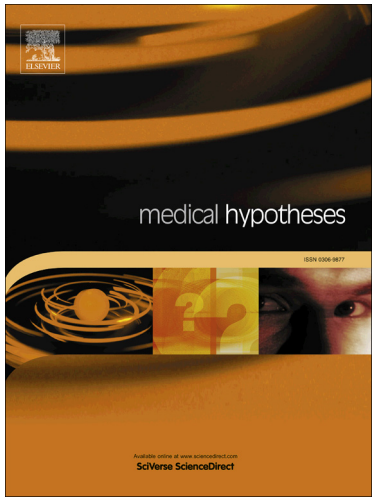

The Hormonal Sensitivity Hypothesis: A Review and New Findings

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Abbreviated title: The Hormonal Sensitivity Hypothesis

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ABSTRACT

Previous women's health practitioners and researchers have postulated that some women are particularly sensitive to hormonal changes occurring during reproductive events. We hypothesize that some women are particularly sensitive to hormonal changes occurring across their reproductive lifespan. To evaluate this hypothesis, we reviewed findings from the existing literature and findings from our own lab. Taken together, the evidence we present shows a recurring pattern of hormonal sensitivity at predictable but different times across the lifespan of some women (i.e., menarche, the premenstrual phase, hormonal contraceptive use, pregnancy, the postpartum period, and menopause). These findings provide support for the hypothesis that there is a subgroup of women who are more susceptible to physical, psychological, and sexual symptoms related to hormonal shifts or abrupt hormonal fluctuations that occur throughout the reproductive lifespan. We propose that this pattern reflects a Hormonal Sensitivity Syndrome.

Keywords: Hormonal Sensitivity Syndrome; Oral Contraceptives; Premenstrual Syndrome; Menopause; Postpartum; Pregnancy

INTRODUCTION

A number of women's health practitioners and researchers have postulated that certain women may be more sensitive than others to hormonal changes associated with reproductive events [1-7]. While there is ample evidence that some women experience adverse symptoms related to various reproductive events [for example see 8], only a minority of these studies [for example see 9-10] have investigated how the experience of adverse symptoms during one reproductive phase may relate to other reproductive phases. Furthermore, these studies have generally focussed on emotional symptoms, and have not concurrently looked at physical and sexual symptoms. To our knowledge, no study as of yet has looked at the experience of adverse hormonal shift symptoms across the entire female reproductive life-span. Thus, the purpose of the present paper was to explore hormonal sensitivity across the entire female reproductive life-span by examining previous research findings and reanalyzing a large dataset from our own laboratory.

Hypothesis:

We hypothesized that there exists a specific and identifiable subgroup of women who may experience a pattern of physical, sexual, and emotional symptoms associated with two or more hormonal reproductive events across their life-spans. We also argue that, once identified, this subgroup of women might also differ on other relevant hormonal and clinical variables, which may help clinicians prospectively identify and predict which women will experience this lifespan pattern. We propose that such a pattern may be considered a Hormonal Sensitivity Syndrome (HSS), reflecting a sensitivity to endogenous or exogenous gonadal hormone shifts.

Evidence of hormonal sensitivity provided by existing research

Physical and emotional symptoms are reported to varying degrees by women in response to hormonal shifts experienced during various reproductive phases. For instance, puberty, which for females usually begins between the age of 9 and 10 years old, has been associated not only with physical changes, such as breast development and the appearance of pubic hair [11], but also with the emergence of psychological difficulties for some girls. For example, the ratio of girls to boys who suffer from depression is approximately equal prior to puberty but shifts to a 2:1 (or even higher) female to male ratio after puberty [12-14]. Although there are many competing hypotheses as to why this shift may occur, one explanation focuses on the changes in hormones during the pubertal period [15]. Specifically, some researchers have suggested that negative mood during puberty in girls could be a result of higher levels of testosterone and cortisol, lower levels of dehydroepiandrosterone sulphate (DHEA-S), and/or rapidly increasing estradiol levels [16]. In contrast, others theorize that it is not the hormone levels per se, but rather that some girls and women are more sensitive to hormonal shifts or relatively abrupt changes, and it is this sensitivity that is responsible for the resulting symptoms [8].

After puberty, hormonal changes across the menstrual cycle can also be associated with a variety of physical and psychological symptoms, albeit to varying degrees and intensities. Epidemiological studies have found that approximately 80 to 90 percent of menstruating women report at least one premenstrual symptom. Approximately 10 to 20 percent of menstruating women have moderate premenstrual symptoms, and 3 to 8 percent have severe symptoms that result in significant impairment [17]. Although definitions of premenstrual syndrome (PMS) or premenstrual symptoms vary, they include physical, behavioral, and emotional symptoms that occur during the late luteal phase of the menstrual cycle [18]. Currently, the etiology of PMS is unknown. However, it has been suggested that fluctuations in estrogens and progestins are

partially responsible [18] and that some women are particularly sensitive to these hormonal fluctuations [8].

Pregnancy and the postpartum period are other phases in women's lives that are associated with varying physical and emotional symptoms, which are often attributed to the significant hormonal shifts that occur during these reproductive events. Specifically, during pregnancy, gastrointestinal complaints are particularly common [19]. Although the cause of gastrointestinal complaints during pregnancy is not fully understood, increases in chorionic gonadotropin, progesterone, and/or estradiol levels have been suggested. Other physical symptoms include fatigue, breast tenderness, frequent urination, and changes in appetite [20]. Some women experience depressive symptoms during pregnancy or the postpartum period, which in approximately 7 to 12 percent and 13 to 19 percent of cases (respectively) meet the criteria for a clinical diagnosis of major depressive disorder [21-22]. Individual differences in women's experience of the various prenatal and postnatal symptoms suggest differential sensitivity to hormonal change or hormone levels during these reproductive events.

Hormonal contraceptive use is very common in reproductive-aged women, particularly in industrialized countries, and the use of these exogenous hormones causes hormonal shifts that, for some women, are related to both physical and psychological side effects [23]. Hormonal shifts are due to increases in exogenous hormones and resulting changes in endogenous hormones. Physical side effects may include bleeding irregularities, nausea, weight gain, breast tenderness, and headaches [24]. Further, while research suggests that many women who are taking oral contraceptives (OC) experience less variability in affect across the menstrual cycle or in response to mood primes, and less negative affect during the menstrual phase of their cycle, some women experience emotional side effects distressing enough to result in discontinuation or

a change in type of OC [4,24-25]. Some women also experience side effects related to sexual functioning (i.e., decreased frequency of sexual thoughts, decreased psychosexual arousability) or report negative changes in mood [for example see 26]. Women are reported to be at an increased risk for OC negative mood side effects if they have a history of depression or other symptoms of psychological distress, premenstrual mood symptoms prior to OC use, dysmenorrhea, a history of pregnancy-related mood symptoms, or being in the postpartum period [see review in 4]. Hence, OC side effects have been linked to symptoms during other reproductive events characterized by hormonal shifts, lending support to the idea of a HSS.

Menopause is the last major hormonal milestone experienced by women that is also associated with both physical and psychological effects. Vasomotor symptoms, including hot flashes, hot flushes, and night sweats, as well as vulvovaginal symptoms, appear to be specifically related to hormonal changes in menopause [27-29]. Further, research suggests that the perimenopausal transition is related to an increased number of depressive symptoms for many women [30], which may also be a consequence of the hormonal shifts experienced during this transition.

Considering that both physical and psychological consequences are associated with various hormonal shifts for many women, it would be beneficial to know if some women are more susceptible than others to experiencing physical and/or psychological symptoms during any significant hormonal shifts across their life-span. As hormonal shifts occur over the course of an approximately 50-year lifespan, it is very challenging for researchers to prospectively investigate the symptom course over such an extensive period of time. However, the few studies that have retrospectively or concurrently investigated the association of the experience of symptoms

between some of these reproductive phases have found that some women are more susceptible than others to the experience of symptoms related to hormonal shifts [for example see 30].

A few studies have found associations between the experience of negative symptoms during two or more reproductive events during the reproductive years. For instance, premenstrual irritability has been reported to be associated with depression during pregnancy and the postpartum period [10]. As well, Premenstrual Dysphoric Disorder (PMDD), mood symptoms experienced during the first 2 to 4 days postpartum, a past history of depression, and mood symptoms during past oral contraceptive use were found to be significant risk factors for postpartum depression [9]. A history of postpartum depression, past depressive episodes, a family history of affective disorders, past PMDD, and mood symptoms during the third trimester of pregnancy were all significantly associated with postpartum depressive symptoms in the first 1 to 3 days postpartum [31]. Similarly, in a more recent large population-based study, Sylvén and colleagues [32] found a positive association between self-reported postpartum depression and a history of PMS or PMDD. In contrast, one study that examined whether postnatal depressive symptoms predicted subsequent premenstrual distress did not report a significant association [33].

There have also been a few studies that have included the perimenopausal transition when specifically examining the relationship between mood changes across reproductive events. In this research women who reported high psychological distress during menopause also reported more psychological distress associated with past reproductive events. Women who had high psychological distress during the perimenopausal period reported a history of psychological distress associated with: the premenstrual period, the use of oral contraceptives, and the postpartum period [34]. Flores-Ramos and colleagues found that menopausal women who were

suffering from depression were significantly more likely to have suffered from PMDD and postpartum depression in the past, compared to those who were not depressed during the menopausal transition [35]. As well, a significant positive correlation between premenstrual and perimenopausal mood ratings, as well as another significant correlation between postpartum and perimenopausal mood ratings has been reported by Gregory and colleagues [36]. Furthermore, depressed mood during the menopausal transition has been reported to be significantly correlated with depressed mood during the premenstrual period [37]. However, Becker and colleagues did not find a significant association between depressed mood during perimenopause and emotional difficulties in the postpartum period [37]. In related research, Richards and colleagues found that women with perimenopausal depression were significantly more likely to meet the criteria for PMDD than were perimenopausal women who were not suffering from depression [38]. As well, Payne and colleagues found that premenstrual mood symptoms were associated with postpartum and postmenopausal mood symptoms [39]. However, a similar study conducted by Steinberg and colleagues found that neither premenstrual dysphoria nor postpartum depression were significant predictors of perimenopausal depression [40]. Taken together the majority of relevant studies suggest that there is a link between depressed mood across reproductive events, up to and including the menopausal transition.

Unfortunately, there is limited data available that examine the link between symptoms occurring across reproductive events, and almost none on non-emotional symptoms. Furthermore, to our knowledge there has not been one study that has looked at women's experiences and symptoms (i.e., emotional, physical, and sexual) during all of the relevant hormonal/reproductive events (i.e., puberty, premenstrual phase, hormonal contraceptive use, pregnancy, postpartum period, and the perimenopausal transition). To address this gap, we have

included an examination of data from our lab that has allowed us to evaluate the relationship between physical, psychological/emotional, and sexual symptoms related to hormonal shifts occurring at distinct reproductive phases across the female life-span. The objective was to begin to evaluate the proposed hypothesis by providing longitudinal evidence of HSS (i.e., the re-emergence of hormonal sensitivity symptoms at reproductive events over the course of the entire female reproductive lifespan). In addition to reproductive events characterized by hormonal shift, other factors believed to reflect or be influenced by hormonal variation [e.g., second to fourth digit ratio (2D:4D), neuroticism symptoms (emotional instability and negative affectivity)] were also considered in the analyses of this data to determine how they might relate to a HSS.

Evidence of hormonal sensitivity provided by our own lab

We re-examined data from a study of 289 perimenopausal or postmenopausal women. The women ranged in age from 39 to 65 years (mean [SD], 52 [4.72]). Additional demographic information may be found in Stone and colleagues [41] or on the corresponding author's website. Detailed descriptions of many of the measures that were used in the original study are also available in Stone and colleagues [41]. Briefly, the measures used included: (a) a modified version of the Menstrual Distress Questionnaire (MDQ), which assess the severity of past premenstrual symptoms across seven domains (pain, concentration, behavioral change, autonomic reactions, water retention, negative affect, and arousal) [42]; (b) a modified version of the Oral Contraceptive Side Effects Scale (OC-SES), which measures the severity of adverse physical, emotional, and sexual effects of oral contraceptives [41, 43]; (c) the Pregnancy Experiences Questionnaire (PEQ), which measure physical and emotional symptoms experienced during pregnancy [41]; (d) the Postpartum Physical Symptoms Questionnaire (PPSQ), created to assess for physical symptoms experienced during the postpartum period [41];

(e) the Edinburgh Postnatal Depression Scale (EPDS) a commonly used and empirically validated scale that assesses postpartum depression [44-45]; (f) the Menopause-Specific Quality of Life Questionnaire (MENQOL), which measures symptoms experienced during menopause tapping four symptom domains: physical, vasomotor, psychosocial, and sexual [46-47]; and (g) the Neuroticism Subscale from the NEO-Five Factor Inventory - (NEO-FFI), which was included to explore the relationship between symptoms related to reproductive events and general psychological wellbeing, particularly given existing evidence of links between hormones and neuroticism [48-50]. We also included a measure of Second to Fourth Digit Ratio (2D:4D), which serves as a proxy indicator of fetal estrogen to testosterone exposure [51-53]. Lower 2D:4D is associated with higher levels of fetal testosterone compared to fetal estrogen exposure, independent of sex [54]. Scale means, standard deviations, and internal consistencies obtained from the current analyses are presented in a supplementary table on the corresponding author's website.[1]

Re-examination of the data

Table 1 shows the inter-correlations among all variables used in the analyses. As can be seen in the table there are many positive associations between the experience of various hormonal symptoms both within and across reproductive events. While many small and medium effect size relationships were found, there were a few large effect size relationships across reproductive events. In particular, women who reported premenstrual distress were significantly more likely to endorse the experience of all adverse perimenopausal symptoms as measured by the MENQOL [e.g., $r(273) = .52$, $p < .001$ for MDQ pain and MENQOL physical; $r(276) = .63$, $p < .001$ for MDQ negative affect and MENQOL psychological]. As another example, physical

pregnancy symptoms were also found to be related to postpartum physical symptoms [e.g., $r(218) = .58$, $p < .001$ for PEQ physical symptoms and PPSQ score].

INSERT TABLE 1 ABOUT HERE

As correlational analyses showed many positive relationships between symptoms across reproductive events, we next assessed if the various hormonal symptoms experienced across reproductive phases could be captured using exploratory factor analysis (EFA). Examination of the eigenvalues on the scree plot suggested the retention of four to seven factors, with no clear elbow or break. Thus, four-factor, five-factor, six-factor, and seven-factor solutions were explored.

While all solutions provided very similar factor clusters, a six-factor solution accounting for 44.34% of the variance provided what appeared to be the most interpretable solution with a minimum number of cross-loading variables. The description of the factors in the six-factor solution were best represented by the following labels 1) PMS symptoms, 2) Sex drive, 3) Pregnancy and postpartum symptoms, 4) Menopause symptoms, 5) 2D:4D, and 6) OC side effects. There were moderate correlations found between factors 1 and 3 ($r = .57$), 1 and 4 ($r = .52$), and 3 and 4 ($r = .40$), which are all factors related to natural hormonal experiences (i.e., endogenous hormones) that involve changes in estradiol and progesterone. Thus, the experience of having high PMS symptoms is associated with high pregnancy and postpartum symptoms as well as high menopause symptoms. Similarly, high pregnancy and postpartum symptoms are positively related to menopause symptoms. A supplementary table presenting the six-factor solution is presented on the corresponding author's website.[1]

While the scree plot is a common and empirically supported method for determining number of factors used, an alternative method, Horn's Parallel Analysis has been argued to be a

superior technique for determining number of factors [55-56]. Thus, the factor analysis was repeated extracting three factors, accounting for 32.76% of the variance. Based on the results presented in Table 2 it appears that the factors represent: (1) Hormonal Symptoms, (2) Sex Drive, and (3) 2D:4D.

INSERT TABLE 2 ABOUT HERE

Note that the variable Sex Drive (prior to menopause) loaded negatively onto factor 3 (2D:4D), while MENQOL Sexual Symptoms loaded positively. There were trivial to small effect size correlations between the three factors. The Hormonal Symptoms factor is negatively correlated with the Sex Drive factor (r = -.23) and did not correlate with the 2D:4D factor (r = .03), while the Sex Drive factor is negatively correlated with the 2D:4D factor (r = - .13).

The results of a cluster analysis of women's hormonal symptom scores are presented in Figure 1. As can be seen in the figure, the two-group cluster analysis separated the women based on hormonal symptom susceptibility across reproductive phases. Those reporting minimal or no history of hormonal symptoms are represented in the group we labeled "No Hormonal Sensitivity Syndrome" (No HSS) and those with high endorsement of hormonal symptoms across the lifespan are represented in the group we labeled "Hormonal Sensitivity Syndrome" (HSS). Discriminant analysis revealed that means between group clusters differed significantly ($p < .001$) for all variables assessed apart from the OC-SES Sexual variable [*Wilks' Lambda* = .32; χ^2 (18, N = 177) = 194.73, $p < .001$].

INSERT FIGURE 1 ABOUT HERE

To assess how individuals characterized by each cluster may differ on a number of other variables related to hormonal variation we tested several variables, which we have detailed in a supplementary table presented on the corresponding author's website.[1] The t-tests revealed that

compared to cluster 2 (HSS) women, women in cluster 1 (No HSS) indicated greater sexual desire ($p < .05$), orgasm frequency ($p < .01$), and higher sex drive ($p < .05$) prior to menopause; as well as greater current sex drive ($p < .01$). Also, compared to cluster 1 (no HSS), women in cluster 2 (HSS) had higher neuroticism scores ($p < .001$). No differences were found for: body mass index, 2D:4D, age at menopause, age at menstruation, average cycle length, masturbation prior to menopause, or number of sexual partners.

Chi-square analyses showed that compared to women in cluster 1 (no HSS), women in cluster 2 (HSS) were also more likely to report use of hormone replacement therapy during the menopausal transition ($p < .05$), a history of some form of reproductive surgery prior to the menopausal transition ($p < .05$), history of antidepressant use ($p < .05$), and experiencing at least one pregnancy ($p < .05$). No differences were found with respect to the endorsement of polycystic ovarian syndrome symptoms or ever receiving a formal diagnosis of either endometriosis or postpartum depression.

Integration of the evidence supporting the existence of a Hormonal Sensitivity Syndrome

The primary aim of this article was to explore whether there may be a subgroup of women who could be described as having what we have defined as a HSS. That is, are there women who appear more prone to experiencing adverse symptoms related to hormonal shifts occurring over their life span? It appears from our review of the existing research and the reanalysis of our own data that there may indeed be a subset of women who are more susceptible to the experience of physical, psychological, and sexual symptoms related to hormonal shifts or abrupt hormonal changes across the lifespan.

To evaluate our hypothesis, we reviewed the findings from previous studies related to hormonal shifts experienced over the life-span. The previous literature, which evaluated

symptoms or negative experiences emerging in association with two or more reproductive events over the reproductive life-span, suggests that a subgroup of women with hormonal sensitivity exists. The emergence of symptoms at one event appears associated with the emergence of symptoms at subsequent hormonal events or was related to the experience of symptoms at previous events. The reproductive events investigated in this literature included menarche, the menstrual cycle, use of hormonal contraceptives, pregnancy, the postpartum period, and menopause. We also re-examined some of our own data using two different types of analyses, factor analyses and a cluster analysis. The primary findings from these analyses was that three readily interpretable factors emerged: Hormonal Symptoms, Sex Drive, and 2D:4D. Factor 1 appears to include symptoms related to all the major hormonal shifts across the female life span that are primarily characterized by changes in estrogens and progestins. The strong intercorrelations between all of these symptoms resulted in all of the symptoms loading onto one factor, supporting the HSS hypothesis.

Moreover, cluster analysis provided further support for the existence of HSS and suggested a method to classify women with and without the syndrome (or those low and high on HSS symptoms), and allowed us to further explore the distinguishing features of the groups. When only looking at symptoms related to reproductive events involving hormonal shifts, two distinct groups of women were identified using a cluster analysis. The first cluster comprised women who were low on the endorsement of symptoms related to life-span hormonal shifts. The second cluster comprised women who more readily endorsed symptoms related to hormonal shifts across the reproductive life-span. Women in cluster two with HSS were more likely to report: (a) using hormone replacement therapy, (b) a history of reproductive surgery, and (c) a history of antidepressant use, which speaks to the severity and legitimacy of the women's

experiences. Also interesting is that the women in the HSS cluster were more likely to report a history of pregnancy. Women in cluster one without HSS endorsed higher sex drive, sexual desire, and frequency of orgasm; and a notably lower level of neuroticism symptoms compared to women in cluster two.

It is striking that women who were not classified as having HSS were the ones who reported higher sex drive, sexual desire, and orgasm occurrence. As women's sexual desire and motivation is modulated by ovarian hormones [for example see 57], which are positively associated with estradiol and negatively associated with progesterone, the non-HSS women identified here are clearly hormonally sensitive in terms of their sexual response [58]. It may be that the women identified here as having a HSS are those women: (a) who are most likely to experience adverse emotional and physical symptoms with decreasing or decreases in endogenous estradiol and progesterone levels (as in the premenstrual phase, postpartum period, menopausal period, or with oral contraceptive use), or (b) who do not experience high sexual desire and behaviour in response to normal/high levels of estradiol. Thus, while it is possible that the cluster analysis differentiated between a group with HSS and one without, it is also possible that the cluster analysis differentiated between two different types of hormonally sensitive women, one group with a negative HSS and one with a positive HSS. In this second possibility, women with a negative HSS would experience adverse physical and emotional symptoms with extreme hormone levels (very low and possibly very high levels such as in pregnancy) whereas the women with positive HSS may remain sexually responsive to estradiol throughout a larger range of hormone levels. Alternatively, positive HSS women may maintain the ideal *ratio* of hormones when hormone levels fall or they may have some other feedback mechanism that helps their sexual response system adapt to the drop in hormone levels. The positive HSS group may

be a group of women who are simply more hormonally sensitive or responsive to the positive effects of estradiol on sexual feelings and behaviour. While the present findings may well reflect two different types of HSS, a positive sexual HSS does not appear to be the cause of significant distress or impairment in women. Thus, at this time, a single HSS appears to be the most useful interpretation of the evidence.

It is difficult to implicate specific hormones that women endorsing HSS may be sensitive to. It is likely a combination of hormonal shifts that are responsible for the variety of symptoms experienced by some women during these reproductive phases. However, as all of the hormonal shifts involve changes in endogenous or exogenous estrogens, progestins, or androgens, it is possible that a sensitivity to shifts in these hormones in particular plays a central role in HSS. One possibility is that HSS, and women's susceptibility to symptoms as a result of these shifts, may be the result of one or more genetic polymorphisms or some other vulnerability [59]. Further research is needed to identify genetic and other variables that differ between these two clusters of women (i.e., those with and without HSS). The use of cluster analytical techniques to group women into those who are low and high on HSS, as done here, may be one useful strategy for identifying these two groups of women and determining other identifying characteristics or predictors of HSS.

There was agreement between the three-factor structure, six-factor structure, and the cluster analysis in suggesting that neuroticism was associated with HSS. While the three-factor solution provides a more readily interpretable factor structure, both sets of factor analyses are discussed here as they each provide a unique and valuable perspective on hormonal sensitivity. With the exception of menopausal psychological symptoms, the six-factor analysis separates the reproductive shifts by specific events, yet correlational analyses of the factors revealed moderate

correlations between events related to shifts in endogenous hormones. When examining the three-factor structure, all symptoms related to all reproductive shifts load onto the same factor, apart from sexual side effects related to OC use. The latter symptoms negatively loaded onto the sex drive factor (the direction theoretically expected), though it did not reach our threshold criteria of ≥ .30. Taken together this appears to suggest that there may be something unique about women's sex drive and sexual experiences related to exogenous hormone use. Furthermore, the three-factor structure highlights that there is a relationship between various forms of symptoms/side effects related to individual reproductive events. The six-factor structure provided evidence of an even stronger relationship between reproductive events with naturally occurring hormonal shifts. Finally, a relationship further emerges between symptoms related to all reproductive events, signifying a HSS. That is, each analysis presented above provided evidence of HSS while providing some additional information about predictors of HSS.

In addition, we also examined the relationships between the isolated hormonal events. The correlation matrices suggest consistent associations between symptoms experienced during a number of reproductive events throughout the female life-span from gestation through to the perimenopausal transition. Specifically, low 2D:4D (i.e., higher prenatal testosterone or lower prenatal estradiol exposure) is associated with higher menopausal/postmenopausal sex drive for women during/after menopause. It may be that a positive influence of prenatal androgen exposure (or a negative influence of prenatal estradiol exposure) on sex drive is unmasked during menopause with the reduction in estradiol and progesterone. We are not aware of any previous report of an association between 2D:4D and sex drive or menopausal symptoms. However, unpublished data from our lab has not found any significant associations between 2D:4D and sex drive in premenopausal young women. This finding of an association between digit ratio and sex

drive in women at/after menopause suggests a possible organizational role for prenatal hormones on sex drive (i.e., high prenatal androgen exposure and low prenatal estradiol exposure associated with higher sex drive) that may only become apparent, unmasked, or measurable after menopause once the activating effects of circulating estradiol and progesterone have been removed.

Further, our correlational results suggest that women who experience premenstrual distress are also likely to experience OC side effects and a variety of symptoms related to pregnancy, the postpartum period, and menopause. This seems to indicate that premenstrual distress may be an early indicator of HSS. This observation is further supported by the results of the cluster analysis which distinguished women based on high or low endorsement of hormonal symptoms across all of these reproductive phases. Such women differed in that women with HSS had higher neuroticism scores, and were more likely to have experienced at least one pregnancy, to have had reproductive surgery, and to have taken antidepressants than women without HSS. Thus, women with HSS experience more distress than women without HSS as evidenced by surgical and pharmaceutical interventions that have putative hormonal relevance.

As well, correlational analyses also showed that women who reported greater OC side effects reported more symptoms related to pregnancy, the postpartum period, and the perimenopausal transition. Emotional and physical symptoms during pregnancy were related to postpartum emotional and physical symptoms, and symptoms during each of these time points were associated with the experience of more symptoms during the perimenopausal transition.

The notion that some women are more susceptible to hormonal shifts stems from research that has found that women experiencing symptoms related to isolated reproductive phases do not have hormone levels that differ significantly from women who do not report symptoms related to

the same time periods. Investigation into the potential differences in hormone levels between women with and without particular psychological symptoms, especially depression, has been a primary focus of research. The results from our retrospective data suggest associations between the experience of physical and psychological symptoms both within and across different reproductive phases (e.g., women who experience high levels of negative affect during the premenstrual/menstrual phase also experience high levels of physical symptoms at menopause, r = .49). This finding supports the HSS hypothesis and suggests the importance of further research into the potential endocrinological processes that are responsible for psychological and physical hormonal symptoms, both in isolation and unison.

In interpreting the new findings we present, there are some considerations that should be taken into account. First, as our results are based on retrospective data, accuracy of participant recall is a potential limitation. However, questions posed to participants were in reference to events that are not only salient (e.g., pregnancy) but often also occur repeatedly over many years (e.g., the premenstrual phase), which, theoretically, should increase the reliability of responses. Second, while the reliability of this work would be augmented using a prospective design, we are considering events that occur over a period of roughly 50 years, which is a significant strength of our study. Logistically speaking, a prospective design would not only be a tremendously challenging endeavour for a research team, it would also likely be compromised by participant attrition. Third, the methodology we employed to obtain the data does not permit us to determine directionality of the associations we report, nor do the data confirm any causal relationships. Finally, these participants were generally well educated, which may limit the generalizability of our data specifically. However, we had a considerable sample size and our participants displayed a wide range of symptoms, which enhances the utility of our findings.

Combined, the evidence from past research and the data presented from our lab suggest the need for additional research that might further evaluate the HSS hypothesis. Why, for instance, are some women more susceptible and others less so? What exactly are the mechanisms? Future research could evaluate how HSS relates to other physical and psychological concerns that show sex differences. It would also be useful to determine whether women with HSS are at greater risk for a diagnosis of disorders such as major depressive disorder and eating disorders [60-62], particularly given evidence of a role for hormones in each of these disorders [63-64]. As well, it may be valuable to investigate HSS as it relates to physical illnesses that are more commonly diagnosed in women, such as breast cancer and lupus [65-66]. Subsequent researchers might re-examine some of the conditions we evaluated here (e.g., formal diagnosis of postpartum depression and endometriosis) as these conditions may have returned null findings because they have historically been underdiagnosed. It may also be valuable to explore the possibility that women with HSS show a kindling effect or sensitization effect on symptoms due to repeated exposure to hormonal shifts across the lifespan. Finally, future research might look at the potential positive effects of hormonal shifts as a result of reproductive events, as the hypothesis evaluated here was primarily concerned with the experience of adverse experiences or symptoms.

CONCLUSION

While the endocrinological mechanisms of HSS are still unclear, this review of evidence from the existing literature in combination with our retrospective data suggest that some women are more likely to experience symptoms during a number of hormonal shifts across their reproductive life-span. Consequently, we hypothesize that a subset of women may be classified as having a HSS. While some experts have recognized a connection between hormonal shifts

across the female reproductive life-span, to our knowledge this is the first paper to both systematically examine this issue and propose that this re-occurrence of adverse symptoms related to reproductive events may be a result of a *Hormonal Sensitivity Syndrome*. To date research has primarily evaluated symptoms related to hormonal shifts by focusing on individual reproductive events in isolation. In some cases, studies have looked at the association of symptoms across two events. The evidence we present here supports our hypothesis for the existence of a HSS, or the tendency for a subgroup of women to experience adverse physical, sexual, and psychological symptoms related to hormonal events across the entire female life-span.

Footnote:

1. Supplementary tables are posted at https://www.researchgate.net/profile/Dwight_Mazmanian

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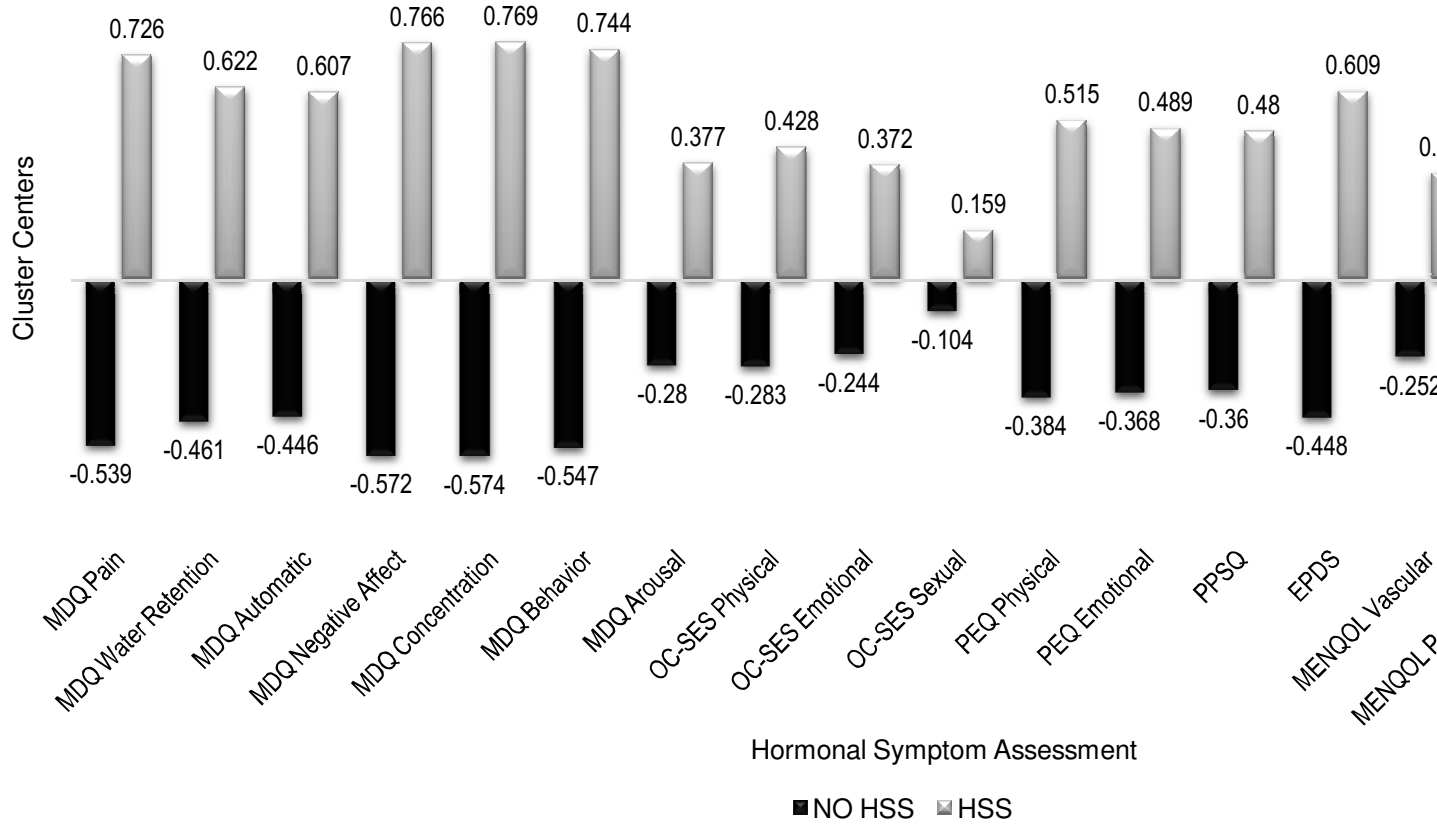
Figure 1. Hormonal Symptom Clusters Determined Through Cluster Analysis.



Note. The two clusters depicted in this figure represent a No Hormonal Sensitivity Syndrome Group (No HSS) and a Hormonal
(HSS) and reflect the symptoms that most strongly discriminate these two groups of women. MDQ = Menstrual Distress Questi
Contraceptives Side-effects Scale; PEQ = Pregnancy Experiences Questionnaire; PPSQ = Postpartum Physical Symptom Questio
Postnatal Depression Scale; MENQOL = Menopause Quality of Life Questionnaire.

Table 1. Pearson's Product-Moment Correlations Indicate Associations between Hormonally-Relevant Symptoms Across Reproductive Phases (N =283[a])

		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.
1.	Right 2D:4D																
2.	Left 2D:4D	.62**															
3.	Age of Menses	.13	.16														
4.	MDQ Pain	-.05	-.11	-.10													
5.	MDQ Water Retention	.01	.01	-.14*	.59**												
6.	MDQ Autonomic	-.02	-.05	-.05	.54**	.27**											
7.	MDQ Negative Affect	.07	.07	-.05	.62**	.50**	.48**										
8.	MDQ Concentration	-.02	-.03	-.02	.52**	.38**	.57**	.72**									
9.	MDQ Behavior	.07	.01	-.04	.58**	.39**	.52**	.68**	.74**								
10.	MDQ Arousal	.10	.08	.06	.26**	.09	.36**	.30**	.38**	.29**							
11.	OC-SES Physical	.13	.02	-.06	.30**	.26**	.27**	.20**	.19**	.18**	.12						
12.	OC-SES Emotional	.05	.10	.05	.22**	.15*	.23**	.30**	.25**	.30**	.07	.55**					
13.	OC-SES Sexual	.03	-.00	.04	.05	-.08	.14*	.12	.16*	.14*	.13	.23**	.26**				
14.	PEQ Physical	.04	.09	-.06	.33**	.35**	.21**	.37**	.34**	.27**	.15*	.26**	.23**	.12			
15.	PEQ Emotional	.03	.13	.01	.28**	.14*	.14*	.40**	.42**	.32**	.10	.12	.20**	.08	.58**		
16.	PPSQ	.05	.15	-.02	.29**	.21**	.22**	.28**	.29**	.30**	.15*	.37**	.28**	.13	.58**	.40**	
17.	EPDS	.12	.18	-.03	.31**	.27**	.31**	.49**	.41**	.40**	.20**	.24**	.27**	.15*	.44**	.49**	.51**
18.	Age of Menopause	-.06	-.08	-.05	-.12	-.03	-.07	-.10	-.06	-.07	-.11	-.10	-.08	.01	-.07	-.18*	-.07
19.	Reproductive Life Span[b]	-.08	-.13	-.35**	-.12	.00	-.05	-.12	-.09	-.08	-.12	-.08	-.09	.00	-.05	-.19**	-.06
20.	MENQOL Vasomotor	.01	.04	.01	.26**	.26**	.33**	.20**	.21**	.17**	.14*	.18**	.04	.04	.11	.05	.17*
21.	MENQOL Psychological	.11	.16	.01	.41**	.38**	.29**	.63**	.51**	.52**	.19**	.09	.18**	.07	.32**	.40**	.28**

22.	MENQOL Physical	.02	.10	-.08	.52**	.47**	.41**	.49**	.51**	.43**	.27**	.27**	.19**	.04	.40**	.30**	.33**
23.	MENQOL Sex	.12	.30**	-.03	.31**	.31**	.24**	.29**	.23**	.22**	.16*	.17*	.11	.07	.14*	.10	.11
24.	NEO-FFI Neuroticism	.25*	.20	-.06	.32**	.27**	.31**	.54**	.45**	.48**	.16**	.13	.20**	.10	.28**	.40**	.18**
25.	BMI	-.10	-.14	-.25**	.04	.03	.06	-.06	-.12	-.07	-.04	.08	.03	-.07	-.03	.01	-.06

Note. Shading highlights assessment subscales or similar measures based on reproductive time-point; 2D:4D = finger length ratio of 2nd digit to 4th digit; MDQ = Menstrual Distress Questionnaire; PCOS = Polycystic Ovary Syndrome; OC-SES = Oral Contraceptives Side-effects Scale; PEQ = Pregnancy Experiences Questionnaire; PPSQ = Postpartum Physical Symptom Questionnaire; EPDS = Edinburgh Postnatal Depression Scale; MENQOL = Menopause Quality of Life Questionnaire; NEO-FFI = NEO Five-Factor Inventory.

[a] The maximum possible sample size for all correlations excluding those with 2D:4D variable is N = 283 (range N = 113 to 283); For correlations with 2D:4D variable maximum possible sample size N = 100 (range N = 53 to 100);

[b] Age of menopause subtract age of menses

***** Correlation is significant at the.05 level (2-tailed); ****** Correlation is significant at the.01 level (2-tailed)

Table 2. Three-Factor Analysis of the 32 Reproductive Event Measures Across the Female Lifespan

	Factor		
	1	2	3
	Hormonal Symptoms	Sex drive	2D:4D
Right 2D:4D	.114	-.044	.670
Left 2D:4D	.130	-.129	.868
Age of menses	-.047	-.029	.175
Sexual desire [a]	-.135	.862	-.050
Orgasm [a]	-.130	.705	-.074
Masturbate [a]	-.080	.588	-.044
Sex drive [a]	-.164	.373	-.339
Current sex drive	-.127	.785	-.133
MDQ Pain	.703	-.113	-.206
MDQ Water Retention	.558	-.036	-.072
MDQ Automatic	.595	-.184	-.149
MDQ Negative Affect	.836	-.194	-.044
MDQ Concentration	.790	-.228	-.162
MDQ Behavior	.763	-.216	-.099
MDQ Arousal	.370	-.067	.020
Endometriosis[b]	-.104	.062	-.063
PCOS[b]	.045	-.114	-.028
OC-SES Physical	.327	.050	.026
OC-SES Emotional	.360	.063	.057
OC-SES Sexual	.157	-.259	.007
Ever pregnant [b]	.095	-.056	-.153
PEQ Physical	.499	-.156	.068
PEQ Emotional	.500	-.133	.093

PPSQ	.443	-.124	.125
EPDS	.581	-.221	.152
Postpartum depression [b]	-.146	.056	.104
Reproductive life span [c]	-.135	-.044	-.112
MENQOL Vascular	.344	-.075	.023
MENQOL Psychological	.721	-.147	.120
MENQOL Physical	.696	-.093	.041
MENQOL Sexual	.420	-.248	.278
NEO-FFI Neuroticism	.630	-.218	.190
Eigenvalues (% variance)	6.423	2.434	1.621

Note. Shading represents variables considered for factor label; 2D:4D = finger length ratio of 2nd digit to 4th digit; MDQ = Menstrual Distress Questionnaire; PCOS = Polycystic Ovary Syndrome; OC-SES = Oral Contraceptives Side-effects Scale; PEQ = Pregnancy Experiences Questionnaire; PPSQ = Postpartum Physical Symptom Questionnaire; EPDS = Edinburgh Postnatal Depression Scale; MENQOL = Menopause Quality of Life Questionnaire; NEO-FFI = NEO Five-Factor Inventory.

[a] Prior to Menopause

[b] Coded 1 (yes) 2 (no)

[c] Age of menopause subtract age of menses.