., 2001). One of the standard indicators of the menopause transition is increasing irregularity of menstrual cycles, as length of time between menses becomes more variable (Soules et al., 2001). Other common symptoms include vasomotor symptoms (i.e., hot flashes, night sweats), cognitive difficulties, and sleep interruptions (Berent-Spillson et al., 2012; Jaqtap, Prasad, & Chaudhury, 2016; Joffe et al., 2009; McEwen, Akama, Spencer-Segal, Milner, & Waters, 2012).

During this time, some women seem more susceptible to dysphoric mood than others. For example, women are 2-4 times more likely to experience a depressive episode while in the menopause transition compared to when they are pre- or post-menopausal (Bromberg et al., 2011). This finding has been replicated, as researchers from different studies have found prevalence of a depressive episode for 26% to 37% of their participants (Freeman, Sammel, Lin, & Nelson, 2006; Jaqtap et al., 2016; Li et al., 2016). Though the association between mood disorders and the menopause transition is well-established, thus far the exact mechanism by which some women are more susceptible to depression is poorly understood.

The Hormonal Environment of the Menopause Transition

One possibility is that the hormonal changes that drive the menopause transition also affect mood regulation. This is because some of the key hormones involved in female reproduction appear to mediate mood regulation, such as estradiol and progesterone (Gordon et al., 2015a; Kobayashi et al., 2016). Estradiol and progesterone are synthesized and released by the ovaries, which are regulated via the hypothalamic-pituitary-gonadal axis (Morrison et al., 2006). This feedback system allows for bidirectional communication between the reproductive system and the brain. As women age, the number of follicles produced by their ovaries decreases (Soules et al., 2001). Fewer estradiol-producing follicles lead to a dysregulation of the hypothalamic-pituitary-gonadal axis, causing erratic hormone fluctuations during the menopause transition. In the early stages of the menopause transition, women first experience marked elevations in estradiol; in the late stages of the menopause transition, women experience both elevations of estradiol and periods in which estradiol is unusually low (Morrison et al., 2006). This results in greater overall estradiol fluctuations and decreased progesterone (Soules et al., 2001).

Greater variability in estradiol fluctuation may increase the risk of depression for some women during the menopause transition. Three studies found increased within-person variability in estradiol to be associated with higher depressive symptoms (Freeman et al., 2006; Gordon, Eisenlohr-Moul, Rubindow, Schrubbe, & Girdler, 2016; Gordon, Rubinow, Eisenlohr-Moul, Leserman, & Girdler, 2015b). In contrast to the positive findings, there are also null findings. Three studies did not find a significant association between estradiol fluctuations and depression (Avis, Crawford, Stellato, & Longcope, 2001; Bromberger et al., 2011; Woods, Cray, Mitchell, & Herting, 2014). It is important to note that null findings may have been a result of infrequent

sampling, as estradiol levels were only compared annually. Given the erratic hormonal environment of the menopause transition, it is likely more beneficial to examine week-to-week fluctuations as performed by Gordon et al. (2016).

Progesterone is also speculated to be involved in mood regulation during the menopause transition, due to its role in modulating the action of the gamma-aminobutyric acid ($GABA_A$) receptor (Gordon et al., 2015a). $GABA_A$ receptors serve as the primary inhibitory system in the brain, producing an anxiolytic effect in response to stress (Bäckström et al., 2014). It has been found that when the progesterone metabolite allopregnanolone, binds to $GABA_A$ receptors, it enhances $GABA_A$'s anxiolytic effect and reduces amygdala activation (Pibiri, Nelson, Guidotti, Costa, & Pinna, 2008; Sripada et al., 2013; Xia & Li, 2018). However, rapid changes in allopregnanolone concentrations have been shown to result in a paradoxical effect: rather than enhancing $GABA_A$ tone, allopregnanolone inhibits $GABA_A$ receptors increasing amygdala activation (Andréen et al., 2009; Bäckström et al., 2014; Shen et al., 2007; van Wingen et al., 2009). It is hypothesized that fluctuating progesterone levels may induce negative mood (e.g., anxiety, aggression, depression) as a result of allopregnanolone fluctuation (Andréen et al., 2009; Henningsson et al., 2015; Maguire & Mody, 2009; van Wingen et al., 2009). In the context of the menopause transition, it is possible that erratic hormone fluctuations may make women more susceptible to developing a negative mood in response to stressors (Gordon et al., 2015a).

Reproductive History

Currently, very little is known about what factors are most relevant in predicting which women will be most sensitive to the changing hormonal environment of the menopause transition. However, a growing body of research in animal models suggests that one's prior reproductive history may be an important factor (Bridges, 2016). Specifically, reproductive

events such as a past pregnancy appear to alter neural regions and the endocrine system such that responsivity to estradiol and progesterone is permanently altered (Bridges, 2016; Bridges & Byrnes, 2006; Byrnes, Babb, & Bridges, 2009; Stolzenburg & Champagne, 2016). Although the exact mechanisms are not entirely understood, it is believed that exposure to the hormonal environment of pregnancy induces lasting physiological changes (Bridges & Byrnes, 2006; Zimberknopf, Xavier, Kinsley, & Felicio, 2011). Under this assumption, history of prior pregnancies would impact how estradiol and progesterone are regulated by women in the menopause transition (Bridges, 2016).

Evidence from research conducted on rodents shows that pregnancy causes both behavioural and physical changes. Even though some changes (e.g., elevated hormone levels) are reversed following parturition (Oberto et al., 2002), others are retained into middle-age. For example, middle-aged rats with a prior history of pregnancy will continue to exhibit maternal behaviours such as increased protection of offspring and lower anxiety-like behaviours when exposed to a stressor (Nephew, Bridges, Lovelock, & Byrnes, 2010; Zimbernopf et al., 2011). Furthermore, initiation and intensity of these behaviours are positively correlated with number of prior pregnancies (Nephew et al., 2010; Zimberknopf et al., 2011).

There is evidence to suggest that permanent neuroendocrine changes underlie these long-lasting behavioural changes that follow pregnancy. Researchers found that middle-aged rats have a higher number of estrogen receptors in certain neural regions, such as the striatum and medial preoptic area of the hypothalamus, if they have had a past pregnancy compared to those without a reproductive history (Bridges & Byrnes, 2006; Byrnes et al., 2009; Stolzenburg & Champagne, 2016). The amount of serum estradiol is conversely lower in middle-aged rats with a history of pregnancy than those without (Bridges & Byrnes, 2006; Byrnes et al., 2009). In terms of

progesterone, exposure to elevated progesterone levels during pregnancy has been found to alter the subunit expression of $GABA_A$ receptors in mice (Maguire & Mody, 2008; Maguire & Mody, 2009; Oberto et al., 2002). It is speculated that $GABA_A$ subunit changes may serve to maintain appropriate $GABA_A$ regulation in response to hormonal flux to prevent excitotoxicity (Maguire & Mody, 2009). Based on this evidence, it is proposed that reproductively experienced individuals (i.e., those who have borne at least one child) are more efficient at processing estradiol and progesterone, providing a protective effect against stressors (Bridges & Byrnes, 2006).

Whether these findings generalize to humans is not yet known, though preliminary evidence suggests that they may. One medical study found changes in estrogen and progesterone receptors in breast tissue based on different reproductive factors, including pregnancy history and age when first gave birth (Lord et al., 2008). Women who were exposed to the hormonal environment of pregnancy earlier (i.e., gave birth at a younger age) demonstrated a protective effect against cancer in their estrogen and progesterone receptors. Other research found reproductive history (i.e., more pregnancies) to be predictive of increased physical menopausal symptoms, such as vaginal dryness, suggesting long-lasting estrogen and progesterone receptor alterations (Hess et al., 2008; Nelson et al., 2011). Thus, it seems plausible that reproductive history may permanently alter hormone receptors in the brain, affecting women's emotional response to the hormonal changes associated with the menopause transition.

Purpose

The goal of the current study was to test, in humans, whether there is a correlation between reproductive history (e.g., number of pregnancies, length of time since last pregnancy) with mood sensitivity to weekly estradiol and progesterone fluctuations in the menopause

transition. It was hypothesized that past exposure to elevated estradiol and progesterone will result in long-term decreases in mood sensitivity to hormone fluctuation. Subsequently, it was predicted that a greater number of past pregnancies and less time since a woman's last pregnancy would be associated with decreased mood sensitivity to week-to-week estradiol and progesterone fluctuations in the menopause transition.

Methods

Participants

One hundred women ages 45 to 55 years currently in the menopause transition were recruited. Perimenopausal (i.e., those in the menopause transition) status was assessed according to menstrual bleeding patterns, as outlined by Stages of Reproductive Aging Workshop (STRAW) guidelines (Soales et al., 2001). According to STRAW criteria, a woman is classified as being in the menopause transition once she has had at least two consecutive menstrual cycles in which the length of time between cycles is at least seven days shorter or longer than usual, or she has experienced a period of at least 60 days without menstruation. Once a woman has gone 12 months without a menstrual cycle, she is deemed postmenopausal and was therefore ineligible for this study.

Due to the importance of menstrual cycles as an indicator of menopausal status, women with a complete hysterectomy or endometrial ablation were ineligible. Since the proposed study aimed to assess the natural estradiol fluctuations and mood changes that occur during the menopause transition, there were also restrictions on the medications and supplements allowed. Participants could not be in individual psychotherapy, on anti-depressants, any form of hormonal birth control, or substances used to treat menopause symptoms. Participants could not be pregnant or nursing. Women experiencing a current major depressive disorder or a mental illness

requiring immediate intervention were excluded and referred to the appropriate mental health resources.

Measures

Demographic details and reproductive history. A survey collected demographic information with a subsection of the survey dedicated to reproductive history. A total of 46 demographic questions focused on the participant's age, ethnicity, marital status, and medical history (e.g., "What is your age?"). In terms of reproductive history, a total of 12 questions revolved around pregnancies and past birth control use (e.g., "Have you ever used any form of birth control?"). All answers were recorded in Qualtrics and linked to participants using identification numbers.

Mental health assessment. The Structured Clinical Interview for the Diagnostic and Statistical Manual-5-Research Version ([SCID-5-RV]; American Psychological Association, 2013) was used to assess mental health and diagnose several categorical aspects of past or current psychopathology. Participants were assessed for axis I disorders using SCID-5-RV protocol. The SCID-5-RV has been found to be a reliable and valid scale for measuring symptom severity (Shankman et al., 2017). It is also more accurate than other interview techniques for making diagnoses (Nakash, Nagar, & Kanat-Maymon, 2015).

Positive and negative mood. The Positive and Negative Affect Schedule – Expanded Version ([PANAS-X]; Watson & Clark, 1999) was used to assess weekly mood changes (see Appendix). The PANAS-X is a 60-item self-report measure in which participants rated the weekly emotions they experienced on a scale from 0 (very slightly or not at all) to 5 (extremely). The PANAS-X includes items to capture negative (e.g., "upset") and positive affects (e.g., "happy"). The PANAS has been found to have high internal consistency and reliability, as well

as being a valid measure for assessing subjective mood (Bagozzi, 1993; Terracciano, McCrae, Hagemann, & Costa, 2003).

Enzyme immunoassay. An enzyme immunoassay with high cross-reactivity to estrone-3-glucuronide (E1G) and estradiol-like compounds assessed weekly within-person E1G fluctuations (Arbor Assays, Ann Arbor, MI). Arbor Assays reports that their assays are sensitive to E1G at concentrations less than 22.5 pg/mL, indicating that they are appropriate for capturing low levels of hormones. An enzyme immunoassay was also used to assess progesterone levels by measuring weekly within-person pregnanediol glucuronide (PdG) fluctuations (Arbor Assays, Ann Arbor, MI). Ann Arbor reports assay sensitivity to PdG at concentrations less than 0.180 ng/mL with high cross-reactivity to PdG and 20-alpha-hydroxyprogesterone. Many prior studies on hormone fluctuations in the menopause transition used serum concentrations from blood draws (Avis et al., 2001; Bromberger et al., 2011; Freeman, et al., 2006), but the proposed study relied on urinary concentrations. Urine is an acceptable medium and was less invasive to participants (Soales et al., 2001).

Procedure

Participants were recruited using advertisements on Facebook, as well as posters distributed to medical clinics and service stations around Regina, SK. Interested women were scheduled for a phone screen interview to determine their eligibility. An enrollment session was conducted for eligible women, either over the phone or in-person at the University of Regina. Participants received an overview of study, including a detailed consent form and instructions about completing mood surveys and sample collection. They were assessed for major depressive disorder or other severe psychiatric disorders using the SCID-5-RV. Eligible participants received an identification number associated with any data collected to protect their privacy.

During the enrollment session, demographic details were recorded in a Qualtrics survey which included the reproductive history survey. For specimen collection, participants were given an insulated cooler containing supplies for urine collection. This included 12 plastic cups, 12 disposable syringes, 12 labelled 5.0 mL test tubes (Fisher Scientific), one cardboard storage box, and two ice packs. Participants were instructed to store their samples in their home freezer until all samples have been collected. This was to preserve the integrity of samples and prevent hormone metabolites from degrading.

Over the course of 12 weeks, participants answered a mood survey and collected a urine sample one time per week. Participants received a link to each mood survey through email, and completed the survey using Qualtrics. Since hormone levels in urine reflect blood levels of that hormone from the previous day, participants collected their first voided urine sample on the next morning in one of the cups provided (Soales et al., 2001; Woods et al., 2014). They were instructed on how to use a syringe to transport approximately 2.5 mL of urine into the appropriate test tube before storing it in a freezer. In total, participants were to complete 12 mood surveys corresponding to 12 urine samples. A courier was arranged to transport the samples to the University of Regina when all 12 weeks were completed. Participants were reimbursed up to $205 (Canadian) for the enrollment session and samples they provide.

Samples were stored in a locked freezer at the University of Regina at – 40.0°C prior to being assayed. The assays measured levels of E1G and PdG, which are urinary metabolites of estradiol and progesterone respectively (Woods et al., 2014). All assay procedures were followed according to instructions provided by Arbor Assays (Ann Arbor, MI). To test precision, samples were assayed in duplicates to obtain intra-assay coefficients of variability (CV). Any sample with a CV higher than 15.0% was redone to ensure accuracy.

Data analysis. Linear mixed models (PROC MIXED in SAS 9.4) assessed the relationship between weekly hormone fluctuations (E1G, PdG) and mood as a function of reproductive history. Two models were used: in the first model, week-to-week E1G and PdG change (within-person factor), the number of previous pregnancies (between-person factor), and the interaction between these two variables were the predictors in a model with weekly PANAS-X score as the outcome. In the second model, week-to-week E1G and PdG change, number of years since the last pregnancy, and the interaction between these two variables were the predictors of the PANAS-X score. It was expected that the relationship between week-to-week E1G and PdG change and weekly PANAS-X score would be weaker among women with a greater number of pregnancies and a more recent pregnancy. Thus, reproductive history would serve to decrease mood sensitivity to E1G and PdG fluctuations.

Sample size calculations. A sample size of 100 was chosen based on the main objective of the parent study. However, a post-hoc power analysis conducted using G*Power suggests that this sample size provides over 99% power to detect a small interaction (partial eta squared = 0.02) between number of previous pregnancies and weekly hormone fluctuation on weekly PANAS-X, assuming an alpha of 0.05 and a correlation of 0.5 between weekly measurements. This high level of power is due to the inclusion of 11 measurements of E1G and PdG change and subsequent PANAS-X score, providing a large denominator for degrees of freedom.

Results

Participant Demographics

Refer to Table 1 for information about participants' demographic characteristics. The majority of participants were Caucasian, working full-time, with a gross household income of ≥$113,000 annually. The mean age of participants was 49.9 years old (SD = 2.7, range = 44-55).

Participants had a mean of 2.2 children (SD = 1.3, range = 0-8) an average of 19.9 years ago (SD = 6.0, range = 3-30).

Weekly E1G Fluctuation and PANAS-X Scores

A significant interaction was found between number of pregnancies and weekly E1G fluctuation on negative affect (β(SEM) = -0.16(0.08), p = .04), such that women with a greater number of pregnancies were less sensitive to increases in E1G. Weekly E1G change was positively associated with negative affect on the PANAS-X (β(SEM) = 0.33(0.12), p = .007) among women with ≤2 pregnancies (Figure 1) but was not associated with negative affect among women with ≥3 pregnancies (β(SEM) = -0.25(0. 24), p =.30, Figure 2).

Similarly, there was a significant interaction between weekly E1G change (β(SEM) = -0.14(0.05), p = .004) and number of pregnancies on fear score, such that women with a greater number of pregnancies were less sensitive to increases in E1G. E1G change was positively associated with fear scores among women with ≤2 pregnancies (β(SEM) = 0.24(0.08), p = .002, Figure 3) but not associated with fear among women with ≥3 pregnancies (β(SEM) = -0.06(0.14), p = .68, Figure 4). No significant effects were found for E1G change and number of pregnancies for positive affect, hostility, guilt, or sadness on the PANAS-X (ps > .05). Length of time since last pregnancy interacting with E1G change was not significant for any mood outcomes (ps > .05).

Weekly PdG Fluctuation and PANAS-X Scores

Number of pregnancies interacting with weekly PdG changes was not significant for any mood outcomes (ps > .05). Length of time since last pregnancy interacting with PdG change was also not significant for predicting any mood outcomes (ps > .05).

Discussion

The current study aimed to assess whether there is a correlation between reproductive history (e.g., number of pregnancies, length of time since last pregnancy) with mood sensitivity to weekly estradiol and progesterone fluctuations in the menopause transition. In partial support of our hypothesis, it was found that women with fewer or no previous pregnancies were more sensitive to acute increases in E1G, as indicated by higher scores of negative affect and fear on the PANAS-X. Women with a greater number of pregnancies were less sensitive to weekly E1G fluctuations, as weekly E1G change was not predictive of their mood. This pattern was not seen for PdG, as reproductive history was not predictive of women's mood sensitivity to weekly PdG change. Our prediction that a more recent pregnancy would decrease mood sensitivity was also unsupported, as length of time since last pregnancy did not influence weekly mood scores. Thus, this finding may imply that previous exposure to excess levels of estrogen has a lasting impact on sensitivity regardless of how recently exposure occurred.

The findings from the current study support previous studies that found estradiol fluctuations to be associated with greater depressive symptoms for women in the menopause transition (Freeman et al., 2006; Gordon et al., 2016; Gordon et al., 2015b). This emphasizes the importance of estradiol in mood regulation, specifically for women experiencing acute changes in their estradiol levels (e.g., menopause transition, post-partum). It is possible that some are more sensitive to changes due to physiological differences, such as how efficiently their estrogen receptors and hypothalamic-pituitary-gonadal axis respond to estradiol flux (Kobayashi et al., 2016; Morrison et al., 2006). Women who are able to quickly adjust to shifting estradiol levels at a neurobiological level are more likely to maintain more constant neurotransmitter levels and

activation of emotion-regulating brain areas, reducing their risk of developing depressive mood from an estradiol imbalance (Kobayashi et al., 2016).

One potential mechanism hypothesized to enhance estradiol regulation is the increased number of neural (e.g., striatum, medial preoptic region) estrogen receptors following pregnancy (Bridges & Byrnes, 2006; Byrnes et al., 2009; Stolzenburg & Champagne, 2016). Both animal and human models have demonstrated a lasting increase in post-pregnancy estrogen receptors, evident in middle-aged and post-menopausal females (Bridges & Byrnes, 2006; Byrnes et al., 2009; Stolzenburg & Champagne, 2016; Lord et al., 2008). The current study supports the hypothesis that permanent physiological changes caused by pregnancy may alter cognitive and behavioural responses to estradiol flux (Nephew et al., 2010; Soares & Zitek, 2008; Zimberknopft et al., 2011). Similar to previous research using rodent models, women in the current study with fewer or no pregnancies displayed greater sensitivity to estradiol changes corresponding to increases in dysphoric mood (Bridges & Byrnes, 2006; Byrnes et al., 2009; Zimberknopft et al., 2011). This implies that women with more previous pregnancies may undergo neurological changes that enable them to process estradiol more efficiently due to repeated exposure to excess estradiol (Kobayashi et al., 2016; Morrison et al., 2006; Oberto et al., 2002).

An alternative explanation to physiological adaptation is that some women are genetically predisposed to greater estradiol sensitivity. There is evidence that variations in estrogen receptors polymorphisms (e.g., AA alleles) are associated with higher lifetime depressive symptoms (Keyes et al., 2015). This is consistent with Freeman et al.'s (2006) finding that women with a history of depression are more sensitive to estradiol fluctuations, and more likely to experience depressive symptoms in the menopause transition. Specifically, a history of

premenstrual dysphoric disorder and post-partum depression appears to increase the risk of developing depression during the menopause transition (Freeman et al., 2006; Woods et al., 2008). Thus, it is possible that women who experience post-partum depression may be genetically predisposed to a neuroendocrine imbalance and greater sensitivity to hormonal changes (Meltzer-Brody & Stuebe, 2014). Women who are vulnerable to developing dysphoric mood in response to reproductive hormone changes may choose to have fewer children to avoid the adverse effects of hormonal flux. To clarify the results of the current study, past mental health history (e.g., depressive episodes) would need to be taken into account to determine whether estradiol sensitivity influenced child-bearing decisions.

In contrast to estradiol, PdG flux did not have a significant impact on mood in the current study. It is possible that this reflects the plastic nature of $GABA_A$ receptors, as $GABA_A$ subunits are able to undergo recombination or alter their level of expression depending on their hormonal environment (Oberton et al., 2002). This supports the contradiction from previous studies that found progesterone elicits an anxiolytic effect on $GABA_A$ receptors (Pibiri et al., 2008; Sripada et al., 2013; Xia & Li, 2018), as well as an anxiogenic effect (Andréen et al., 2009; Bäckström et al., 2014; Maguire & Mody, 2008; van Wingen et al., 2009). Assuming women in the current study were not genetically susceptible to $GABA_A$ subunit deficiencies and had a strong GABAergic tone, their $GABA_A$ receptors may be resilient to progesterone flux (Maguire & Mody, 2008; Shen et al., 2007). Since progesterone levels tend to stabilize in the menopause transition, it may also be that increased sensitivity to estradiol flux is more easily detected in the menopause transition. In other words, reproductive history may have a long-term influence on progesterone fluctuation sensitivity but our ability to detect it was limited.

Limitations, Strengths, and Implications

Some of the main limitations of the current study include our reliance on participant adherence in collecting their urine samples on the correct day. Although weekly survey completion could be tracked online, the research team relied on participants' self-report to confirm that urine samples were collected on the correct day. Furthermore, once a week measurement of mood and hormone levels is an imperfect measure of hormone sensitivity, given that hormone changes can induce mood changes relatively rapidly. Daily measurements would better capture instances in which hormone flux triggers temporary depressive symptoms. Another issue is determining whether women with fewer children chose to stop having children because of their sensitivity to hormone flux. We will address this by assessing history of post-partum depression in the future.

In contrast, the current study had several strengths. Having a relatively large sample size of 100 participants enabled the study to have a high level of statistical power. Including multiple repeated measures for each variable compensates for not using daily measurements. This allows the current study to sufficiently measure hormone sensitivity. Considering the attempts to overcome limitations, this study has potential implications for understanding women's mental health. For example, this study demonstrated that certain reproductive factors, such as number of previous pregnancies, may demonstrate a carryover effect for how hormones are processed in the menopause transition. Contrasting the evidence that number, but not recency, of past pregnancies has an influence on response to estrogen may suggest some of the underlying physiological mechanisms associated with hormone regulation.

Results could be used to help therapists and clinicians identify women who may be at greater risk for depressive symptoms in the menopause transition as well as those who may

benefit most from the stabilising effects of hormonal therapy. Based on the current study, women with fewer pregnancies may be more responsive to pharmacological treatments, especially those using estrogen to treat dysphoric mood in the menopause transition. This may be helpful in determining which form of treatment would be the most beneficial for the individual (e.g., pharmacological versus cognitive behavioural therapy). Using reproductive history as a predictor in psychological assessment may also become relevant as more women choose not to have children, since the majority of women in the current study had at least one child (Bridges, 2016; Byrnes et al., 2009). There is the possibility that as birth rates decrease the prevalence of dysphoric mood in the menopause transition may increase due to greater estrogen sensitivity.

Conclusion

Women with fewer previous pregnancies displayed greater negative affect and fear in response to acute increases in estradiol. As a result, women with fewer pregnancies may be at greater risk for developing a depressive episode during the menopause transition. These results confirm animal research suggesting that reproductive events can have long-lasting effects on a woman's responses to reproductive hormones, and may be helpful for informing clinical treatment.

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Table 1

Participant Demographics

Variable	Mean (SD) or %
Age	49.9 (2.7)
Caucasian (%)	86%
Gross Household Income	≥$113,000
Works Full Time (%)	77%
Years of Education	12.8
Number of Children	2.2 (1.3)
Years Since Last Pregnancy	19.9 (6.0)

Figure Caption

Figure 1. Predicted week-to-week E1G change and negative affect score for women with fewer pregnancies (≤ 2)

Figure 2. Predicted week-to-week E1G change and negative affect score for women with more pregnancies (≥ 3)

Figure 3. Predicted week-to-week E1G change and fear score for women with fewer pregnancies (≤ 2)

Figure 4. Predicted week-to-week E1G change and fear score for women with more pregnancies (≥ 3)

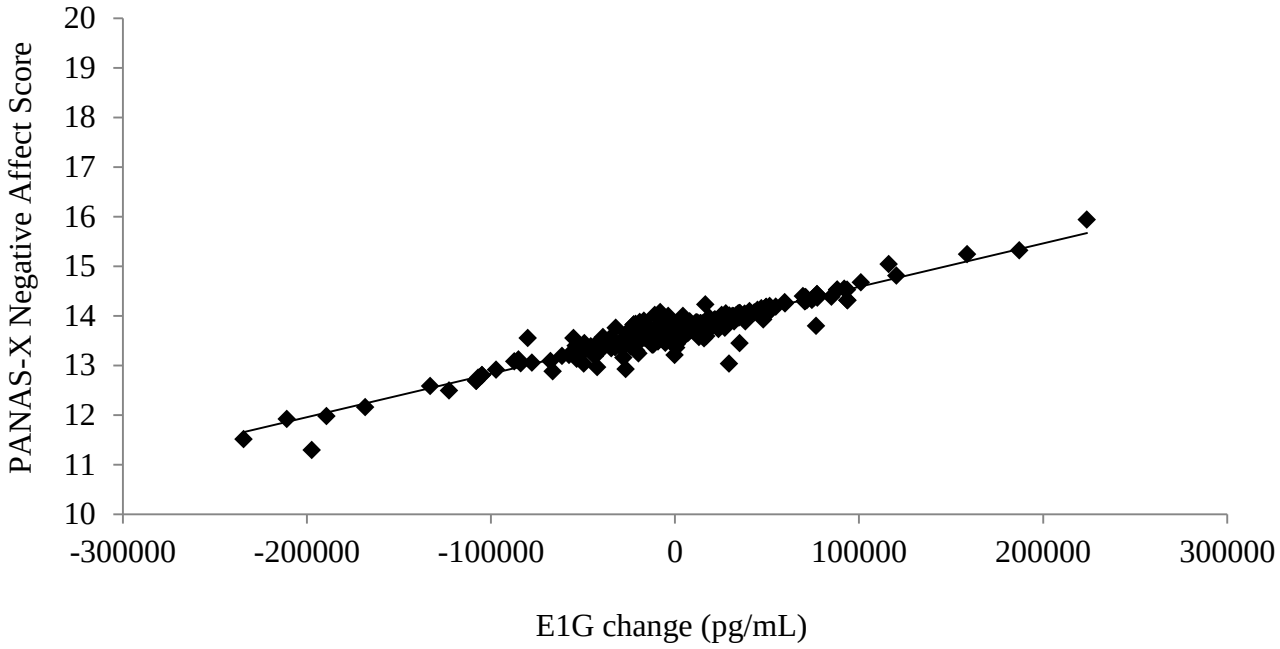

Figure 1. Predicted week-to-week E1G change and negative affect score for women with fewer pregnancies (≤ 2)

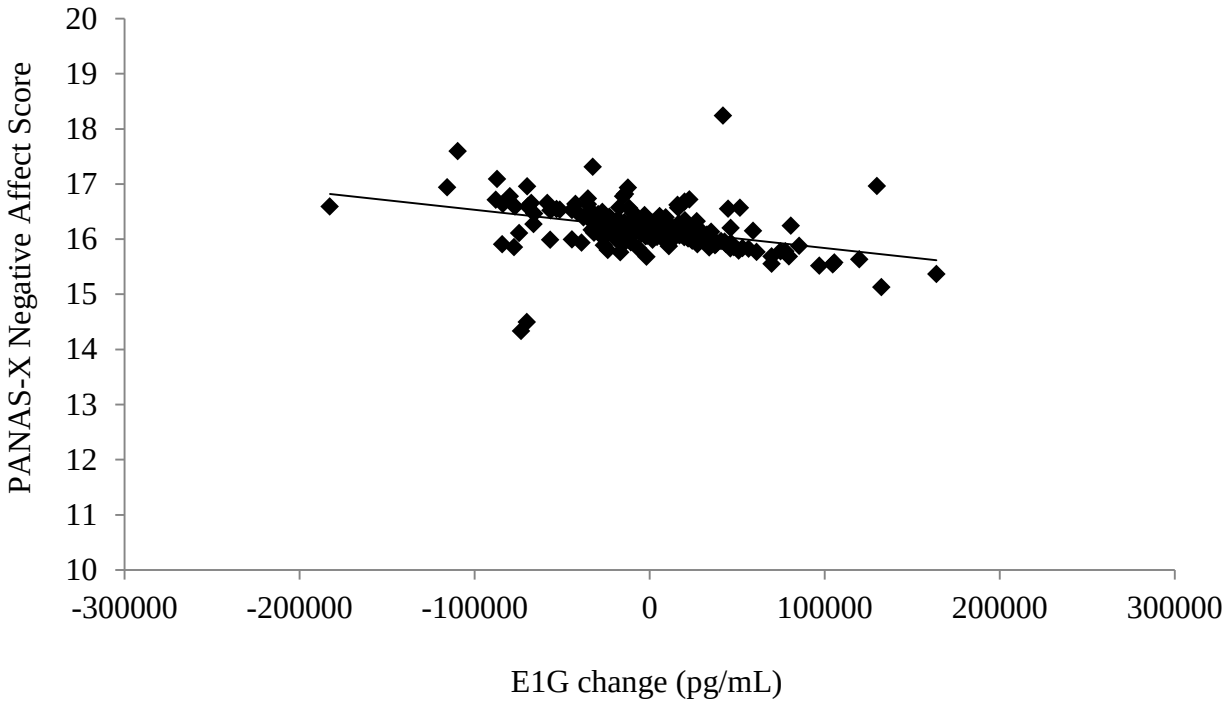

Figure 2. Predicted week-to-week E1G change and negative affect score for women with more pregnancies (≥ 3)

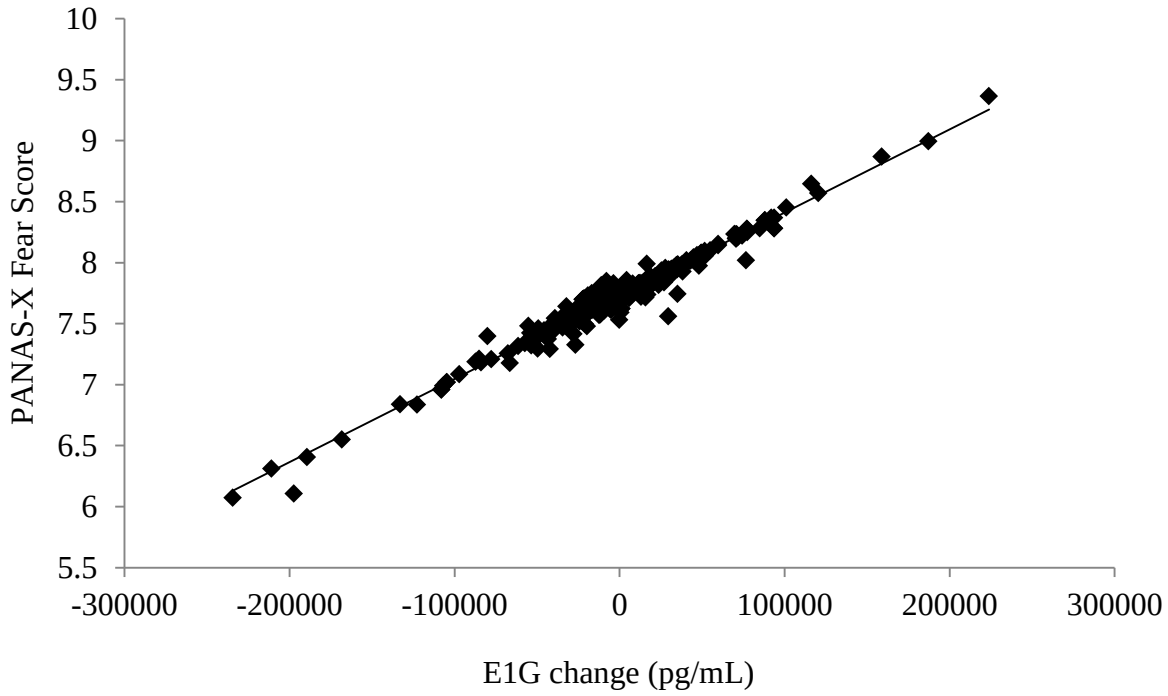

Figure 3. Predicted week-to-week E1G change and fear score for women with fewer pregnancies (≤ 2)

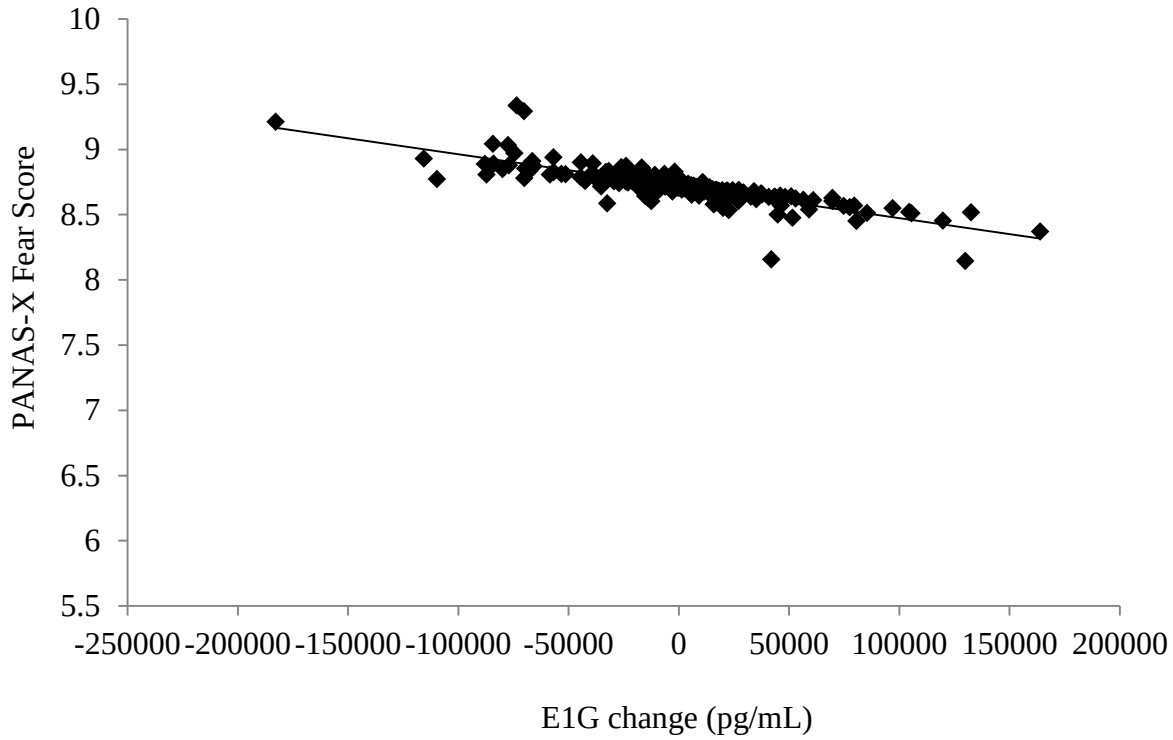

Figure 4. Predicted week-to-week E1G change and fear score for women with more pregnancies (≥ 3)

Appendix: 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:

1 very slightly or not at all	2 a little	3 moderately	4 quite a bit	5 extremely
_____ cheerful	_____ sad	_____ active		_____ angry at self
_____ disgusted	_____ calm	_____ guilty		_____ enthusiastic
_____ attentive	_____ afraid	_____ joyful		_____ downhearted
_____ bashful	_____ tired	_____ nervous		_____ sheepish
_____ sluggish	_____ amazed	_____ lonely		_____ distressed
_____ daring	_____ shaky	_____ sleepy		_____ blameworthy
_____ surprised	_____ happy	_____ excited		_____ determined
_____ strong	_____ timid	_____ hostile		_____ frightened
_____ scornful	_____ alone	_____ proud		_____ astonished
_____ relaxed	_____ alert	_____ jittery		_____ interested
_____ irritable	_____ upset	_____ lively		_____ loathing
_____ delighted	_____ angry	_____ ashamed		_____ confident
_____ inspired	_____ bold	_____ at ease		_____ energetic
_____ fearless	_____ blue	_____ scared		_____ concentrating
_____ disgusted with self	_____ shy	_____ drowsy		_____ dissatisfied with self