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Review

A lack of consistent evidence for cortisol dysregulation in premenstrual syndrome/premenstrual dysphoric disorder

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ABSTRACT

Although decades of research has examined the association between cortisol regulation and premenstrual syndrome/premenstrual dysphoric disorder (PMS/PMDD), no review exists to provide a general set of conclusions from the extant research. In the present review we summarize and interpret research that has tested for associations between PMS/PMDD and cortisol levels and reactivity ($n = 38$ original research articles). Three types of studies are examined: correlational studies, environmental-challenge studies, and pharmacological-challenge studies.

Overall, there was very little evidence that women with and without PMS/PMDD demonstrate systematic and predictable mean-level differences in cortisol, or differences in cortisol response/reactivity to challenges. Methodological differences in sample size, the types of symptoms used for diagnosis (physical and psychological vs. only affective), or the type of cortisol measure used (serum vs. salivary), did not account for differences between studies that did and did not find significant effects.

Caution is recommended before accepting the conclusion of null effects, and recommendations are made that more rigorous research be conducted, considering symptom-specificity, within-person analyses, and multiple parameters of cortisol regulation, before final conclusions are drawn.

Contents

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1. Introduction

Cyclical changes in psychological, somatic, and vegetative symptoms of the menstrual cycle are well-documented and lead to significant impairment for many women (Halbreich et al., 2003). Specific symptoms include psychological changes such as depression, anxiety, moodiness, difficulty concentrating, and feeling out of control; physical changes such as cramps, painful breasts, back and joint pain, gastrointestinal symptoms, and acne; and vegetative symptoms involving sleep and appetite (Hartlage et al., 2012). When severe these symptoms may result in a diagnosis of premenstrual syndrome (PMS; American College of Obstetricians and Gynecologists, ACOG, 2000) or a more severe form referred to as premenstrual dysphoric disorder (PMDD; DSM-V, American Psychiatric Association, 2013). It should be noted that although PMDD is often considered to be a more severe form of PMS, there are also qualitative differences between PMS, which has an equal emphasis on psychological and physical symptoms, and the psychiatric diagnosis of PMDD, which has a clear emphasis on psychological symptoms.

It is estimated that 13–19% of reproductive-aged women experience clinically significant dysphoric PMS, that 3–8% meet strict diagnostic criteria for premenstrual dysphoric disorder (PMDD), and that the impairment and lowered quality of life associated with PMDD is similar to that of dysthymic disorder and only slightly lower than that observed for major depressive disorder (Halbreich et al., 2003). Moreover, PMS and PMDD show significant comorbidity with mood disorders associated with other reproductive life events, including post-partum depression (Bloch et al., 2005) and menopausal depression (Freeman et al., 2004), as well as non-reproductive mood disorders, including major depressive disorder (Halbreich and Endicott, 1985; Pearlstein et al., 1990). Evidence also suggests that PMS/PMDD longitudinally predicts later episodes of depression (Graze et al., 1990; Hartlage et al., 2001). It should be noted, however, that multiple nosological systems are used for PMS/PMDD, with very different diagnostic criteria (e.g., DSM-V, 2013; ACOG, 2000; and the International Classification of Diseases (ICD-10), World Health Organization, 1996; see also Halbreich et al., 2007; for discussion). For example, whereas the DSM-V requires at least five premenstrual symptoms in most cycles for a diagnosis of PMDD; ACOG criteria requires only one somatic and one psychological symptom for three consecutive cycles for a diagnosis of PMS. These differences have resulted in heterogeneity across studies in diagnostic criteria, sample characteristics, and prevalence rates. For the remainder of this review these conditions will generally be referred to as PMS/PMDD.

Although the etiology of PMS/PMDD is not understood, research suggests that it is likely the result of individual differences in response to normal levels of gonadal hormones (Rubinow and Schmidt, 2006; Schmidt et al., 1998; Segebladh et al., 2009), and that these individual differences are partially influenced by genetic variations in the estrogen receptor alpha gene (ESR1 gene; Huo et al., 2007). In addition to research focusing on gonadal steroids as a putative cause of PMS/PMDD, at least 30 years of research has also attempted to investigate the role of hypothalamic–pituitary–adrenal (HPA) axis reactivity and regulation. However, although this has been a topic of scientific inquiry for decades (at least since early reports by Haskett et al., 1984; Steiner et al., 1984; Varma, 1984), the actual number of studies is relatively small, which is likely the consequence of inconsistent and contradictory results combined with historically prohibitive costs and invasive procedures associated with steroid measurement. Nonetheless, there is a sufficiently large base of research from which to draw tentative conclusions and recommendations. The goal of the present study is to review research that has examined cortisol, the primary product of HPA activity, as it relates to a PMS/PMDD diagnosis. Before examining this research, however, the hypotheses and motivations frequently cited for studying this association will be outlined, although a detailed discussion of each theory is beyond the scope of the present paper.

1.1. Theoretical motivations

First, because PMS/PMDD demonstrates a number of similarities with major depressive disorder (MDD), and because MDD is associated with multiple indices of cortisol dysregulation, including cortisol hypersecretion (Gillespie and Nemeroff, 2005; Goodyer et al., 2001; Wong et al., 2000), non-suppression to the dexamethasone suppression test (DST; Carroll et al., 1981; Rush et al., 1996), and flattened diurnal cortisol secretion (Doane et al., 2013; Jarcho et al., 2013), researchers have also tested whether cortisol dyregulation is associated with PMS/PMDD. Specifically, because of overlapping symptoms and high comorbidity between major depression and PMS/PMDD (Endicott et al., 1981; Fava et al., 1992; Graze et al., 1990; Halbreich and Endicott, 1985; Pearlstein et al., 1990), and because some research suggests that SSRIs are effective in treating both major depression (Baker et al., 2003; Lanzenberger et al., 2012; Villafuerte et al., 2009) and PMS/PMDD (Dimmock et al., 2000), it has been hypothesized that these disorders share common neurological or neuroendocrinological substrates (Bancroft and Cook, 1995). According to this model, cortisol levels are viewed as a biomarker of a similar pathological condition (Bancroft and Cook, 1995; Bancroft et al., 1991).

Second, it has been hypothesized that PMS/PMDD may be the result of endogenous opioid withdrawal (β-endorphin; Halbreich and Endicott, 1981). According to this hypothesis, a late-luteal phase drop in endorphins leads to opioid withdrawal resulting in PMS/PMDD symptoms (Giannini et al., 1990, 1995; Facchinetti et al., 1987). Because opioids may regulate the HPA axis (Facchinetti et al., 1994) it has been hypothesized that opioid withdrawal would also influence HPA regulation and cortisol levels.

A third hypothesis involves allopregnanolone, which is a neurosteroid progesterone metabolite and a potent modulator of the $GABA_A$ receptor, thus having important anxiolytic effects (Brot et al., 1997). This model is based on (1) findings that stress increases levels of allopregnanolone which exerts modulatory effects on the inhibitory $GABA_A$ network (Girdler et al., 2001), which then down regulates the HPA axis, and (2) involvement of allopregnanolone in PMS/PMDD (Freeman et al., 1993, 2002; Monteleone et al., 2000; Rapkin et al., 1997) Taken together, low allopregnanolone levels are expected to result in an attenuated anxiolytic effect of the $GABA_A$ system and thus increased anxiety and stress reactivity, which for some women depends on menstrual cycle regulation of allopregnanolone levels.

A fourth hypothesis cites dysregulated stress response as a causal mechanism linking PMS/PMDD with cortisol levels, independent of allopregnanolone involvement. For example, Girdler et al. (1998) has suggested that PMS/PMDD may be caused by an altered stress response, possibly the result of chronic or severe stress such as a history of abuse (Girdler et al., 2007), although allopregnanolone is not specifically part of this study's conceptual framework. A common denominator across these studies are individual differences in dysregulated stress response being associated with the menstrual cycle (PMS/PMDD).

Finally, some studies are presented as general hormonal models involving a range of endocrine processes (e.g., Parry et al., 1991), or draw from multiple causal hypotheses (e.g., Roca et al., 2003). One study noted anatomical overlap between the HPA and the HPG axes (Cahill, 1998).