Psychoneuroendocrinology 75 (2017) 83–90

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

A specific profile of luteal phase progesterone is associated with the development of premenstrual symptoms

Thelma A. Lovick[a,b,*], Vinicius G. Guapo[c], Janete A. Anselmo-Franci[d], Camila M. Loureiro[c], Maria Clara M. Faleiros[c], Cristina M. Del Ben[c], Marcus L. Brandão[b]

[a] School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol B15 2TT, UK
[b] Instituto de Neurociências e Comportamento, Avenida do Café, 2450, Ribeirão Preto, SP, Brazil
[c] Departments of Neuroscience and Behavior, Ribeirão Preto Medical School, University of São Paulo – Campus, Ribeirão Preto, SP, Brazil
[d] Departamento de Morfologia, Fisiologia, e Patologia Básica, Faculdade de Odontologia, Universidade de São Paulo – Campus, Ribeirão Preto, SP, Brazil

ARTICLE INFO

Article history:
Received 27 June 2016
Received in revised form 12 October 2016
Accepted 27 October 2016

Keywords:
Premenstrual symptoms
Progesterone
Luteal phase
Saliva

ABSTRACT

There is a consensus that the development of premenstrual dysphoric states is related to cyclical change in gonadal hormone secretion during the menstrual cycle. However, results from studies seeking to link symptom severity to luteal phase progesterone concentration have been equivocal. In the present study we evaluated not only the absolute concentrations of progesterone but also the kinetics of the change in progesterone concentration in relation to development of premenstrual symptoms during the last 10 days of the luteal phase in a population of 46 healthy young adult Brazilian women aged 18–39 years, mean 26.5 ± 6.7 years. In participants who developed symptoms of premenstrual distress, daily saliva progesterone concentration remained stable during most of the mid-late luteal phase, before declining sharply during the last 3 days prior to onset of menstruation. In contrast, progesterone concentration in asymptomatic women underwent a gradual decline over the last 8 days prior to menstruation. Neither maximum nor minimum concentrations of progesterone in the two groups were related to the appearance or severity of premenstrual symptoms. We propose that individual differences in the kinetics of progesterone secretion and/or metabolism may confer differential susceptibility to the development of premenstrual syndrome.

1. Introduction

Premenstrual syndrome (PMS) refers to a cluster of adverse psychological and physical symptoms experienced by many women in the late luteal phase of their menstrual cycle. The most commonly reported psychological symptoms included anger and irritability, mood swings/tearfulness, fatigue/lack of energy and food cravings, whilst physical symptoms include bloating, weight gain and breast tenderness (Dennerstein et al., 2011, 2012; Tschudin et al., 2010). Although the syndrome is not distinguished by a specific set of symptoms, there is a consensus that certain symptoms should be present for 2 or more days during the 14 days prior to menstruation, and subside by the end of the menstrual flow (Halbreich et al., 2007).

Premenstrual dysphorias are extremely common. In large surveys of European and Canadian women up to 90% of participants reported experiencing one or more symptoms. Up to 30% felt them to be considerably bothersome, whilst a smaller proportion of women (3–8%) who experienced severe and debilitating symptoms, were diagnosed with premenstrual dysphoric disorder (PMDD; American Psychiatric Association, 2013), which is considered a distinct psychiatric disorder (Halbreich et al., 2003; Tschudin et al., 2010; Wittchen et al., 2002). It is not clear however, whether PMS and PMDD are separate entities or whether PMDD is an extreme form of PMS. However, since the incidence of PMS is some 10-fold higher than PMDD; its effects are far more wide-reaching, due to the negative impact on family, friends and work colleagues as well as the individual herself. PMS and PMDD are undoubtedly multifactorial; at least three clinical subtypes have been recognised (Dennerstein et al., 2011; Freeman et al., 2011). Risk factors include high body mass index, stress, smoking, and early life emotional and physical abuse (Bertone-Johnson et al., 2010, 2014; Dennerstein et al., 2011). A genetic component is another contributory factor (Jahanfar et al., 2011).

* Corresponding author at: School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol B15 2TT, UK.
E-mail address: Thelma.lovick@bristol.ac.uk (T.A. Lovick).

http://dx.doi.org/10.1016/j.psyneuen.2016.10.024
0306-4530/

Whilst it is well established that the menstrual cycle modulates the integration of emotional and cognitive processing in women (Hoyer et al., 2013), not all women develop premenstrual symptoms. In those who do, the main trigger factor is the cyclical production of sex hormones during the ovarian cycle (O'Brien et al., 2011). Apart from rare cases (O'Brien et al., 2011) premenstrual symptoms do not occur in anovulatory cycles (Muse et al., 1984; Hammarbäck et al., 1991) or following oophorectomy (Cronje et al., 2004). The luteal phase of the menstrual cycle, when premenstrual symptoms appear, is characterized by significant changes in secretion of progesterone: production increases rapidly following ovulation and remains elevated throughout the luteal phase, before returning to basal levels prior to the onset of menstruation. Progesterone passes readily through the blood brain barrier (Pardridge et al., 1980). In post menopausal women (low stable progesterone concentration) administration of low doses of progesterone, which raised the concentration of the native steroid and its neuroactive metabolite allopregnanolone into the physiological range, induced negative mood whilst higher doses induced positive mood (Andréen et al., 2006, 2009).

Although we are not aware of comparable studies on women with PMS, several studies in PMDD sufferers have investigated the relationship between severity of symptoms and plasma concentration of progesterone during the luteal phase. The results from these studies have been equivocal, with reports of decreased (Rapkin et al., 1997; Wang et al., 1996; Ziomkiewicz et al., 2012), increased (Backström et al., 1983; Girdler et al., 2001; Hammarbäck et al., 1989; Redei and Freeman, 1993; Watts et al., 1985) or no difference (Hsiao et al., 2004; Rubinow et al., 1988) in luteal phase concentration of progesterone or its neuroactive metabolite allopregnanolone in women with PMDD versus asymptomatic controls. Interestingly, a more recent study has proposed an inverted U-shaped curve relationship between the severity of negative mood symptoms and allopregnanolone serum concentration (Bäckström et al., 2014).

In an effort to resolve this conundrum, we carried out a study in a population of healthy adult women in whom we made daily assessments of the presence of PMS-like symptoms during the luteal phase and the concentration of progesterone in the saliva. We considered not only the absolute concentrations of progesterone but also the kinetics of the change in progesterone concentration during the luteal phase. We found that neither maximum nor minimal concentrations of progesterone measured during the luteal phase could be linked to the appearance or severity of premenstrual symptoms. However, in the women who experienced significant symptoms of premenstrual distress, progesterone concentration remained stable during most of the luteal phase before declining sharply during the last 3 days. In contrast, progesterone concentration in asymptomatic women underwent a gradual declined over the final 8 days prior to menstruation.

2. Methods

2.1. Participants

The sample was composed of healthy female volunteers, aged between 18 and 40 years, who were recruited from the local university population. The volunteers were invited through print ads, e-mail and social networks to participate in research into the menstrual cycle. Premenstrual dysphoric states were not mentioned. The local ethics committee approved the study (process number 8172/2014) and all participants signed a consent form. We included women who reported regular menstrual cycles and who had not used hormonal contraceptives in the last three months. Since the presence of other medical conditions might interfere with the evaluation of premenstrual symptoms, we excluded participants with a history of past diagnosis of severe mental illness, such as schizophrenia, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, or who met criteria for any current psychiatric disorder. We also excluded women with a current use of psychoactive substances (except alcohol and tobacco), psychiatric medications or suspected pregnancy.

2.2. Clinical assessment

The absence of psychiatric diagnosis was confirmed by the application of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997), no patient version, translated and adapted to Portuguese (Del-Ben et al., 2001). The menstrual cycle was characterized by means of a questionnaire specifically developed for this study, when information regarding the duration of the menstrual cycle in the last 3 months, the regularity of the menstrual cycles, and the date of the last period were registered.

Screening and diagnostic interviews, and monitoring were performed by research assistants (nurses, psychologists) familiar with clinical research and properly trained in the assessment tools used in this study. These research assistants were also involved in the recruitment of participants, as well as telephone calls and face-to-face contacts, in order to ensure that the procedures for data collection were met properly.

The next ovulatory date (Ov) for participants was estimated from the date of their last menstrual period (LMP) and the average duration of their menstrual cycles (MC) according to the following formula: Ov = LMP + MC − 14. If the interview happened between Ov and LMP, the volunteer was asked to contact the research assistants on the first day of her next period so that the Ov could be calculated. Participants were instructed to collect daily saliva samples and to complete symptom questionnaires (described below) during their luteal phase from the time of their estimated day of ovulation to the onset of menses or for 20 days, whichever was the shorter.

2.3. Premenstrual symptoms

The occurrence of premenstrual symptoms was measured by the short form of the Daily Record of Severity Problems Scale (DRSP, Endicott et al., 2006), translated into Portuguese. The DRSP is a 14-item self-report instrument, which accesses the presence of symptoms of common occurrence in the premenstrual period and their impact in the global functioning. The first 11 items of the DRSP are related to the following symptoms: depressed mood; anxiety; mood swings; irritability; less interest in usual activities; difficulty in concentration; lethargy; increased appetite; sleeping problems; feeling out of control; and physical symptoms. The 3 functional items evaluate the consequences of the reported symptoms on the quality/frequency of productivity, social activity and relationships. Each participant was directed to evaluate the occurrence of symptoms at the end of each day by applying a score on a 6-point scale: 1 = not at all, 2 = minimal 3 = mild; 4 = moderate, 5 = severe, 6 = extreme. Although initially designed to reflect DSM-IV criteria for PMDD, the DRSP can also be used to assess lesser degrees of severity of the premenstrual syndrome to track daily levels of severity of symptoms and impairment (Endicott et al., 2006).

We recorded the occurrence of premenstrual symptoms daily, from the 14th day of the menstrual cycle based on the total score in the DRSP. As a reference point to assess the development of premenstrual symptoms we used the mean of the total score of the DRSP on the first two days of the analysis period i.e. in the early luteal phase 9 and 10 days prior to onset of menstruation. We defined symptomatic participants as individuals in whom the daily total DRSP score (sum of response to the 14 questions) increased