Is it Just the Hormones?

Sex Steroids, Chronic Stress and Violence in Premenstrual Dysphoric Disorder

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Abstract

Premenstrual depressive symptoms and mood swings affect 3-8% of women in fertile age. The female hormones are believed to be the cause. Progesterone is well studied, but estrogen is not, and either are other causes such as intimate partner violence and chronic stress.

The aim in this thesis was to investigate the influence of hormones as well as psychological aspects on the most common problems among women seeking care for premenstrual symptoms.

In a cross-sectional study, four groups of women were included: ongoing users of oral contraceptives, with or without adverse mood symptoms and previous users, with or without experience of adverse mood. Depression and anxiety were significantly more common in both groups with reported adverse mood, in comparison with their control groups with no adverse mood. Self-reported PMS was significantly more common in those women who reported adverse mood, however, there was no difference in prospectively defined PMS or PMDD between the two groups of previous users.

In a RCT with 25 women completing the study, GnRH treatment were tested in combination with two different HRT add-back doses of estradiol, in combination with progesterone and placebo. The higher dose of estrogen 1.5 mg in combination with progesterone induced significantly more pronounced symptoms than in combination with placebo. The lower dose, 0.5 mg gave less symptom recurrence in combination with progesterone.

Exposure to violence was investigated among PMDD patients, healthy controls and gynecological patients. Among the participating women, gynecological patients, reported physical and/or emotional abuse significantly more often than did PMDD patients, as well as healthy controls.

Chronic stress was investigated with diurnal cortisol, and low-dose dexamethasone test. There was no difference in diurnal secretion of cortisol between PMDD patients and controls. No difference in the degree of dexamethasone suppression was found between PMDD patients and controls.

According to the results from these studies, the main symptom provoking factor in women with PMDD appears to be the estradiol and progesterone fluctuations across the menstrual cycle, whereas chronic stress and intimate partner violence appears to be less relevant.

Keywords: premenstrual dysphoric disorder; combined oral contraceptive; GnRH agonist; add-back; estradiol; progesterone; chronic stress; intimate partner violence; depression, anxiety; allopregnanolone

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To my mother and father

“Sakta
men steg för steg
går det
framåt
det måste man tro”

Märta Tikkanen
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV  Segebladh B, Bannbers E, Nyberg S, Bixo M, Bäckström T, Sundström Poromaa I. Diurnal cortisol and allopregnanolone variation and low-dose dexamethasone test in women with premenstrual dysphoric disorder and healthy controls. *Manuscript.*

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Abbreviations

ACOG    American College of Obstetricians and Gynecologists
ACTH    Adrenocorticotropic hormone
ANOVA   Analysis of variance
APA     American Psychiatric Association
BMI     Body mass index
CNS     Central nervous system
COC     Combined oral contraceptive
CD      Cyclicity Diagnoser
DSM-IV  Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EEG     Electroencephalography
E2      Estradiol
FSH     Follicle-stimulating hormone
GnRH    Gonadotropin-releasing hormone
HPA     Hypothalamic pituitary axis
HRT     Hormonal replacement therapy
ICD-10  International Classification of Diseases
LH      Luteinizing hormone
LLPDD   Late Luteal Phase Dysphoric Disorder
MADRS   Montgomery-Asberg Depression Rating Scale
MDD     Major depressive disorder
MINI    Mini-International Neuropsychiatric Interview
P       Progesterone
PMDD    Premenstrual Dysphoric Disorder
PMS     Premenstrual Syndrome
PMT     Premenstrual Tension
PMDS    Premenstruelle dysforiskt syndrom
PMTS    Premenstrual tension syndrome
SEM     Standard Error of the Mean
SSRI    Selective Serotonin Reuptake Inhibitors
STAI    State Trait Anxiety Inventory
RCT     Randomized clinical trial
Introduction

History of premenstrual dysphoric disorder (PMDD)

Six hundred years before Christ, Hippocrates wrote: “The blood of females is subject to intermittent ‘agitation’ and as a result the ‘agitated blood’ makes its way from the head to the uterus whence it is expelled” (1). This is probably the first description of what is now referred to as premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD). In the 11th century, the first academic description of PMS appeared, written by a female scholar in Padua, Italy, who described women’s suffering before the onset of menses. In 16th century Italy, Giovani da Padua first described the link between menstruation and depression (2).

In 1835, the English physician James Cowles Prichard presented a description of PMS that is close to modern definitions: “Some females at the period of the catamenia undergo a considerable degree of nervous excitement, morbid disposition of mind are displayed by them at these times, a wayward and capricious temper, excitability in the feelings, moroseness in disposition, a proneness to quarrel with their dearest relatives, and sometimes a dejection of mind approaching to melancholia” (3).

During the 19th century, most patients in psychiatric wards in England were female, and it was assumed by scientists and writers that women were more vulnerable to insanity. Great efforts were made to prove that women, maybe because of their vulnerability, were unsuited for studies and intellectual work (4). During the second half of the 19th century, gynecology developed quickly, mainly because of improved anesthetics and increased number of ovarian operations (4): all suffering and discomfort in women could, in one way or another, be related to the uterus or ovaries. As this was such a common belief, a gynecological examination was recommended for every symptom in a female. This recommendation, in fact, became known as Tait’s law, named after Lawson Tait (5). Thus, gynecology became the specialty for all female problems, physical, neurological and psychiatric (4). Many of the problems described during these times would now probably be classed as premenstrual syndrome or PMDD, although the interpretations were more in terms of hysteria and neurasthenia (6).

In 1931, R.T. Frank was the first to describe PMS (7), although he named it premenstrual tension (PMT): and his legendary work has been cited in many studies and reviews in the field. In the same year, K. Horney, a Ger-
man psychoanalyst, presented a description of premenstrual depression in otherwise healthy women (8). In 1953, Green and Dalton coined the term premenstrual syndrome: in their opinion, the term syndrome was relevant, as it was not only tension that was important (9). In the premenstrual phase, many other symptoms could also be present, and PMS risked being overlooked, if there was no tension. Later, Dalton stated “PMS does exist and has only one definition: it is a syndrome needing treatment... and it is common and has innumerable manifestations....” (10).

Between 1931 and 1962, a number of scientific papers described PMT and associated symptoms: almost 150 different symptoms were described including severe headache, edema, increased weight, oliguria, asthmatic attacks, rhinorrhea, fever, ulcerative stomatitis, lumbar pains, and even nymphomania and other “psychosexual disorders” (11). Nowadays, a discrete cluster of symptoms is outlined in the diagnostic manual of PMDD see further on (DSM-IV, 1994). However, a number of somatic diseases are known to worsen or exacerbate during the luteal phase of the menstrual cycle, although this generally is not referred to as PMS (12). Among the CNS-related disorders linked to the menstrual cycle, migraine and epilepsy are the most commonly known (13).

Even though many different definitions of PMS/PMDD have been proposed, and even more treatments advocated, the female hormones, i.e. estrogen and progesterone are the most studied. Greene and Dalton strongly believed progesterone deficiency caused the symptoms and prescribed progesterone treatment as a viable option in PMS patients (9, 14-15).

In the 1980, the term PMS became known to the layman through feminist writings (16). However, the legal effects of premenstrual agitations were already known the mid 19th century. In 1865, Mary Harris was charged with murdering her lover and during the trial, she explained she periodically had “fits” that coincided with her menstruations: she was later diagnosed with congestive dysmenorrhea and the verdict was not guilty (17-18). In 1961, a study of female prisoners concluded almost half of the women had committed their crimes during the premenstrual or menstrual period (19): premenstrual tension was an important factor in these crimes and 63% of the women had committed their crime at the time of their symptoms (19). In the 1980s, several similar cases were brought to court in the UK, and in 1981, Sandra Craddock, among others, was placed on probation and treatment with progesterone for her PMS (20).

Definition of premenstrual dysphoric disorder

Over the years, it became obvious there was a need for strict diagnostic criteria, as there were many different symptoms addressed as PMS. Many patients had been under-diagnosed, over-diagnosed, and mistreated for their
symptoms. In 1985, the workgroup for DSM-III (The American Psychiatric Association’s Diagnostic and Statistic Manual of Mental Disorder) decided to introduce a subset of PMS conditions where mood disturbance was the dominant symptom: this was the late luteal phase dysphoric disorder (LLPDD). The important change was that psychological symptoms were emphasized, whereas, physical symptoms, although included in the list, were not required for diagnosis. The DSM criteria also stated prospective rating of symptoms was a prerequisite. In the subsequent version, DSM-IV 1994, the syndrome was renamed to premenstrual dysphoric disorder (PMDD): the diagnostic criteria for PMDD are given in Table 1.

Table 1. Diagnostic criteria for PMDD, according to DSM-IV.
A. Symptoms must occur during the week before menses and remit a few days after onset of menstruation. Five of the following symptoms must be present and at least one must be 1); 2); 3), or 4)
1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. Marked anxiety, tension, feelings of being “keyed up”, or “on edge”
3. Marked affective lability (e.g. feeling suddenly sad or tearful or increased sensitivity to rejection)
4. Persistent and marked anger or irritability, or increased interpersonal conflicts
5. Decreased interest in usual activities (e.g. work, school, friends, hobbies), or subjective sense of difficulty in concentrating
6. Lethargy, easy fatigued, or marked lack of energy;
7. Marked change in appetite, overeating, or specific food cravings
8. Hypersomnia or insomnia
9. A subjective sense of being overwhelmed or out of control
10. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, sensations of “bloating”, weight gain
B. Symptoms must interfere with work, school, usual activities, or relationships.
C. Symptoms are not merely an exacerbation of another disorder.
D. Criteria A, B, and C must be confirmed by prospective daily ratings for at least two cycles.

As all these symptoms are also present in major depression, psychiatric disorders need to be excluded. Prospective ratings are crucial for two reasons: for evaluating the recurrence of the symptoms in the luteal phase, and for excluding exacerbation or deterioration of pre-existing mood and/or anxiety disorders.

According to these criteria, the prevalence of PMDD is estimated to about 3-8% among reproductive women living in western societies (21-22). Despite the requirement of prospective symptom ratings, several well-designed epidemiological studies, which use strict criteria, have demonstrated questionnaire- or telephone interview-based diagnoses of PMS/PMDD can be
used for scientific purposes (23-29). These epidemiological studies have rendered prevalence rates comparable to traditional prospective symptom ratings (23-29) and are valuable for estimating stability and time-course (26, 29), associated life-style factors (23-24) and, prevalence rates in different age groups and societies (25, 27-28).

PMT, PMS, LLPDD, PMDD, PMTS, PMDS - confusing terminology

Since the first description by Frank 1931, there have been many different names for this syndrome, including PMT, PMS, LLPDD and PMDD. In 2010 the Swedish Medical Products Agency proposed a new Swedish acronym PMDS (premenstruellt dysforiskt syndrom).

To further increase confusion, proposals to redefine PMS as a lighter form of PMDD have been made. PMS, premenstrual tension syndrome (PMTS), is included in the nomenclature of the gynecological section of The World Health Organization’s International Classification of Diseases, 10th edition (ICD-10); however, the definition is vague and diagnosis depends on the physician’s specialty, awareness and, skills. In the ICD-10, the cyclicity and timing of symptoms according to the menstrual cycle is stressed, but no definition of the severity of symptoms or exclusion criteria are presented.

Another definition of PMS is proposed by the American College of Obstetrics and Gynecology (ACOG) 2000 (30), which implies the presence of at least one out of six affective symptoms and one out of four somatic symptoms. Symptoms should exist during five days before menses and be relieved within four days after the onset of menses. Symptoms cannot be present during the rest of the month and have to be confirmed by prospective ratings (30).

These definitions suggest a dichotomy between PMDD and PMS, which is unclear. Sometimes PMDD is loosely explained as a more severe form of PMS but this is unsupported by any data (31). As this thesis used PMDD criteria according to DSM-IV, this term will be used throughout, if not otherwise stated. As far as possible, reference to papers where PMDD diagnosis is not established by prospective ratings has been avoided, but in certain fields, these studies could not be avoided because of the scarcity of data.

Premenstrual dysphoric disorder – a hormonal approach

Many attempts have tried to prove PMS/PMDD in terms of fluctuations of gonadal steroids but other hormones have also been investigated such as cortisol, testosterone, prolactin and, thyroid hormones. However, neither
excess nor deficiency of these hormones is proven as the cause of the disorder (32-33).

The only consistent endocrine finding in PMDD is that symptoms appear in the luteal phase of the menstrual cycle when a functional corpus luteum is developed. As symptoms disappear during spontaneously anovulatory cycles and during GnRH agonist-induced anovulation (34-41), it is suggested progesterone produced by the corpus luteum is the main symptom-provoking agent. However, the exact mechanism by which progesterone precipitates the symptoms of PMDD is unknown, although interactions with the serotonin system (42) and the GABAergic system (43-45) are plausible.

Even though progesterone appears the main symptom-provoking factor in PMDD, the role of estradiol is less well studied. Studies of postmenopausal women indicate higher doses of estradiol, when combined with progestagens, are more symptom-provoking than lower doses of estradiol (46). Furthermore, within individual PMDD patients, menstrual cycles with higher estradiol levels are associated with more pronounced symptoms (47) and, estradiol on its own appears to be as symptom provoking as progesterone on its own (48). PMDD patients have a differential gonadotropin response to estradiol challenge (49) and tend to react with adverse mental changes when given a predominantly estrogen contraceptive treatment (50).

Induced anovulation is successful treatment for PMDD, but the clinical use of this specific treatment is limited by the hypo-estrogenic side effects and by the long-term risk of bone demineralization (51). In order to eliminate the side effects and long-term risks, add-back with a cyclic combination of estradiol and progestagens have been tried in several studies. Although some authors report alleviation of PMS symptoms through GnRH analogue treatment is maintained during estrogen and progestagen add-back (35, 39-40, 51), others have found women with PMS to be intolerant to progestagens (38, 48); however, there is no evaluation of the optimal add-back hormone replacement therapy (HRT) in PMDD patients.

PMDD – the psychiatric perspective

As PMDD is mainly characterized by mood symptoms, it is diagnosed according to DSM-IV and treated with antidepressants and, the syndrome has predominantly interested US psychiatrists. There are numerous pathophysiological similarities between PMDD and major depression and, between PMDD and anxiety disorders. However, many epidemiological and clinical studies suffer from major shortcomings, such as selection bias, retrospective symptom ratings or, inadequate prospective ratings. In addition, women seeking care in PMS clinics might not be representative of the average woman with premenstrual symptoms or PMDD. Clinical samples may be
prone to the use of psychotropic drugs or, have had one or more episode of depression.

Up to the age of 50-60 years, major depression (MDD) is twice as common in women as in men (52). Thus, lifetime prevalence of major depressive disorder is reportedly increased in women with PMDD, found in approximately 30-70% of patients (53). There is an association between PMDD and post-partum depression, and 29% of parous PMDD patients experience post-partum depression of more than one month’s duration (54). In a group of 92 females with bipolar depression, Fornaro et al (55) found 27.2% had retrospective PMDD diagnosis.

Depressive disorders are more common among women in childbearing ages and attention has focused on hormonal, biochemical and neurophysiological abnormalities and, as there are many associations between major depressive disorders and PMDD, interactions between the disorders have been studied. The most focus is on serotonin, a neurotransmitter identified in the 1950s by Brodie et al (56), which is involved in several physiological processes such as aggression, impulse control, anxiety, sexual behavior, pain, sleep and appetite. Dysfunction of serotonergic transmission is considered an important mechanism in several psychiatric disorders, primarily major depression and anxiety disorders (57-59). Serotonergic dysfunction also contributes to PMDD, with the tremendous efficacy of selective serotonin reuptake inhibitors (SSRI) being the most convincing evidence (60). In a study by Jovanovic et al, the 5-HT1A receptor binding potential in the dorsal raphe nuclei relative to the menstrual phase differed in women with PMDD and asymptomatic controls. In the asymptomatic controls there was a higher binding potential in the luteal phase than in the follicular phase, whereas, this menstrual cycle effect was not present in PMDD patients (61). Furthermore, brain serotonin precursor trapping is inversely associated with premenstrual irritability and depressed moods in women with PMDD (62).

Although menstrual cycle related changes in serotonin function are consistently reported in healthy women (63-68) (however, see (69)), findings in PMDD patients are less conclusive. Some studies identify the expected luteal phase alteration (70-76), whereas, others find no difference from controls (77-80), or differences confined to the follicular phase (81-83). Thus, the changes in serotonergic neurotransmission is may be a trait finding in PMDD, rather than the key event leading up to symptom surfacing in the luteal phase (84).

Altered sleep is commonly reported by women diagnosed with PMDD and is one of the criteria for diagnosis. Evaluations of objective polysomnographic recordings in PMDD patients are inconsistent. In a study from 1999 (85), no differences in sleep electroencephalography (EEG) between PMDD patients and controls was found, but there was a difference between the follicular phase and luteal phase. In another study, sleep-quality was measured by
laboratory-based polysomnographic recordings, sleep-EEG and, self-recorded sleep in two phases of the menstrual cycle (86). Generally, both PMDD patients and controls showed the same sleep-EEG differences across the menstrual cycle, with increased spindle activity in the luteal phase, compared to follicular phase. However, some small trait-like differences in sleep-EEG was found in women with PMDD (86). Compared with MDD, there is no consistency in the quality of EEG analysis, which may partly be due to variation in disease severity and expression. Furthermore, PMDD is not a homogenous disease, some women experience more depressive symptoms and others may suffer predominantly from anxiety and irritability, which may account for the different outcomes (87).

Few studies examine co-morbidity of PMDD and depressive and anxiety disorders; although there are two studies investigating the incidence of depressive disorders and PMDD in community samples. In a well-designed longitudinal community survey of 1488 women (29), co-morbidity rates were 47.4% for anxiety disorders and 22.9% for mood disorders: only 26.5% had no other mental disorder. As expected, co-morbidity with depressive disorders is associated with PMDD symptom profile. A higher frequency of co-morbid depression is found in women who predominantly reported depressive symptoms in the premenstrual phase, whereas, women with more pronounced irritability are less likely to be diagnosed with co-morbid depressive disorders (88).

PMDD is suggested to be a risk factor for major depression, although conclusions from available prospective studies are limited by relatively small sample sizes (89-90). Generally, although PMDD and MDD have much in common, there are several differences. The most obvious difference is the response to SSRI treatment, where a rapid treatment effect is observed in PMDD patients (91), whereas, the treatment effect in depression is usually not observed until after 4-6 weeks of treatment. Another difference is the treatment response to GnRH agonist, which is useful for PMDD patients but, is ineffective in women with premenstrual worsening of major depression (36).

For anxiety disorders, there is sparse evidence for an association with PMDD, with the exception of panic disorder. Of the seven experimental panic challenge studies in women with PMDD, reviewed by Vickers and McNally (92), the most convincing study used CO₂ inhalation or placebo, which induced panic in 64% of PMDD patients but none of the controls responded with panic symptoms. Other experimental panic challenge studies with sodium lactate, cholecystokinin-tetrapeptide (93) and flumazenil (94) report similar, although less pronounced findings. The predisposition to panic response is a commonality that cannot be explained by a history of panic attacks in PMDD women (95).
PMDD the psycho-social perspective

Whether premenstrual symptoms should be regarded as a disease, illness or just every woman’s normal cyclicity has been argued for many decades. As more than 90% of women suffer symptoms to some extent (both physical and psychological) in the days before onset of menstruation, it has been argued whether premenstrual syndrome and premenstrual dysphoric disorder could be classed as syndromes (96).

One of the major reasons for not accepting PMDD and PMS as syndromes is that women are considered warm and gentle. When a woman expresses feelings of irritability and anger, it is not accepted by herself or her family. When cultural beliefs describe premenstrual women as erratic and even dangerous, it will restrict women’s opportunities in society (97).

Some authors argue PMS or PMDD are not biologically driven diseases but is a socially learnt phenomenon or a market driven indication (98). This hypothesis suggests every woman learns how she should relate to her menstruation. Menstrual-related expectations and attitudes were investigated in a group of college students in the 1970s (99) and the findings were more complex than previously thought, involving differential perception of physical and psychological symptoms and a variety of dimensions of menstrual-related attitudes. Attitudes towards menstruation and own experiences of menstruation are reported to have an association with premenstrual symptoms in family members and negative messages during adolescence (100). Furthermore, young women whose mothers encouraged them to adopt a sick role during their menses, later report more premenstrual symptoms (101). In 2003, Ussher concluded “premenstrual symptoms arise out of an ongoing interaction of material, discursive and intrapsychic phenomena, with family relationship being one of the major arenas in which PMS emerges” (102).

Treatments for PMDD

As well as describing premenstrual tension, Frank also suggested a number of possible treatments for the syndrome including venisection, calcium lactate in combination with caffeine and, roentgen therapy of the ovaries. However, roentgen therapy was not to be used in milder cases, as it could provoke severe neurovascular problems of menopause in nervous labile women (7).

SSRIs are now used as a first-line treatment for PMDD and, the clinical effects, in particular for psychological symptoms, are documented (42, 103). Forty randomized clinical trials were included in the 2009 Cochrane review, which concluded an overall reduction of symptoms for all tested SSRI, compared to placebo (60). After the Cochrane review, a placebo-controlled trial (104) on two different doses of luteal phase ecitalopram (10 and 20 mg/day)
reported a 90% decrease in irritability, depressed mood, tension and affected lability with the higher dose and, a response rate among participants of 80%. The optimum duration of treatment has not been settled. Relapse rate is reportedly greater after short-term (4 months) treatment than with long-term treatment (12 months) and subjects with more severe symptoms at baseline are more likely to relapse than those with less pronounced symptoms (105).

Serotonin and noradrenaline reuptake inhibitor (SNRI) compounds are less well studied. Thus far, the largest randomized clinical trial (RCT) on venlafaxine enrolled 143 women, who were given continuous treatment. In the first (of four) treatment cycles, less symptoms were reported in the venlafaxine group than in placebo (106): similar results with venlafaxine are reported from a smaller study (107).

Whether intermittent or continuous SSRI treatment is the superior treatment regimen is under debate. In the largest RCT (108) on intermittent and continuous treatment, the efficacy for the psychological symptoms was similar between the two treatment groups, and subjects reporting more depressive symptoms were more likely to be better off with the continuous treatment (108). The rationale for intermittent treatment is based on the short onset of effect of SSRI in PMDD patients. The number of women experiencing SSRI-induced reduction in irritability is higher than for placebo even 14 hours after drug uptake, whereas, symptom ratings of irritability reached significance by day three (91).

Although SSRI treatment tremendously improves the lives of women with PMDD, the side effects of SSRI, especially sexual dysfunction, may be intolerable for many women (109). Decreased libido and other side effects are often the direct cause for termination of SSRI therapy, reflected by the high rate of withdrawal in clinical trials and in follow-up studies of PMDD patients who have been prescribed SSRI in the clinic (42, 110). Therefore, it is necessary to provide additional efficient and safe treatment options for women who are unable to comply with SSRI treatment.

Although not a first line therapy, gonadotropin releasing hormone (GnRH) agonist treatment is still important. In comparison with the SSRI, the evidence is limited; a meta-analysis only included four studies where women had proven anovulation. Nevertheless, the meta-analysis concludes GnRH agonist induce an overall improvement in all premenstrual symptoms, including physical ones (111). In addition, a low-dose GnRH regimen aimed at reducing corpus luteum function without inducing anovulation, thus, improving symptoms, has been evaluated, but, the effect of treatment was only evident in anovulatory cycles and, ovulatory cycles did not differ from placebo (41). The major drawback of GnRH agonist is that it induces a climacteric state, with vasomotor symptoms and increased risk of bone demineralization; therefore, it is important to include estrogens for preventing hot flashes and the risk for osteoporosis. Add-back hormone replacement ther-
apy (HRT) with GnRH agonists has been evaluated in three RCTs but with no significant reduction in efficacy (111). The most suitable add-back HRT to GnRH agonist treatment has not yet been evaluated.

Besides these treatments (and oral contraceptives), numerous treatments for PMS/PMDD have been advocated over the years. Among these are high dose progesterone, spironolactone, calcium, herbal drugs and, vitamin preparations. The results have been variable and few of these treatments are evaluated in studies of acceptable quality. In a systematic review from 2009 (112), sixty-two herbs, vitamins and minerals were identified as potential treatment for PMS/PMDD, but RCT-based evidence was only found in ten of them, and only calcium had sufficient quality of evidence for use in PMS.

Non-pharmacological treatments such as cognitive-behavioral therapy (CBT), acupuncture and homeopathic remedies have been suggested as treatment of PMS/PMDD. CBT has been evaluated in seven different studies, of which three were RCT and included prospectively diagnosed PMS/PMDD patients; however, the scientific evidence was low and methodological flaws lowered the strength of all three studies. Although CBT is a possible option for less severe symptoms and as a complement to medical treatment in special cases, further studies are needed (113). The evidence for acupuncture as a treatment is limited because of various methodological flaws in trials (114). Homeopathic medicine is poorly studied and a review (115) of one RCT study from 2001 found poor evidence for homeopathy as a form of treatment.

Progesterone therapy has been used for premenstrual syndrome since the 1950s. In a Cochrane review on progesterone treatment (116), only two studies of 17 were RCT and double-blinded: both studies had methodological flaws and there was limited evidence for relief with progesterone treatment. With the multitude of treatment options available, prescription patterns vary in different parts of the world. In North America and the UK, the US guidelines on the use of SSRI are generally followed. In France and UK various analgesics and hormonal therapies are mostly prescribed, and in Germany is Vitus agnus-castus the most common treatment (117).

**PMDD and oral contraceptives**

The oral contraceptive pill has been in the market for fifty years, and the number of users has grown rapidly. It is the most common contraceptive method and most women report unchanged or improved wellbeing (118). Even in the 1960s, it was hoped oral contraceptives could be used to treat premenstrual symptoms but, placebo-controlled studies were (possibly) not feasible and clinical trials were restrained to uncontrolled trials (119) or head-to-head comparisons between different oral contraceptives (120).
Over the years, combined oral contraceptives (COC) have been revived as a potentially useful treatment for PMDD (121), mainly due to the publication of two placebo-controlled, randomized clinical trials of a COC containing a low-dose ethinylestradiol (20 μg) and drospirenone for treatment of PMDD (122-123). Although the results of these two trials are promising, long-term studies are needed before clinical usefulness can be established. After the successful results of these two trials, other pharmaceutical companies began evaluating potential COC for the treatment of PMDD.

However, from a clinical perspective many women with PMDD claim they are unable to use oral contraceptives because of mood deterioration. Patients with premenstrual symptoms may suffer more from adverse mood symptoms during COC use than healthy women (50), and certain combinations or different progestogens may be less suitable for women with premenstrual syndrome (PMS), such as triphasic compounds (120) and levonorgestrel containing COCs (120). Women who use COCs and respond with negative mood symptoms could be hypothesized as having more severe premenstrual symptom or PMDD, although this remains to prove.

Adverse mood symptoms during treatment with combined oral contraceptives

When COC were introduced, the adverse mood symptoms from treatment attracted attention (124-126). Despite COC having been available for 50 years, little is known about the prevalence of truly COC-related adverse mood symptoms or the underlying neurobiology of these changes in mood and their effects. This may be due to the difficulty in designing studies where drug-related causality can be established. Placebo-controlled trials are unfeasible for healthy women with contraceptive needs and clinical trials evaluating safety and adverse event profiles in COC users are hampered by the high rates of users with negative expectations and high discontinuation rates (possibly resulting in a “healthy survivor” effect) (127).

One of the few placebo-controlled COC clinical trials was presented by Johan Cullberg (50) in his monographic thesis. Three hundred women were randomized to three different combined oral contraceptives or placebo; the women were unaware they were taking a contraceptive instead of a “weak female hormones or sugar pills”. This precaution was to minimize the negative expectation associated with oral contraceptive use, although ultimately, most women were right about being treated with hormones or placebo. The COC used contained different amounts of gestagen, whereas, the ethinylestradiol dose was constant, thus, evaluating preparations with different gestagenic profile. The overall mental change during the study was rated as unchanged by slightly more than 50% in all four treatment groups, and there
was no significant difference in either worsening or improvement. Conversely, when treatment groups were compared group wise to placebo, there was significant adverse mental change in the treated groups. The subjects were sub-grouped according to self-rated premenstrual symptoms: 60% were symptom free or “deniers”. The remaining women were classified into three groups: mainly psychological premenstrual symptoms but low scores for neuroticism; mainly psychological premenstrual symptoms and a high neuroticism score; and, mainly somatic premenstrual symptoms. All symptom groups responded more negatively to the low-gestagen pill than the symptom free group, whereas, the responses to COC with higher gestagen doses were similar between all groups.

There are few clinical trials where well-being, mood and anxiety are included as primary outcome measures, and much of the reporting of mood effects arises from the adverse-effect reporting within trials. In addition, very few clinical trials have addressed mood-related side effects prospectively. In one prospective observational study with 3679 participants (118), 10% of women reported adverse mood symptoms and 7% reported increased anxiety. Among adolescent girls prescribed OC for dysmenorrhea, depressed mood was assessed with the Center for Epidemiologic Studies Depression Scale (CED-D): the mean CED-D scores decreased slightly during the study, and was the same in a subgroup of potentially more vulnerable women with higher depression scores at baseline (128). A large community-based study including 1716 mainly poor, young, Hispanic women found that although the majority were satisfied with the pill (at least among the previous users), at 6 months, 57% of the participants had discontinued. The authors conclude women who report increased headache and moodiness during the first months of OC use are more likely to discontinue, even though only half of the subjects attribute the symptoms to the pill (129). In retrospective studies, the rates for adverse mood effects are usually higher than in prospective studies (130): the most common drug-related reason discontinuing COC treatment is adverse mood symptoms (131). In a Spanish study, the pill users reported a high frequency of noncompliant behavior and noncompliant behavior, in turn, had negative effects on work activities and relationships (132).

Not all adverse mood symptoms experienced by COC users can be assumed drug-related. Psychiatric history, personality traits, interpersonal relationships and, socioeconomic factors are can also contribute to adverse events often attributed to COC treatment (133).
Domestic Violence and PMDD

Violence and sexual assault are underestimated health problems among women worldwide, and occur across all social settings (134). Lifetime experience of partner violence is associated with self-reported ill health, emotional distress, suicidal thoughts and, suicidal attempts (135). A Swedish prevalence study (136) reported 7% of married (or cohabiting) women had experience of physical violence at some time by their current male partner, and 28% from a former partner.

Within the gynecological setting, the prevalence rates are likely to be increased, as the experiences of lifetime physical, emotional and sexual abuse are associated with gynecological problems (137-139). Prevalence rates of lifetime abuse among gynecological patients in a Nordic cross-sectional study (139) were 38-66% for physical abuse, 19-37% for emotional abuse and 17-33% for sexual abuse.

As violence and sexual assault are associated with emotional distress and menstrual problems, it can be assumed that women with premenstrual dysphoric disorder may have experience of lifetime physical and/or sexual abuse. In two small studies, a history of sexual abuse was more common among PMDD patients than among control subjects (140-141).

To address the scarcity of data regarding PMDD and physical and sexual abuse, it is benefit to estimate prevalence rates of physical, emotional and sexual abuse in a cohort of patients with prospective diagnosed PMDD.

Chronic stress and PMDD

In the clinic, many women with PMDD state their symptoms worsen during periods of intense workload and stress, and these complaints are confirmed by recent epidemiological studies (142-143). In humans, the price of repeated biological adaptation to stress is termed allostatic load and refers to the long-term effect of physiologic responses to stress (144). Allostatic overload may be expressed as: repeated elevations of cortisol or other neurohormonal stress mediators over long periods; a failure to adapt to a certain stressor; a failure to shut off the normal stress response; or, as an inadequate hormonal response to stress that may allow other systems that are normally counter-regulated to become overactive, eventually resulting in hypoactivation of the stress response (144). Both animal and human studies indicate chronic or severe stress exposure, especially early in life (145), can result in persistent alterations in neurobiological systems that are stress responsive (146-147): this is also true for women with PMDD (140-141, 148).

Many depressed patients, especially those with melancholic depression, display signs of hypothalamus-pituitary-adrenal (HPA) axis dysregulation, such as hypercortisolism (52, 149), chronic activation of the HPA axis, in-
cluding greater corticotrophin releasing hormone (CRH) concentrations and gene expression (150-151), altered cortisol responses to psychological stressors (152) and, dysregulation in glucocorticoid negative feedback mechanisms or altered circadian rhythm (153-155).

HPA axis dysregulation is less well studied in PMDD patients, but results suggest blunted HPA axis function in PMDD. For example, a lower circulating adrenocorticotropic hormone (ACTH) or cortisol concentrations in PMDD women is reported (141, 156-157) (however see (158-159)), but especially in those with history of previous major depressive disorder (160). Furthermore, PMDD patients display increased ACTH response to CRH (156), blunted HPA axis response to serotonergic agents (82, 161) and, absence of normal plasma cortisol and ACTH responses to exercise stress in the luteal phase (162).

Progesterone metabolites are also involved in the stress response, and the most studied of the progesterone metabolites is allopregnanolone. After swim stress in male rats, a 4- to 20-fold increase in cortical allopregnanolone concentration has been observed (163). Allopregnanolone attenuates methoxamine-stimulated CRH release and to prevent gene expression of CRH in the rat hypothalamus after adrenalectomy (164). Pretreatment with allopregnanolone attenuates the elevation of plasma ACTH and serum corticosterone after emotional stress (164). Thus, these findings suggest allopregnanolone plays a role as an endogenous stress-protective compound.

Two studies have assessed allopregnanolone response to stress in PMDD patients, with variable results. Girdler et al (165) found decreased allopregnanolone response to speech stress (instead of an expected increase). However, the same group failed to reproduce these results, except for PMDD patients with a prior history of depression (166).
Aims

The aims of this thesis were:

- to compare the prevalence of mood and anxiety disorders in women with different experience of oral contraceptives (Paper I)

- to investigate which add-back hormone replacement therapy would be most beneficial in terms of mood effects for premenstrual dysphoric disorder patients on GnRH agonist treatment (Paper II)

- to investigate if domestic violence was more common among PMDD patients than among healthy women or other gynecologic patients (Paper III)

- to investigate if PMDD patients displayed hypothalamic-pituitary-adrenal axis dysregulation compared with healthy controls (Paper IV)
Material and Methods

Study populations

Paper I
This study was undertaken at the Department of Obstetrics and Gynecology at Uppsala University Hospital, Uppsala, Sweden. Two-hundred and eighty-five women with ongoing or past experience of combined oral contraceptives (COC) were screened for inclusion. Patients were recruited by advertisement in newspapers and on advertisement boards at Health Care Centers. After telephone screening, 118 women with different experience of COCs were included in the study. Of those, 30 women were currently on COCs with no report of adverse mood symptoms (COC-fine), 28 women were currently on COC and experienced mood-related side effects (COC-mood), 27 women had discontinued COC use for reasons other than adverse mood symptoms (pCOC-fine) and, 33 women had discontinued COC use due to adverse mood effects (pCOC-mood).

Inclusion criteria for COC-fine subjects were they did not report any adverse mood effects on the current COC and they had never changed COC brands due to adverse mood effects in the past. The inclusion criterion for the COC-mood group was they reported mood symptoms, such as increased depression, anxiety, mood swings or irritability during ongoing COC use. The pCOC-fine group was required to have discontinued COC use for reasons other than adverse mood symptoms, for example because of planned pregnancy or end of a relationship. The pCOC-mood group had discontinued COC due to adverse mood effects. Further inclusion criteria for both groups of prior COC users were regular menstrual cycles (between 25 and 31 days) and no use of hormones or hormonal contraceptives (including the hormone releasing intrauterine device) during the last three months.

Ongoing psychiatric disorders were evaluated by a structured psychiatric interview (M.I.N.I) (167) and, prevalence rates of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) was assessed by daily prospective ratings on the Cyclicity Diagnoser Scale (41).
Papers II-IV

These studies were undertaken at the departments of Obstetrics and Gynecology at three different Swedish hospitals: Uppsala University Hospital, Umeå University Hospital and, Sundsvall Hospital. Patients were recruited from women seeking help for premenstrual symptoms at the outpatient obstetric-gynecology wards of the participating clinics and from advertisements in local newspapers. In all 58 PMDD patients were included in the studies for Papers II – IV: 27 women took part in the study for Paper II, of which 18 also participated in the study for Paper IV.

For the purpose of Paper II, ninety-six women were screened for the; however, 47 women did not fulfill the inclusion criteria. The remaining 49 women were enrolled into the screening phase of the study, of which, 27 women fulfilled the diagnostic criteria for PMDD. Hence, 27 patients, aged 25 to 47 years and who had experienced premenstrual mood changes for more than six months were included.

For the studies in Papers III and IV, 47 asymptomatic healthy controls were recruited, who were physically healthy aged 20-46 years and had regular menstrual cycles with no self-report of premenstrual symptoms. According to the daily prospective ratings, control subjects displayed no significant cyclicity in mental symptoms between the follicular and luteal phase and, impact on daily life never exceeded a score of two during the luteal phase (no impact or only the patient notices any symptoms).

A second control group consisting of 102 gynecological outpatients was recruited for the study in Paper III. All women seeking care at the gynecologic outpatient ward at the department of Obstetrics and Gynecology, Sundsvall Hospital, were invited: the response rate was 82.3%.

Among the PMDD patients included, only 22 were able to participate in complete diurnal blood sampling: the most common reason for non-compliance was lack of time. Hence, complete diurnal blood sampling was available for 22 PMDD patients, whereas, saliva samples (before and after dexamethasone suppression) were available for 26 PMDD patients. All control subjects had complete blood and saliva samples.

The exclusion criteria for both PMDD patients and healthy controls were ongoing treatment with any hormonal compounds, ongoing treatment with benzodiazepines or other psychotropic drugs, including serotonin reuptake inhibitors and, presence of any ongoing psychiatric disorder. The presence of psychiatric disorders was evaluated with a structured psychiatric interview (M.I.N.I.).
Methods

PMDD diagnosis

The PMDD diagnoses in Papers II-IV were based on daily, prospective symptom ratings on the Cyclicity Diagnoser (CD) scale during one to two cycles prior to inclusion (41). Patients severely disabled by PMDD symptoms, and who fulfilled PMDD criteria during the first screening cycle, were not required to score symptoms for more than one cycle. The CD scale consists of eight negative mood parameters (depression, fatigue, irritability, anxiety, mood swings, affected lability, difficulties in concentrating and, sleeping disturbances), three positive mood parameters (interest in usual activities, cheerfulness, energy) and, four somatic symptoms (food cravings, bloating, breast tenderness and, menstrual bleeding). In addition, the CD scale contains a score for measuring every-day social functioning and work performance. The CD scale is a Likert scale ranging from 0 - 8, with 0 being complete absence of a particular symptom and 8 as the maximal severity of the symptom. Patients were considered to have PMDD if they had a 100% increase in at least five symptoms during seven premenstrual days, compared to seven mid-follicular days, and associated with a clinically significant social and occupational impairment. The threshold score for impact on daily life was set at a score of four or more for at least two days during the luteal phase. This score indicated subjects avoided social interaction during these days. All patients displayed at least one week of sparse symptoms (scores less than two) in the mid-follicular phase.

PMDD diagnosis in prior COC-users

Provisional diagnosis of PMS and PMDD were based on prospective symptom ratings on the Cyclicity Diagnoser (CD) scale (Paper I). Diagnoses were provisional as they were based on prospective daily ratings made by the women during 36 days after the visit to the clinic, and not for two entire menstrual cycles, as stipulated in the criteria for PMDD (defined in DSM-IV, 1994) or PMS (according to the American College of Obstetricians and Gynecologists (30)). Details on the diagnostic procedures are presented in Paper I.

Psychiatric diagnostic interviews

All participants (Papers I, II and IV) and PMDD patients and healthy controls (Paper III) were evaluated for the presence of any psychiatric disorder with the Swedish version of Mini International Neuropsychiatry Interview (M.I.N.I.), based on DSM-IV and ICD-10 (167). M.I.N.I is based on a standardized algorithm of questioning that is easily administered and is validated
with high specificity across major Axis I psychiatric disorders and is compatible with ICD-10 and DSM-IV (167). M.I.N.I. evaluates a number of mood disorders (major depressive disorder, dysthymia, bipolar disorder) and anxiety disorders (panic disorder, generalized anxiety disorder, obsessive-compulsive disorder and, social phobia). In addition, two sub-threshold diagnoses such as minor depressive disorder and anxiety UNS were assessed with M.I.N.I. (Paper I). Ongoing anxiety symptoms were evaluated by the State and Trait Anxiety Inventory (STAI) (168).

Abuse Assessment Screen

To collect information on physical and sexual abuse, the Abuse Assessment Screen (ASS) Swedish version (169) was chosen, which has previously been validated in a Swedish Maternity Care setting (170). For the purpose of the present study, the question concerning physical abuse during pregnancy was omitted. The questions included in the AAS were:

1) Have you ever been emotionally or physically abused by your partner or someone important to you? (Yes/No).

2) During the last year, have you been hit, kicked or shoved or, otherwise physically hurt by someone? (Yes/No). If yes, by whom? (Husband, ex-husband, boyfriend, ex-boyfriend, stranger, other).

3) Have you ever been forced to participate in or subjected to sexual activity against your will? (Yes/No) If yes, at what age? (0-12; 13-19; 20 or older). If yes, by whom (husband, ex-husband, boyfriend, ex-boyfriend, acquaintance, other).

4) Are you afraid of your partner or anyone you have mentioned here? (Yes/No).

Hormone analyses

Progesterone serum concentration was analyzed on Immulite 1000 (DPC, Los Angeles, CA, USA). Progesterone intra-assay coefficient of variation was 16% at 2.9 nmol/L and 6.3% at 25.1 nmol/L.

Allopregnanolone in serum were analyzed by radioimmunoassay (RIA) for serum and tissue after extraction with diethyl ether and purification with high performance chromatography (HPLC). The antibody used was raised against 3α-hydroxy-20-oxo-5α-pregnan-11-yl carboxymethyl ether coupled with bovine serum albumin as antigen (AgriSera AB, Umeå, Sweden). Due to the cross reactivity of the antibody, separation by HPLC was used before radioimmunoassay. All samples were counted in a RackBeta (Wallace, Finland) scintillation counter. The radioimmunoassay and extraction procedure are described by Timby et al (171) and the chromatography procedure is described by Turkmen et al (172).
Saliva cortisol was measured by radioimmunoassay designed for quantitative measurements of cortisol concentrations in human saliva (Orion Diagnostica Oy, Espoo, Finland). All salivary samples were collected in Salivette saliva collecting tubes and stored in -20°C until analysis. The serum cortisol levels were analyzed with a solid-phase, competitive chemiluminescent enzyme immunoassay (Siemens medical solutions diagnostics, Los Angeles, USA).

Study protocols
Paper I
Paper I was a cross-sectional study, and part of a larger study evaluating different aspects of adverse mood symptoms in COC users.

Paper II
The effect of three different add-back hormone replacement treatments (HRT) in combination with leuprolide acetate on daily symptoms was evaluated in a randomized, double-blinded, crossover design (Figure 1).

![Figure 1. Schematic description of the study design (Paper II).](image-url)
Leuprolide acetate (Enantone Depot®, Orion Pharma, Espoo, Finland) was given openly in a dose of 3.75 mg as a first subcutaneous injection, followed one month later by a subcutaneous injection of 11.25 mg: the effect lasted for the remaining three months of the study. During the first month of leuprolide acetate treatment, no add-back HRT was given. The add-back HRT was administered during three 28-day cycles and started at the same time as the second leuprolide acetate injection. The add-back treatments consisted of continuous, daily transdermal administration of estradiol gel, with a vaginal progesterone or placebo addition during the last 14 days of each treatment cycle. The different treatment cycles were:
1) 1.5 mg estradiol gel once daily in combination with 400 mg vaginal progesterone once daily during the last 14 days of the study cycle (1.5E2P)
2) 1.5 mg estradiol gel once daily in combination with placebo once daily during the last 14 days of the study cycle (1.5E2-only)
3) 0.5 mg estradiol gel once daily in combination with 400 mg vaginal progesterone once daily during the last 14 days of the study cycle (0.5E2P)
The primary outcome was the mean daily symptom ratings on the CD scale during the last ten days of each treatment cycle.

Paper III
Paper III had a cross-sectional design. Fifty-eight PMDD patients and 47 healthy controls were included in the study. It was assumed prevalence rates of lifetime physical, emotional and sexual abuse were likely to be increased in the gynecologic setting, thus, a second control group was recruited, which consisted of 102 women seeking care at the gynecologic outpatient ward at the department of Obstetrics and Gynecology, Sundsvall Hospital. Consecutive patients at this center were approached during four one-week periods in 2008. All scheduled and walk-in patients who presented with acute gynecologic problems were approached and asked to participate in the study. At this center, acute patients are given rapid appointments (within a few days or the same day) and are attended by one gynecologist. Exclusion criteria for participation in this study were age younger than 18 years or older than 45 years; patients were too ill or in severe pain; patients attended the clinic with their partner; patients scheduled for legal abortion; and, patients who did not provide informed consent.

The Swedish version of the Abuse Assessment Screen (AAS) was used to collect information on physical and sexual abuse. For PMDD patients and asymptomatic controls, the AAS interviews were performed by the physician who established their PMDD/control status. All women who acknowledged ongoing abuse were offered help.
Paper IV

Blood samples were collected at set times during one day and night during the luteal phase (1-7 days prior to menstruation). After an overnight fast, women arrived at the Department of Obstetrics and Gynecology by 07.30. Blood samples were drawn at four set times: 08:00, 11:00, 16:00 and 23:00. To provide as accurate results as possible, the women were not allowed to eat two hours before each sampling and had to arrive at the clinic 30 minutes prior to sampling to calm down.

At 08:00 on the same morning as the blood samples were taken, a salivary sample was also taken and, at 23.00 the same day, the patient was administered 0.25 mg of dexamethasone (Oredexon Organon Dexamethasonum manufactured by N.V. Organon, Oss, The Netherlands) for the low-dose dexamethasone test. The next morning at 08.00, another sample of saliva was collected and posted to the clinic. The women were asked not to drink, eat or smoke before sampling. As the standard dose of 1 mg of dexamethasone can cause hyper-suppression of cortisol, a lower dose of 0.25 mg was used, thus, increasing the possibility of detecting more subtle disturbances in feedback sensitivity in the HPA system (173).
Results

Paper I

Similar prevalence rates for psychiatric disorders (any mood disorder and/or any anxiety disorder) were found among ongoing users of COC with current reports of adverse mood symptoms, and among previous users with a history of COC-induced adverse mood (Table 2). Mood disorders were more common in both the COC-mood and pCOC-mood groups, compared with their control groups. Prevalence of any anxiety disorder did not differ between the four groups (Table 2).

Self-reported PMS was more common in the COC-mood and pCOC-mood groups than their control groups (Table 3). However, there was no difference in prospectively defined PMS or PMDD between the pCOC-mood and pCOC-fine groups (Table 3).

Table 2. Prevalence of depressive and/or anxiety disorders in women with ongoing or previous use of combined oral contraceptives and with different experiences of adverse mood effects.

<table>
<thead>
<tr>
<th></th>
<th>COC-fine (n=30)</th>
<th>COC-mood (n=28)</th>
<th>pCOC-fine (n=27)</th>
<th>pCOC-mood (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any psychiatric diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any mood disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>0</td>
<td>1 (3.6%)</td>
<td>0</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Minor depression</td>
<td>0</td>
<td>3 (10.7%)</td>
<td>0</td>
<td>5 (15.2%)</td>
</tr>
<tr>
<td><strong>Any anxiety disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>0</td>
<td>1 (3.6%)</td>
<td>1 (3.7%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1 (3.3%)</td>
<td>3 (10.7%)</td>
<td>0</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>0</td>
<td>1 (3.6%)</td>
<td>0</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1 (3.3%)</td>
<td>2 (7.1%)</td>
<td>1 (3.7%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>1 (3.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Significantly different from pCOC-fine, p < 0.05, Chi-Square Test
\(^b\) Significantly different from COC-fine, p<0.05, Chi-Square Test

Some women had more than one diagnosis
Table 3. Prevalence of self-reported PMS and prospectively defined symptom cyclicity, PMS and PMDD.

<table>
<thead>
<tr>
<th></th>
<th>COC-fine (n=30)</th>
<th>COC-mood (n=28)</th>
<th>pCOC-fine (n=27)(^d)</th>
<th>pCOC-mood (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self reported PMS</td>
<td>10 (33.3%)</td>
<td>18 (64.3%)(^a)</td>
<td>13 (48.1%)</td>
<td>27 (81.8%)(^b)</td>
</tr>
<tr>
<td>Duration of PMS, years (range)</td>
<td>4 (0 - 8)</td>
<td>5 (0 - 15)</td>
<td>7 (0 - 11)</td>
<td>6 (0 - 14)</td>
</tr>
<tr>
<td>Contacted physician for PMS</td>
<td>0</td>
<td>3 (16.7%)</td>
<td>0</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Received treatment for PMS</td>
<td>0</td>
<td>1 (5.6%)</td>
<td>0</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Significant luteal worsening of at least five symptoms</td>
<td>1 (3.4%)</td>
<td>4 (14.8%)</td>
<td>5 (20.8%)</td>
<td>13 (39.4%)</td>
</tr>
<tr>
<td>Prospective PMS(^c)</td>
<td></td>
<td></td>
<td>4 (16.7%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Prospective PMDD(^c)</td>
<td></td>
<td></td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) significantly different from COC-fine, p< 0.05, Chi-Square Test
\(^b\) significantly different from pCOC-fine, p<0.05, Chi-Square Test
\(^c\) PMS and PMDD diagnoses according to DSM-IV, however, diagnoses are provisional as prospective ratings were only recorded for 36 days. Only prior COC users were evaluated.
\(^d\) Prospective ratings were available in 24 of 27 pCOC-fine subjects.

**Paper II**

Of the 27 PMDD patients included in the clinical trial, two patients (7.4%) dropped out due to adverse side effects of the GnRH agonist treatment (sweating and headache). Consequently, 25 patients completed the study.

Despite the 18-day wash-out phase during each treatment cycle, significant carry-over effects were evident in all rated negative mood symptoms (cut-off for significant carry over, \(p<0.1\); irritability, \(p=0.005\); anxiety, \(p=0.072\); depression, \(p=0.098\); mood swings, \(p=0.064\); impact on daily life, \(p=0.001\)). For this reason, the results on negative mood symptoms were only analyzed during the first treatment cycle (as a parallel study). No carry over effects or order effects were evident for physical symptoms (bloating, \(p=0.30\); breast tenderness, \(p=0.80\)). Thus, the results for physical symptoms comprised the entire three treatment cycles.

During the first treatment cycle, 2-way ANOVA revealed significant differences between the add-back HRT regimes (premenstrual irritability scores \(p<0.001\); anxiety scores \(p<0.01\); depression \(p<0.001\); mood swings \(p<0.05\); and, impact on daily life scores \(p<0.05\): Figure 2).

According to post-hoc tests, 1.5E2P induced more pronounced symptoms than 1.5E2-only did (irritability scores, \(p<0.001\); anxiety, \(p<0.001\); mood swings, \(p<0.001\); depression, \(p<0.001\); impact on daily life \(p<0.001\): Figure 2).
Figure 2. Mean ± SEM daily symptom ratings on a 9-point Cyclicity Diagnoser scale of irritability, anxiety, depressed moods and impact on daily life during the last ten days of each treatment cycle for 27 PMDD patients. Treatments consisted of leuprolide acetate, and leuprolide acetate plus add-back of 1.5E2P, 0.5E2P or 1.5E2-only. During the first treatment cycle, the two-way ANOVA analyses revealed significant differences between the add-back HRT regimens in premenstrual irritability scores \( p<0.001 \), anxiety \( p<0.01 \), depression \( p<0.001 \), mood swings \( p<0.05 \). Post-hoc analyses are given in the figure.

* \( p<0.05 \), Tukey HSD; ** \( p<0.01 \), Tukey HSD; *** \( p<0.001 \), Tukey HSD

Similarly, the post-hoc tests treatment with 1.5E2P resulted in increased scores for anxiety, depression and impact on daily life, compared to 0.5E2P (anxiety \( p<0.001 \); depression, \( p<0.001 \); Figure 2). Anxiety scores and ratings of impact on daily life increased during treatment with 0.5E2P, compared to 1.5E2-only (Figure 2).

Carry-over effects were observed between the six different sequences of treatment. The summarized negative mood symptoms for the different treatments are displayed in Figure 3. Depending on the first used add-back treatment, women who started with 1.5E2P continued to display higher negative mood ratings throughout the entire study than women who started with
1.5E2-only ($p<0.01$). During the GnRH cycle, there was no difference among the groups for either summarized negative mood symptoms or pretreatment ratings.

**Figure 3.** Summarized negative mood symptoms, depending on which treatment the women started with. Each point represents the group mean ± SEM of the last 10 days of each treatment cycle. PMDD patients who started with 1.5E2P continued to display higher negative mood ratings throughout the study than subjects who started with 1.5E2-only, ($p<0.01$). During the GnRH cycle, there was no difference among the groups for summarized negative mood symptoms.
Paper III

Among the participating women, 12 (20.7%) PMDD patients, 37 (36.3%) ObGyn controls and nine (19.1%) healthy controls acknowledged physical or emotional abuse at any time in life (Table 4). There was no difference between PMDD patients and healthy controls, but ObGyn controls reported physical and/or emotional abuse more often than PMDD patients and healthy controls (p < 0.05).

Lifetime sexual abuse was reported by 17.2% of PMDD patients, 23.5% of ObGyn controls, and by 6.4% of healthy controls (Table 4). There was no difference between PMDD patients and healthy controls, but ObGyn controls reported sexual abuse more frequently than healthy controls (p<0.05).

Ongoing fear of the perpetrator was reported by one PMDD patient and by 15 (14.7%) ObGyn controls (p<0.05: Table 4).

Any lifetime abuse (physical, emotional or sexual) was reported by 31.0% of PMDD patients, 39.2% of ObGyn controls, and 21.3% of healthy controls (Table 4). There was no difference between PMDD patients and healthy controls, but ObGyn controls reported any lifetime abuse more often than healthy controls (p<0.05).

More prior episodes of depression were reported by PMDD patients who had been exposed to violence than by PMDD patients with no reports of violence, although this difference did not reach statistical significance (p=0.095). There were no clinical or sociodemographic differences between PMDD patients with and without exposure to violence.

Table 4. Prevalence of violence among PMDD patients, healthy controls and, gynecological outpatients.

<table>
<thead>
<tr>
<th></th>
<th>PMDD patients (n=58)</th>
<th>Healthy controls (n=47)</th>
<th>Gynecological outpatients (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional and physical abuse some time in life</td>
<td>12 (20.7%)</td>
<td>9 (19.1%)</td>
<td>37 (36.3%)^a</td>
</tr>
<tr>
<td>Physical abuse within last year</td>
<td>0</td>
<td>0</td>
<td>3 (2.9%)</td>
</tr>
<tr>
<td>Sexual abuse at some time in life</td>
<td>10 (17.2%)</td>
<td>3 (6.4%)</td>
<td>24 (23.5%)^b</td>
</tr>
<tr>
<td>Fear of partner or other perpetrator</td>
<td>1 (1.7%)</td>
<td>0</td>
<td>15 (14.7%)^c</td>
</tr>
<tr>
<td>Any violence during lifetime</td>
<td>18 (31.0%)</td>
<td>10 (21.3%)</td>
<td>40 (39.2%)^d</td>
</tr>
</tbody>
</table>

^a p < 0.05 compared to PMDD patients and healthy controls
^b p < 0.05 compared to healthy controls
^c p < 0.001 compared to PMDD patients and healthy controls
^d p < 0.03 compared to healthy controls
There was no difference in diurnal secretion of cortisol between PMDD patients and controls ($F(1,46)=1.60$; $p=0.21$; Figure 4). Similarly, no evidence for diurnal secretion of allopregnanolone was identified, and there was no difference in allopregnanolone diurnal secretion between groups (Figure 5).

**Figure 4.** Mean ± SEM serum cortisol levels in 22 PMDD patients and 26 control subjects taken at four set times during one day in the mid-luteal phase. No difference in the pattern of diurnal cortisol secretion between PMDD patients and control subjects was found.

**Figure 5.** Mean ± SEM serum allopregnanolone levels in 10 PMDD patients and 10 controls taken at four set times during one day in the mid-luteal phase. No difference in diurnal allopregnanolone secretion pattern was found between PMDD patients and control subjects.
Table 5. The effects of the low-dose dexamethasone suppression test presented as salivary cortisol concentrations in patients with PMDD and control subjects at 08.00, before and after administration of 0.25 mg oral dexamethasone.

<table>
<thead>
<tr>
<th></th>
<th>PMDD patients (n=26)</th>
<th>Control subjects (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Cortisol, nmol/l</td>
<td>13.6 ± 20.0</td>
<td>13.4 ± 10.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Post-dexamethasone cortisol, nmol/l</td>
<td>5.3 ± 9.9</td>
<td>5.4 ± 5.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Change in cortisol, nmol/l</td>
<td>9.0 ± 12.0</td>
<td>8.5 ± 7.9</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD and n.s. = non significant.

No difference in the degree of dexamethasone suppression was identified between PMDD patients and controls (Table 5), and there were no differences in diurnal cortisol secretion between PMDD patients with or without prior history of major depression. Similarly, no difference in diurnal cortisol secretion patterns between PMDD patients with prior history of major depression and control subjects was found. In addition, diurnal cortisol secretion did not differ between PMDD patients with or without exposure to violence or between PMDD patients reporting exposure to violence and control subjects.
Discussion

Methodological considerations
This thesis was built on four clinical studies investigating different neurobiologic and psychosocial etiologies of PMDD and COC-induced adverse mood symptoms. The majority of women were recruited after advertising in local newspapers and on official advertisement boards. This meant the study participants were well informed and interested, but this may have also introduced selection bias, which could interfere with the generalization of the study findings. For instance, the women participating in the study for Paper I had a high educational level and were predominantly young female students, from a university city. Thus, the results may not pertain to other patient samples with different experiences of oral contraceptives in other parts of the country. Similarly, the PMDD patients in the studies for Papers II-IV were recruited mainly through advertisements, but these women were from three different cities and mixed with patients who had actively sought care for their problems. Possibly, women who are traumatized by possible assault may be less inclined to respond to an advertisement.

The cross-sectional design of the study in Paper I, with former and current users of COCs, rendered it impossible to determine whether the mood and anxiety disorders identified in ongoing COC users were drug-related, coexisting, or pre-existing. To be able to study this relationship, the women should preferably be followed prospectively with subjective ratings before the start of COC use and only those deteriorating during treatment should be considered as suffering from adverse mood effects. With such a prospective design, it would be possible to exclude subjects with a pre-existing psychiatric disorder before they begin to use COC. However, the prevalence of true COC-induced adverse mood symptoms can only be evaluated in randomized, placebo-controlled trials.

In all studies in this thesis, subjective ratings of mood with the CD scale were used, either for establishing PMDD/PMS diagnosis or as an outcome measure. Various research questionnaires are used within PMDD research, with the Daily Record of Severity of Problems (DRSP) probably being the most commonly used in clinical trials (174). The advantage of the CD scale is that it is easy to use for evaluating patients. As with any ordinal psycho-
logical scale, CD should only be used within subjects, and not for comparisons between subjects. In the study for Paper II, the cross-over effects forced comparisons between groups; however, as the three treatment groups had similar ratings during both baseline diagnostic cycles and the GnRH cycle, this approach was considered feasible. Furthermore, the six-scale DRSP is often used for group comparisons in clinical trials with parallel designs.

PMDD diagnosis should be established after two cycles of prospective ratings. However, only one menstrual cycle was used for evaluation (Paper I), which possibly rendered slightly higher prevalence rates than if two cycles had been used, although, PMDD diagnoses need not to be confirmed in two consecutive cycles, but in two cycles out of three. When the study for Paper I was planned, it was not considered feasible to ask women to rate daily symptoms for three months without losing information. For this reason, it is clearly stated (in Paper I) that PMS/PMDD diagnoses are provisional. In addition, there were women in the studies for Papers II-IV who, due to severe symptoms and imminent need of treatment, only used the CD scale for one menstrual cycle.

The major weakness of the study in Paper II was the cross-over design, which resulted in significant carry-over effects between the different add-back therapies. The main reason for not including a wash-out cycle in the study design was that it would increase the length of the study and increase the risk of drop-outs and time effects (175). Furthermore, as only the last 10 days of each treatment cycle was used, it was anticipated estradiol-only days of each treatment cycle would be sufficient washout from progesterone, which in reality was not the case. The carry-over effects were unanticipated, as similar cross-over designs had previously been used (46, 175-180) in postmenopausal women with no carry-over between the treatment cycles. Thus, the first cycle of treatment could only used due to the carry-over effects, and this rendered a smaller number of subjects for evaluation. The carry-over effect only occurred for psychological symptoms and not for physical symptoms, and was the reason physical symptoms could be evaluated in the intended sample.

The AAS questionnaire (Paper III), which was as a face-to-face interview, was chosen because this method is well accepted by women in the gynecologic setting (181). The choice of a face-to-face interview also made it possible to intervene immediately, if needed. Although AAS has been questioned for not being able to identify all victims (182-183), it was assumed this limitation would affect PMDD patients and the two control groups similarly, and would not alter the overall results of the study. The AAS was known to the researchers participating in the study, which facilitated evaluation of the results. However, even though the face-to-face interview had
many advantages, the primary limitation was that women arriving at the gynecology department together with their partner had to be excluded. Many women (especially young ones) attend the gynecology department with their partner (personal remark). Although the partner may be an invaluable support, there could be a possibility women are accompanied by their partner as a precaution against possible disclosure of partner violence. Another possible drawback with a face-to-face interview is that the interviewer must be confident asking questions regarding violence. Furthermore, when asking about sexual and physical abuse (as well as drinking problems and smoking) completely truthful answers may not be given, as no patient ever divulges more than they are prepared to, and many women may not acknowledge some events as abuse.

In addition, some women who were evaluated did not fulfill the criteria for PMDD diagnosis (Papers II-IV), and for logistical reasons, these women were not interviewed with the M.I.N.I. and AAS questionnaire. However, this group of women would have been important for evaluating the prevalence of violence.

Adverse events in COC treatment

Since the combined oral contraceptive was first introduced, its’ influence (both good and bad) on the female mind and wellbeing has been argued. Psychiatric disorders such as depression and anxiety were common in women who reported adverse mood effects from current or previous COC use (Paper I). Almost one-third of women with ongoing or prior experience of COC-induced mood deterioration fulfilled criteria for any mood and/or any anxiety disorder. As the study design was cross-sectional (Paper I), it was not possible to determine whether the mood and anxiety disorders identified in ongoing COC users were drug-related, coexisting, or pre-existing. However, prior users with experience of COC-induced adverse mood had equally high prevalence rates of anxiety and depression as ongoing users reporting adverse moods, even though they were currently not exposed to COCs. If the depression and/or anxiety disorders revealed in ongoing users were entirely COC-related, it could be assumed the prevalence of depression and anxiety was lower in prior users, i.e., women would have recovered from their depression when COC use was discontinued.

Self-reported PMS was more common in the two groups with adverse effects to COC than their respective control groups. However, when PMS or PMDD diagnoses were verified by daily prospective ratings, no differences between the groups were found. Even though the sample size was small, it was unlikely that a larger sample would have yielded different results. The find-
ing PMS/PMDD was not more prevalent among COC users with adverse mood effects did not support a previous study (50) where women prospectively defined as suffering from PMS were more prone to report negative mood while taking COC. However, the finding agreed with studies indicating COC can be beneficial for women with premenstrual mood symptoms, in particular if symptoms start at an early age (130) and, that treatment with a low-dose ethinylestradiol and drospirenone-containing COC is beneficial for PMDD (122-123).

Another finding of this study was that women who had discontinued COC due to adverse mood effects had a higher frequency of previous induced abortion. Women who discontinue COC use due to adverse mood effects often do so, despite their ongoing need for contraception. Among women seeking legal abortion, almost 60% state they were hesitant about the use of the IUD and COC, although they had had access to these contraceptive methods (184) and, the main reasons for not using contraception at the time of conception are adverse experience, a general disliking of hormones and, concerns about long-term side-effects (184). Therefore, counselors need to respond to the women’s own definition of her situation and, provide her with adequate contraceptive alternatives (184), which means counselors should have experience of a wide range of contraceptive methods, including the non-hormonal options that are available.

The high prevalence of mood and anxiety disorders among women reporting adverse mood symptoms after COC use, suggests there should be greater effort in diagnosing, evaluating and treating depression and anxiety in women. An appropriate treatment for many of these women might be antidepressant therapy rather than discontinuation of COC. The findings of this study are supported by previous findings (130) in COC users, where a history of depression was associated with mood deterioration during COC use.

### Treatment of PMDD

There has been increasing evidence to suggest progesterone from the corpus luteum is the main cause of PMDD symptoms (37, 175, 178, 185-187). The aim of this study (Paper II) was dual; to study the influence of estrogen on symptoms of PMDD and, to evaluate which add-back therapy would be most beneficial when PMDD is treated with GnRH. Treatment with GnRH agonists is an elegant way to study hormonal effects in PMDD patients, as the endogenous production of estradiol and progesterone is abolished. Thus, it is possible to study relatively well-controlled levels of the hormone in relation to mood outcomes, although individual differences in pharmacokinetics may interfere.
Although GnRH-treatment with different add-back has been studied, different estrogen doses have not been evaluated. Studies on postmenopausal women indicate higher doses of estradiol, when combined with progestagens, are more symptom provoking than lower doses of estradiol (46). Even with the limitations imposed by the carry-over effects, the highest dose of estradiol in combination with progesterone was associated with more pronounced symptom recurrence, both in comparison with a lower dose of estradiol in combination with progesterone and with estradiol-only treatment. Hence, the most beneficial add-back HRT consisted of estradiol-only treatment. As estradiol-only add-back is not feasible, a viable alternative could be long-cycle treatment with the addition of progestagen every third month. In postmenopausal women, 14 days of progestagen treatment every third month is sufficient to obtain endometrial safety (188). If the PMDD patient wishes to maintain regular menstrual bleeding, the lowest possible estradiol dose should be used: low-dose HRT is sufficient to alleviate menopausal symptoms while maintaining or improving bone density (189).

PMDD symptoms were not only caused by progesterone fluctuation, serum concentration and/or dose of estradiol and, the estradiol/progesterone ratio might affect symptom provocation. For anxiety and depressive symptoms, there was a dose-dependent increase in symptom recurrence when estradiol doses were increased. This finding only partly agreed with a study by Schmidt et al (48), where both estradiol and progesterone, when given on their own, induced recurrence of symptoms in PMDD patients treated with GnRH agonist; however, no symptom recurrence on estradiol-only treatment was detected in our study, presumably due to the lower estradiol dose used. In a small double-blind cross-over study, Mortola et al (40) found an add-back combination of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) was superior to CEE-only and MPA-only. The findings from the study (Paper II) concurred with results from clinical trials on combined oral contraceptives (COCs) for PMDD, in which an oral contraceptive containing 20 μg ethinylestradiol in combination with drosperinone is efficient for PMDD (122-123), whereas, 30μg ethinyl estradiol and drosperinone is not (190).

Women who started add-back treatment with a higher dose of estradiol in combination with progesterone had increased symptom ratings throughout the study, compared to women who started with estradiol-only. Hence, those who experienced the most severe symptoms during the first add-back cycle continued to do so throughout the study, whereas, those who experienced few symptoms during the first add-back cycle continued to experience low levels of symptom recurrence during the forthcoming cycles. PMDD patients display an abnormal CNS response to normal hormone fluctuations (48-49, 191) and, such abnormal responses may persist over time or induce expecta-
tions or, alternatively, sensitize subjects to a certain degree of symptom recurrence in subsequent cycles. Thus, a certain hormone provocation (being positive or negative) might leave residual traces and vulnerabilities that alter future response to ovarian hormones.

As opposed to negative mood symptoms, experiences of physical symptoms were not carried over between treatment cycles. This implied the wash-out phases used for the study was sufficient in terms of hormone clearance and that subtle changes in hormone levels might induce detectable changes in physical complaints within an individual subject. Thus, long-cycle add-back treatment avoiding the frequent use of progestagens appeared to be the most beneficial treatment for PMDD patients, as PMDD symptoms were affected by progesterone addition, whereas, estradiol dose also influenced symptom expression.

Violence as a provoking event in PMDD

Intimate partner violence is a global problem, with a consequent its influence on women’s health. As intimate partner violence has been suggested as a possible trigger for PMDD (148, 192), the aim of the study (Paper III) was to compare reports of ongoing or prior exposure to violence among women with prospectively defined PMDD and two control groups; one group consisting of gynecological outpatients and one group consisting of healthy controls.

A history of physical, emotional or sexual abuse was not more frequent in PMDD patients than in gynecological outpatients or healthy controls. However, reports of emotional and physical abuse and ongoing fear of perpetrator were more frequent in the gynecological outpatients than in PMDD patients. In addition, the gynecological outpatients reported a history of sexual abuse more often than the healthy controls: there was no difference in lifetime sexual abuse between PMDD patients and healthy controls.

The prevalence of violence exposure among PMDD patients was lower than in studies by Girdler et al (141, 193), where a higher frequency of sexual and physical/emotional abuse was reported among women with PMDD (44% reported physical abuse and 32% reported sexual abuse) than reported by healthy controls. One important reason why prevalence rates were lower in this study was the clinical setting in which PMDD patients were diagnosed, as they were recruited within an obstetric gynecologic setting: Girdler et al recruited PMDD patients at a psychiatric clinic. Thus, women who seek help for premenstrual complaints through a gynecology clinic (or responding to advertisement) might be less burdened by previous traumatic experiences,
which could explain the relatively low frequency of prior depression in these subjects. However, for individual PMDD patients, exposure to violence may have profound effects on their well-being in adulthood. Childhood sexual abuse has lasting effects on multiple biological and psychological variables, including endocrine response to stress and coping styles (140-141).

The prevalence of violence exposure among the PMDD patients was substantially lower than in previous reports on retrospectively defined PMS patients (194-195). The fairly high prevalence rates of prior/ongoing physical and sexual abuse in studies on PMS patients are probably due to less stringent diagnosis, which will inevitably include patients with other psychiatric co-morbidities (196).

PMDD patients with prior history of depression more often report physical and/or sexual abuse (193). However, there was a tendency towards a difference in reports of abuse between PMDD patients with or without previous depression, where half of the abused PMDD patients had a history of prior depression. Besides prior depression, there were no specific clinical or sociodemographic factors distinguishing PMDD patients who reported abuse from those who did not report abuse.

However, although PMDD patients were not more affected by physical, emotional or sexual abuse, any lifetime abuse was common among all women in this study (Paper III): over 30% of PMDD patients and almost 40% of the gynecological outpatients reported any lifetime abuse. Even 20% of the women who identified themselves as healthy controls had been exposed to violence. Health care professionals have an important task in identifying women who have been exposed to violence. Population-based studies in the Nordic countries indicate high prevalence rates of physical symptoms among women who have experienced abuse (136, 197). Furthermore, within the gynecological setting, the prevalence rates of lifetime physical, emotional and sexual abuse are likely to be increased, as these experiences are associated with gynecological problems (138). A cross-sectional Nordic study reports (139) prevalence rates among gynecological patients varies between 38-66% for physical abuse, 19-37% for emotional abuse, and 17-33% for sexual abuse and, sexual abuse among gynecological patients is associated with chronic pelvic pain and psychosomatic symptoms, and increased number of health care visits and a higher incidence of sick leave (198). In the obstetric and gynecologic setting, other somatic complaints associated with abuse include menstrual problems, headache and nausea (137).

Exposure to partner violence is common among women seeking gynecological care. In this study, PMDD patients did not appear to have suffered physical, emotional or sexual abuse more than other gynecological patients or
healthy controls. However, exposure to violence was common in all groups of women interviewed, and for the individual patient, these experiences may contribute to their experience of symptoms.

Diurnal cortisol variation and low-dose dexamethasone test

The primary objective of this study was to determine if diurnal secretion of cortisol and allopregnanolone, or cortisol suppression after low-dose dexamethasone, differed between women with PMDD and control subjects. No difference in diurnal cortisol or allopregnanolone secretion or in degree of dexamethasone suppression was found between PMDD patients and control subjects, nor was there any no difference in diurnal cortisol secretion or degree of dexamethasone suppression between PMDD patients with or without prior history of major depression or prior exposure to physical, emotional or sexual violence.

Many results on HPA-axis dysfunction in PMDD patients suggest blunted HPA axis function, for example, lower circulating ACTH or morning cortisol concentrations in PMDD women (141, 156, 158). However, in this study, normal cortisol levels in women with PMDD were consistent with previous studies suggesting no difference in morning cortisol levels. Lombardi et al (159) measured morning cortisol during three months in the follicular and luteal phases but found no difference in either phase between women with PMDD and controls: similar results were also obtained when morning cortisol levels were assessed three times per week during one menstrual cycle in PMDD patients (158). Parry et al (199) measured cortisol levels every 30 minutes during one night in the mid-follicular and late luteal phases of PMDD patients and healthy controls, but, there was only a difference in the time of secretion, not in the actual levels of cortisol (199).

For this study, the hypothesis was that diurnal cortisol secretion would differ in PMDD patients with prior history of major depression or prior exposure to violence from PMDD patients with no such experiences or from control subjects. These hypotheses were based on reports (140, 160) indicating PMDD patients with a history of previous major depressive disorder display blunted cortisol and neurosteroid responses to mental stress. Furthermore, prior studies on PMDD patients (140-141, 148, 192) indicate childhood sexual abuse results in lasting effects on multiple biological and psychological variables, including endocrine response to stress and coping styles. However, no differences in diurnal cortisol secretion or cortisol dexamethasone suppression were found between patients with or without these experiences.
One possible reason the findings by Girdler et al could not be replicated may be the different settings in which patients were recruited. In the USA, participants for studies on PMDD are typically recruited at psychiatric clinics or PMDD-clinics. In the Nordic countries, PMDD patients more often seek help from their gynecologist and, oral contraceptives are more often used as treatment for their symptom (190). It is possible the difference in recruitment of patients predisposes the milder PMDD cases in this study, that is, the participants are less burdened by previous trauma and psychiatric illnesses; consequently, HPA-axis dysregulation may be less apparent.

In conclusion, there was no evidence that stress, as measured by diurnal secretion of cortisol or allopregnanolone or, low-dose dexamethasone suppression, was involved in the pathophysiology of premenstrual dysphoric disorder.

Is it just the hormones?

Is it just the hormones? The direct answer to the question used as title of this thesis would be yes and no, depending on which patient group is in focus. The main findings from these studies indicated that among women who report adverse mood symptoms while taking COC, the relationship between ovarian steroids and mood might be more complex than just hormone exposure. Although the cross-sectional design excluded the possibility of drawing causal conclusions, factors other than oral contraceptives appeared to influence the prevalence of depressive disorders in COC users. If COC were the main causal agent for the increased prevalence of depression and anxiety in ongoing users, there would be lower prevalence rates in previous users. However, from clinical experience, a number of women suffer from COC-induced adverse moods, which remit when COC use is discontinued. Thus, there is an imminent need for placebo-controlled clinical trials to elucidate the prevalence rate of truly drug-related adverse moods: without such trials, there is no way of knowing how common this problem may be.

Adverse mood in some women may be drug-related, and there is some evidence women with adverse mood symptoms during COC use display reduced prepulse inhibition (PPI) (200). Prepulse inhibition is a measure of sensory motor gating (clinically manifested as decreased ability to concentrate), which is influenced by dopamine, gender and, ovarian steroids (201-203). Besides reportedly lower levels of PPI in COC users, women with PMDD also display this feature in the late luteal phase (204).

The main symptom-provoking factor in women with PMDD appeared to be the estradiol and progesterone fluctuations across the menstrual cycle, and, partner violence and stress appeared less relevant. However, numerous other
psychosocial factors, not studied in this thesis, influence the appearance of symptoms.

All women are under the influence of monthly hormonal fluctuations during the fertile years of their life. As most women are to some extent aware of “what time in the month it is”, the most urgent question to address is why some women are nearly handicapped by their symptoms and others are happy to recognize that everything is functioning properly. Studies on monozygotic and dizygotic twins indicate genetic factors are important in PMS/PMDD, with heritability estimates of approximately 35-39% (205-208). Whether PMS/PMDD genes are shared in part with neuroticism-related personality traits (209-210), with liability to lifetime major depression (211-215) or, being unique for the syndrome itself (210, 216) remains to be proven. It could be speculated these possible genetic factors, in addition to psychosocial influences, may predispose certain women to experience more intense symptoms during the luteal phase.

The exact neurobiological mechanisms underlying symptom surfacing in the luteal phase are unknown, although it is commonly assumed one pathway may be through ovarian steroid influence on serotonergic neurotransmission (61-62). Other possible pathways include ovarian steroid influence on GABA<sub>A</sub> receptor function (43-45, 217-219) or altered neurosteroid sensitivity (177, 187, 220). The findings in this thesis indicated estradiol priming, especially for anxiety symptoms, might be dose-dependent. However, whether the mood-detrimental effect of estradiol is mediated by the influence of ovarian steroids or by up-regulation of progesterone receptors (leading to increased progesterone sensitization) in relevant brain regions remains to be determined. Estrogen treatment up-regulates progesterone receptor expression in the raphe neurons (221-223) and, estradiol alone (or together with progesterone) alters expression of 5HT1A receptors, serotonin transporter and tryptophan hydroxylase protein (224-226), and numerous other genes (227), in the raphe nuclei.

Some final reflection from the author of this thesis: In my work with the women who participated in these studies, it become apparent PMDD is neither a learnt phenomena nor, a social construct for enhancing drug prescription to otherwise healthy women. The women I met have a serious, condition that impairs quality-of-life and which has to be treated with evidence-based treatments. PMDD is an endocrine and psychological challenge to the clinician and any advances in the understanding of the neurobiology of this syndrome will help improve the lives of the women affected.
General conclusions

- Depression and anxiety disorders are as common in COC users with adverse mood symptoms as in previous users with experience of COC-induced adverse mood symptoms.

- Premenstrual syndrome and PMDD are no more common among women with previous experience of COC-induced adverse mood than in women with previous positive experience of COCs.

- Estradiol-only treatment in clinically relevant doses does not appear to influence the symptom expression in GnRH agonist-treated women with PMDD.

- In combination with progesterone, a higher dose of estradiol will induce more anxiety and depressive mood than a low dose of estradiol.

- Long-cycle add-back HRT treatment for avoiding frequent use of progestagens appears beneficial for PMDD patients treated with GnRH agonist.

- Exposure to partner violence is common among women seeking gynecological care, but PMDD patients do not appear to have suffered physical, emotional or sexual abuse more than other gynecological patients or healthy controls.

- There was no evidence stress, as measured by diurnal secretion of cortisol or low-dose dexamethasone suppression, is involved in the pathophysiology of premenstrual dysphoric disorder.

3-8 % av kvinnor i fertile ålder beräknas lida av så pass svåra besvär att det kan klassas som PMDD – på svenska kallat PMDS, premenstruellt dysforiskt syndrom. Orsaken till symtomen har bedömts vara hormonell, och idag vet vi att det krävs en ägglossning och därmed en gulkroppsproduktion för att symtomen ska utvecklas.

Standardbehandling idag är SSRI-preparat som genom studier senaste 20 åren tydligt visat effekt. Detta har gjort att samband mellan PMDS och annan psykiatrisk sjukheter studerats. Tydliga samband mellan PMDS och depression kan ses bland annat med samsjukheter i PMDS och egentlig depression, liksom att postpartum depression är vanligare hos kvinnor med PMDS.

Ett flertal studier på senare år har visat att medicinsk behandling för att tillfälligt ta bort ägglossningen, ger en klar förbättring på PMDS symtomen, dock till priset av att kvinnan försätts i ett klimakteriellt tillstånd.

Vissa studier på senare år har antytt att andra orsaker kan bidra till utvecklingen av PMDS. En sådan faktor skulle kunna vara att kvinnan varit utsatt för våld i nära relation, eller sexuella övergrepp. Även stress av annat slag har studerats. Det är än så länge få studier och med inte helt entydiga resultat.

Kombinerade p-piller innehåller både gulkroppshormon och östrogen och många kvinnor upplever att de mår dåligt av p-piller, detta gör att behandlingen avbryts trots stort behov av ett effektivt preventivmedel.

Inledningsvis har en studie på 118 kvinnor med olika erfarenhet av p-piller behandling gjorts. Kvinnor som upplevde humörbiverkan av p-piller eller hade slutat på grund av detta, hade samma frekvens av psykiatrisk sjuk-
ligt (depressiv och/eller ångest sjukdom). Den var också signifikant högre än hos kvinnor som inte haft humörbiverkningar av p-pillar. Många kvinnor med PMDS har upplevt sig må dåligt av p-pillar behandling. I denna studie var det inte vanligare med PMS/PMDS bland dem som slutat med p-pillar på grund av humörbiverkan än bland dem som slutat av andra orsaker.

Den andra studien bygger på möjligheten att behandla PMDS genom att ta bort ägglossningen med GnRH analog. På så vis kan man få en insikt i hur inte bara gulkroppshormon utan även östrogen påverkar symtombilden. Målet har varit att se viken typ av östrogen ersättning som ger bäst effekt vid behandling av PMDS med GnRH analog.

I denna kliniska studie ingick 25 kvinnor som fick GnRH analog för att ta bort ägglossningen och därmed produktion av gulkroppshormon. För att minska de klimakteriella biverkningarna gavs två olika doser av östrogen i kombination med gulkroppshormon eller placebo. En hög dos av östrogen med gulkroppshormon gav mest symtom medan minst återkomst av besvär sågs vid hög dos östrogen i kombination med placebo.

För att bedöma utsatthet för våld i nära relation och förekomst av PMDS har 58 kvinnor med prospektivt definierad PMDS, 47 friska kvinnor och 102 kvinnor som sökt gynekologisk vård med andra gynekologiska besvär, deltagit. De kvinnor som sökte för andra besvär än PMDS hade i störst utsträckning varit utsatta för våld jämfört med kvinnor med PMDS och lägst frekvens sågs i gruppen friska kvinnor.

Kronisk stress kan mätas via kortisol nivåer i blod och/eller saliv, och hämning av kortisolnivåer i blod kan ses med s.k. dexametasontest. Tjugosex kvinnor med PMDS och 26 friska kontroller genomgick en mätning av kortisolnivåer under ett dygn och en lågdos dexametasontest. Vi kunde inte se någon skillnad i kortisolnivåer över dygnet, inte heller någon skillnad i hämning av kortisolnivåer mellan kvinnor med PMDS och de friska kvinnorna.

Sammanfattningsvis kan jag säga att kvinnorna som deltagit i denna studie har ett uttalat handikapp i form av att de mår dåligt med humörsvängningar, irritabilitet och nedstämdhet 1-2 veckor före menstruationen. Detta kan inte ses som ett inlärt beteende eller en social konstruktion. Symtomen präglar deras liv påtagligt och de har varit hjälpt av den behandling som getts inom ramen för studien. PMDS är ett endokrinologiskt och psykologiskt tillstånd som bör behandlas med den evidensbaserad medicinsk behandling som idag står tillbuds. Det finns många obesvarade frågor och framtida neurobiologisk forskning bör kunna ge svar på detta och därmed förbättrade behandlingsmöjligheter.
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Appendix: CD scale sample (one out of four)
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