



# Ovarian morphology in premenstrual dysphoria

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**Summary** Ovarian cyclicity is a prerequisite for premenstrual dysphoria (PMD), as illustrated by the fact that this condition is effectively eliminated by ovariectomy or by treatment with a GnRH agonist. Despite the possibility of differences in ovarian function between women with and without PMD, no study comparing ovarian morphology in these two groups has ever been published. Fifty-two women were recruited for this study; 26 had premenstrual dysphoria, fulfilling criteria slightly modified from those of the premenstrual dysphoric disorder, and 26 were asymptomatic age-matched controls. Ovarian morphology was assessed using transvaginal 7 MHz ultrasonography on day 5 after the start of menses, and venous blood was sampled for hormone analysis on days 3 and 8, the expected day of ovulation, and day -4 of the menstrual cycle. There were no significant differences between the groups with respect to the prevalence of polycystic ovaries (PCO), the total number of follicles, the total ovarian volume or serum levels of androgen hormones. In addition, serum free testosterone levels in late premenstrual phase showed an inverse association to premenstrual symptoms of irritability and a similar inverse association trend to symptoms of depressed mood. Unexpectedly, the prevalence of ovaries with fewer than five antral or growing follicles was significantly higher in women with PMD than in controls ( $p = 0.016$ ). While the results do not support a role for PCO or androgen hormones in eliciting late luteal phase irritability, the possible relationship between oligofollicular ovaries and PMD deserves further study.

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## 1. Introduction

A severe form of premenstrual syndrome, characterized by mood symptoms appearing regularly in the luteal phase of the menstrual cycle, and disappearing after the onset of menses,

is referred to as premenstrual dysphoric disorder (PMDD) (if the diagnosis has been made using criteria presented in DSM-IVTR) (Yonkers et al., 2008), or premenstrual dysphoria (PMD) (which is a somewhat broader term) (Eriksson et al., 2002; Landén and Eriksson, 2003). While many regard irritability and anger as the cardinal symptoms of this condition (Angst et al., 2001; Hartlage and Arduino, 2002; Landén and Eriksson, 2003; Pearlstein et al., 2005; Steiner

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et al., 2011) depressed mood, tension and affect lability are also common complaints.

Ovarian cyclicality is a prerequisite for premenstrual symptoms to occur, as illustrated by the fact that such symptoms are effectively eliminated by ovariectomy (Casper and Hearn, 1990; Casson et al., 1990; Cronje et al., 2004) or by treatment with a GnRH agonist (Muse et al., 1984; Bancroft et al., 1987; Hammarback and Backstrom, 1988; Wyatt et al., 2004). Although some authors have reported differences between women with and without PMD with respect to serum levels of estradiol (Backstrom et al., 1976; Watts et al., 1985; Seippel and Backstrom, 1998; Blum et al., 2004), progesterone (Backstrom et al., 1976; Watts et al., 1985; Blum et al., 2004), or testosterone (Eriksson et al., 1992, 1994; Lombardi et al., 2004) the weight of the available evidence does not support such a relationship, and suggests that it is the responsiveness of the target organs, including the brain, to the influence of these hormones, rather than ovarian activity, that differentiates women with and without PMD (Dougherty et al., 1997; Bloch et al., 1998; Schmidt et al., 1998). However, no formal comparison of the ovarian morphology of women with and without PMD has been published to date, and differences in ovarian function between these groups cannot, therefore, be excluded.

The polycystic ovary syndrome (PCOS) (Souter et al., 2004; Norman et al., 2007; Diamanti-Kandarakis, 2008) is a condition characterized by (i) oligo- and/or anovulation, (ii) clinical and/or biochemical signs of hyperandrogenism, and (iii) polycystic ovaries; two of these three criteria have to be met for the diagnosis (Rotterdam PCOS Consensus Workshop Group, 2004). Whereas PCOS has a reported prevalence of between 6.5 and 8% in an unselected population of women of fertile age, polycystic ovaries (PCO), not necessarily interfering with menstrual cyclicality, are considerably more common; the prevalence of this condition varies between 17 and 27% in most Western countries (Farquhar et al., 1994; Botsis et al., 1995; Lakhani et al., 2002; Hart et al., 2004).

Numerous studies suggest that PCOS is associated with an increased risk of mood symptoms, including depressed mood, anxiety and aggression (Himelein and Thatcher, 2006; Barnard et al., 2007; Hollinrake et al., 2007; Mansson et al., 2008; Benson et al., 2009; Jedel et al., 2009; Deeks et al., 2010; Dokras et al., 2011), elevated androgen levels is one (but not the only) possible mediator. Whereas there may not be comorbidity between PCOS causing anovulation, as per the definition, and PMD, we speculated that the possibility of an association between PMD and the milder variant of this condition, i.e. PCO, was worth exploring, especially since (i) a negative association between androgen levels and mood in fertile women has recently gained considerable support (Baischer et al., 1995; Bromberger et al., 2010; Roepke et al., 2010), (ii) some (Eriksson et al., 1992, 1994; Lombardi et al., 2004) but not all (Backstrom and Aakvaag, 1981; Watts et al., 1985; Bloch et al., 1998) workers have found higher androgen levels in women with PMD than in those without, and (iii) recent studies have suggested that an oral contraceptive displaying anti-androgenic properties may be effective in PMD (Rapkin, 2008). The primary aim of this study was therefore to compare women with PMD and symptom-free age-matched controls with respect to ovarian morphology type, ovarian volume and the number of ovarian follicles using transvaginal ultrasonography. A secondary aim was to

investigate differences in serum levels of androgen hormones between the groups. Further, in a post hoc analysis, to test these androgen levels for associations to self-rated premenstrual symptoms of irritability and depressed mood.

## 2. Methods

### 2.1. Premenstrual dysphoria group

Twenty-six women with PMD were recruited before entering a larger pharmacologic two-center study comparing the effects of two serotonergic compounds on the cardinal symptoms of PMD, the results of which have been published elsewhere (Landen et al., 2001). The women were recruited for the combined studies by a newspaper advertisement followed by a structured telephone interview and a clinical evaluation, including a structured psychiatric interview comprising the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). Inclusion criteria were: fulfillment of criteria A–C of the Premenstrual Dysphoric Disorder (PMDD), as described in the American Psychiatry Association (APA) Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) (APA, 1994), and fulfillment of criterion D by showing cyclicality of one or both of the core symptoms irritability and depressed mood in two of three VAS-rated reference menstrual cycles. This criterion required a 100% or more increase in the mean VAS rating of the inclusion symptom in the premenstrual phase (i.e. over the 5 days preceding menstrual bleeding) compared with the mean rating in the follicular phase (i.e. over days 6–10 from menstrual bleeding onset), as well as a mean premenstrual rating of the symptom exceeding 30 mm. Other inclusion criteria were: age 18–45 years, regular menstrual cycles of 22–35 days duration, current physical health, no other axis I or II disorder according to the MINI interview, and an MADRS score  $\leq 14$ . Exclusion criteria were: pregnancy, breast-feeding, or intended pregnancy during the study period. All women were free from medication during blood sampling or ultrasonography.

### 2.2. Control group

Twenty-six women, age-matched to the respective PMD group members to within  $\pm 2$  years, were concurrently recruited through the centers for cervical Papanicolaou (Pap) smear screening in the city of Uppsala, Sweden. The automated triennial screening program has a total coverage of about 70% of women of reproductive age, with the screening done for about 40% at the centers for cervical Pap smear screening and for the rest through 'opportunistic' screening (Eaker, 2003). Midwives engaged in Pap smear sampling handed out information sheets about the study to women of the ages required for controls. Women interested in participating in the study underwent a structured telephone interview and a clinical evaluation, including a psychiatric interview (comprising the MINI and MADRS questionnaires) identical to that taken by the PMD group. The control group also rated daily symptoms, using the same VAS instrument as the PMD group, during two menstrual cycles. Inclusion criteria for the controls were: self-stated absence of

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