endocrines

MDPI

Review

Premenstrual Syndrome and Premenstrual Dysphoric Disorder as Centrally Based Disorders

Rossella E. Nappi [1,2,*], Laura Cucinella [1,2], David Bosoni [1,2], Alessandra Righi [1,2], Federica Battista [1,2], Pietro Molinaro [1,2], Giulia Stincardini [1,2], Manuela Piccinino [1], Roberta Rossini [1] and Lara Tiranini [1,2]

[1] Research Center for Reproductive Medicine, Gynecological Endocrinology and Menopause, IRCCS San Matteo Foundation, 27100 Pavia, Italy; laura.cucinella01@universitadipavia.it (L.C.); dd.bosoni@gmail.com (D.B.); alessandra.righi01@universitadipavia.it (A.R.); federica.battista01@universitadipavia.it (F.B.); pietro.molinaro01@universitadipavia.it (P.M.); giulia.stincardini01@universitadipavia.it (G.S.); m.piccinino@smatteo.pv.it (M.P.); r.rossini@smatteo.pv.it (R.R.); lara.tiranini01@universitadipavia.it (L.T.)

[2] Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, 27100 Pavia, Italy

* Correspondence: renappi@tin.it

Abstract: Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) encompass a variety of symptoms that occur during the luteal phase of the menstrual cycle and impair daily life activities and relationships. Depending on the type and severity of physical, emotional or behavioral symptoms, women of reproductive age followed for at least two prospective menstrual cycles may receive one of the two diagnoses. PMDD is the most severe form of PMS, predominantly characterized by emotional and behavioral symptoms not due to another psychiatric disorder. PMS and PMDD are common neuro-hormonal gynecological disorders with a multifaceted etiology. Gonadal steroid hormones and their metabolites influence a plethora of biological systems involved in the occurrence of specific symptoms, but there is no doubt that PMS/PMDD are centrally based disorders. A more sensitive neuroendocrine threshold to cyclical variations of estrogens and progesterone under physiological and hormonal therapies is present. Moreover, altered brain sensitivity to allopregnanolone, a metabolite of progesterone produced after ovulation potentiating GABA activity, along with an impairment of opioid and serotoninergic systems, may justify the occurrence of emotional and behavioral symptoms. Even neuro-inflammation expressed via the GABAergic system is under investigation as an etiological factor of PMS/PMDD. Pharmacological management aims to stabilize hormonal fluctuations and to restore the neuroendocrine balance. The rationale of suppressing ovulation supports prescription of combined hormonal contraception (CHC). Its effect on mood is highly variable and depends on biochemical characteristics of exogenous steroids and on type and severity of symptoms. Hormonal regimens reducing the estrogen-free interval or suppressing menstruation seem better choices. Psychoactive agents, such as serotonin reuptake inhibitors (SSRIs), are effective in reducing the symptoms of PMS/PMDD and may be prescribed continuously or only during the luteal phase. Novel therapeutic approaches include inhibition of progesterone receptors in the brain, i.e., with ulipristal acetate, reduced conversion of progesterone with dutasteride, and modulation of the action of allopregnanolone on the brain GABAergic system with sepranolone.

Keywords: premenstrual syndrome; premenstrual dysphoric disorder; estrogen; progesterone; allopregnanolone; combined hormonal contraception (CHC); serotonin reuptake inhibitors (SSRIs); sepranolone; neuro-inflammation; neurosteroids

Citation: Nappi, R.E.; Cucinella, L.; Bosoni, D.; Righi, A.; Battista, F.; Molinaro, P.; Stincardini, G.; Piccinino, M.; Rossini, R.; Tiranini, L. Premenstrual Syndrome and Premenstrual Dysphoric Disorder as Centrally Based Disorders. *Endocrines* **2022**, *3*, 127–138. https://doi.org/10.3390/endocrines3010012

Academic Editor: Alessandro Genazzani

Received: 24 January 2022
Accepted: 14 March 2022
Published: 16 March 2022

1. Introduction

Periodic menstrual blood loss is the hallmark of womanhood from menarche to menopause and represents a clear biological sign of gonadal hormonal variation [1]. The menstrual lens allows a catamenial view of a multitude of symptoms and conditions related to reproductive function [2,3], which ultimately indicates female adaptive abilities

in order to ensure fertility goals. However, menstruation is much more than a biological phenomenon and still represents a clear "gender gap". Its significance has evolved over time and across culture encompassing intrapersonal and interpersonal aspects [1]. Currently, women have better control over their menstrual periodicity, but catamenial manifestations may generate a significant burden in daily living activities and a certain amount of stigma [4]. Extensive literature covers menstrual health in order to hormonally manage predictable pain syndromes, including menstrual headaches and other conditions associated with the menstrual cycle [5–7]. Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are common medical conditions lacking objective measures or laboratory testing to confirm the diagnosis [8]. The main challenges include the subjective nature of premenstrual symptoms and the variability of menstrual patters across different reproductive stages, which require adequate diagnostic self-report methods or semi-structured clinical interviews in routine practice [8].

In this paper, we present an overview on the evidences supporting the role of the neuroendocrine system in the clinical manifestation of PMS and PMDD. We also describe possible novel therapeutic strategies based on the use of neuroactive and hormonal compounds.

2. Definitions of Premenstrual Disorders

PMS is a multifaceted complex disorder, and very common in women of reproductive age. It encompasses at least one physical, emotional or behavioral symptom, which appears following ovulation in the luteal phase of the menstrual cycle and resolves shortly after the onset of menstruation [9]. A variety of symptoms have been attributed to the premenstrual phase, the most common being breast tenderness, bloating, headache, mood swings, depression, anxiety, anger, and irritability. Moderate–severe PMS is diagnosed when symptoms interfere with daily personal and occupational life during two menstrual cycles of prospective recording [10] (Figure 1). The most severe form of PMS is defined as PMDD, a condition predominantly characterized by emotional and affective symptoms not due to another psychiatric disorder [11]. PMDD diagnosis requires the presence of at least one mood symptom (depressed mood, anxiety or tension, marked affective lability, irritability) in a group of at least five symptoms that affect the luteal phase of two ovulatory cycles prospectively recorded (Figure 1). Symptoms must be associated with clinically significant distress regarding social, academic or working activities and should not be the exacerbation of a chronic condition or the effect of medications [12]. The International Society for Premenstrual Disorders (ISPMD) distinguishes PMS/PMDD, the core premenstrual disorders, from variant premenstrual disorders. The latter includes premenstrual exacerbation of other clinical conditions (i.e., asthma, allergies, epilepsy, migraine, diabetes, irritable bowel syndrome, autoimmune disorders) and symptoms that occur from ovarian activity other than ovulation or even in the absence of ovulation (exogenous progesterone/progestogens administration or suppression of menstruation) [13].

PMDD is a diagnostic category of depressive disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [14], recently coded as a gynecological diagnosis in the World Health Organization's International Statistical Classification of Diseases (ICD-11) [15]. The recognition of PMDD as a neuro-hormonal gynecological disorder and not only as a psychiatric disorder is of paramount importance, pinpointing accurate definition of conditions under the umbrella of "reproductive depression" [16]. Indeed, PMS/PMDD, peri/postnatal and peri/postmenopausal depressive disorders are closely linked, sharing a neuroendocrine vulnerability to critical reproductive events, and should not be confused with other severe psychiatric disorders [17]. Therefore, in the context of a multi-specialty process of care to exclude co-occurrence with bipolar disorders and other mental health conditions [13,18], PMS/PMDD should be a legitimate part of the reproductive history and screened routinely with appropriate psychometric tools [19] to identify women who may be responsive to neuroactive and hormonal treatments [13,17]. There are many screening tools available [19] offering a retrospective diagnosis, for instance, the Premenstrual Symptoms Screening Tool (PSST) [20], and a prospective assessment as the calendar of premenstrual

experiences (COPE) [21]. Both approaches carry some biased reporting which affects the "true" epidemiology of PMS/PMDD [22].

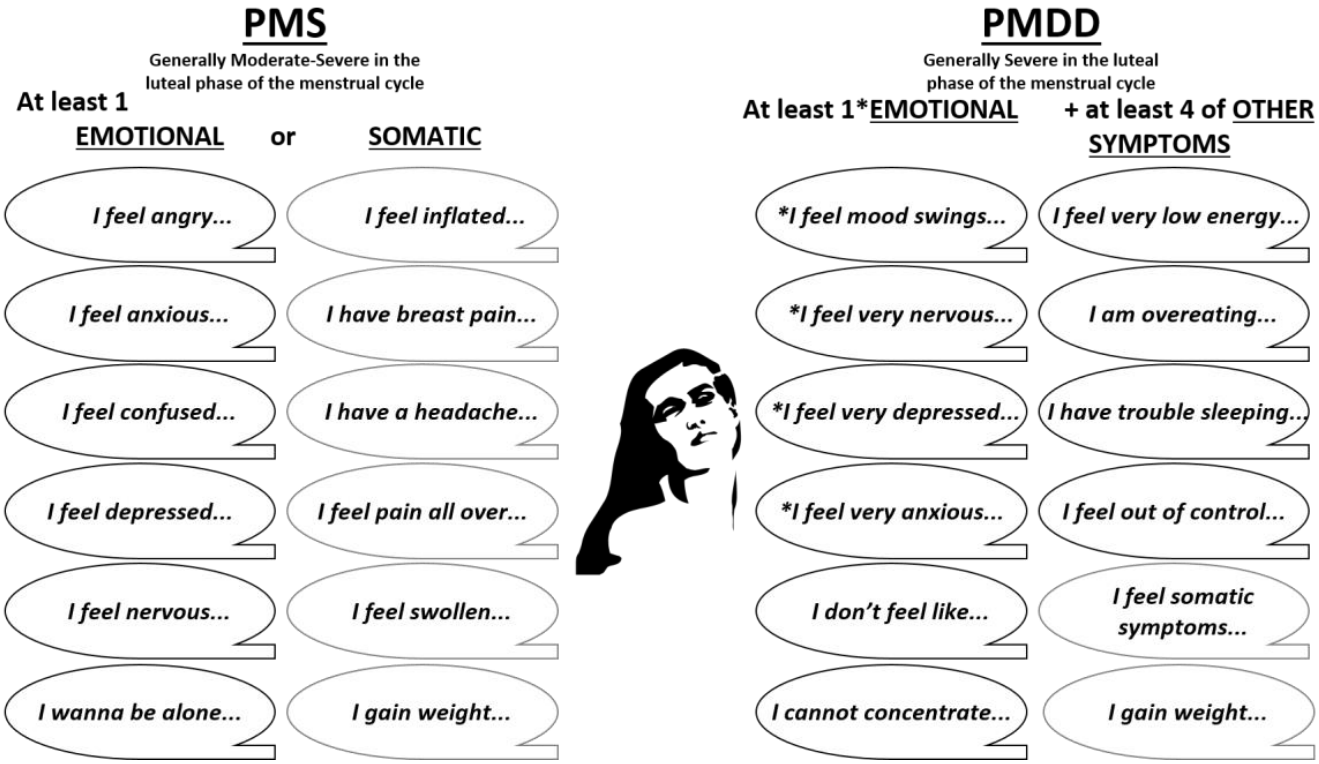

Figure 1. Heterogeneity of PMS/PMDD symptoms [10,11]. * means emotional symptoms in the legend of Figure 1.

3. Epidemiology and Risks Factors of PMS/PMDD

Premenstrual symptoms are very common, affecting about half of women in reproductive age worldwide [22]. However, prevalence rates vary widely in different studies and countries depending on samples, methods of investigation and diagnostic criteria. Disparities may also derive from genetic and socio-cultural factors, including diet and life-style, stressors, personal attitudes, coping behaviors, workload and family responsibilities [22]. Available surveys in community populations indicate that PMS affects 20–30% of women, whereas PMDD ranges between 1.2 and 6.4% [23], with black women being significantly less likely to experience PMDD and PMS than white women (odds ratio (OR) 0.44, 95% confidence interval (CI) 0.25–0.79 and OR 0.64, 95% CI 0.47–0.88, respectively), similarly to what is observed in other mental health disorders [24]. Both conditions significantly reduce quality of life and raise societal costs associated with decreased work productivity, work absenteeism and increased use of health care services [25]. Prevalence and impact of PMS/PMDD are strong priorities to implement preventive strategies in young women [26]. Health care providers (HCPs) should be aware that premenstrual symptoms might fluctuate over time with no clear impact of age or reproductive stage, apart from menopausal transition [27,28]. Another relevant factor is that combined oral contraceptives (COCs), the most studied type of combined hormonal contraception (CHC), may improve overall premenstrual symptomatology in women with PMS/PMDD, but not premenstrual depressive symptoms [29]. Behavioral risk factors, especially smoking and adiposity, are overrepresented in women with PMS/PMDD, confirming their link to emotional vulnerability. Indeed, smoking was associated with an increased risk of premenstrual disorders (OR = 1.56 (95% CI: 1.25–1.93)). Stratified by diagnosis, the effect size estimate was higher for PMDD (OR = 3.15 (95% CI: 2.20–4.52)) than for PMS (OR = 1.27 (95% CI: 1.16–1.39)) [30]. A strong linear relationship between body mass index (BMI) at baseline and

risk of incident PMS, with each 1 kg/m^2 increase in BMI associated with a significant 3% increase in PMS risk (95% confidence interval (CI) 1.01–1.05), was evident [31]. In particular, women with BMI $\geq$ 27.5 kg/m^2 at baseline had significantly higher risks of PMS than women with BMI < 20 kg/m^2, following adjustment for age, smoking, physical activity, and other factors [31]. Intake of alcohol was associated with a moderate increase in the risk of PMS (OR = 1.45, 95% CI: 1.17 to 1.79), especially heavy drinking (OR = 1.79, 95% CI: 1.39 to 2.32) as compared to no or light drinking [32]. Studies on the effect of exercise have many methodological biases with some suggesting improvement of premenstrual symptoms [33]. Other proven risk factors include traumatic events, which greatly increased the odds of developing PMDD at follow-up (OR = 4.2, 95% CI = 1.2 to 12.0). Likewise, a history of anxiety disorder (OR = 2.5, 95% CI = 1.1 to 5.5) and elevated daily conflict scores (OR = 1.6, 95% CI = 1.1 to 2.3) predicted PMDD [34]. Depression may be strongly comorbid [17,18], in particular postnatally [35], and women with PMDD should be considered a high-risk group for suicidality, including increased vulnerabilities for suicidal thoughts, ideation, plans and attempts [36]. Other comorbidities include eating disorders, mainly bulimia and binge eating [37], and migraine [38]. The co-occurrence with pathological manifestations displaying premenstrual exacerbations supports a common neuroendocrine etiology [2,3]. Medical conditions such as anemia and endocrine disorders (namely thyroid and adrenal dysfunctions and hyperprolactinemia) [13], as well as chronic pelvic pain, fibromyalgia and any other inflammatory disorders [39,40], may mimic PMS/PMDD symptoms. HCPs should make a differential diagnosis to establish an individualized treatment plan [3,8,13].

4. Neuroendocrine Aspects of PMS/PMDD

The most characteristic aspect of PMS/PMDD is the temporal relation between the appearance of symptoms and the menstrual phase, indicating a role for gonadal steroid hormones and their metabolites in influencing the plethora of biological systems that contribute to the adjustments required to fulfil reproductive goals. However, women with PMS/PMDD do not show abnormalities in the reproductive hormone release pattern; rather, they seem to display a more sensitive neuroendocrine threshold to cyclical variations of estrogens and progesterone [41,42], which may give origin to catamential symptoms and exacerbation of mood disorders during reproductive transitions [43,44]. Data on other circulating hormones (prolactin, testosterone, cortisol, dehydroepiandrosterone sulphate, and thyroxine) are discordant and fail to separate women with PMS/PMDD from controls. However, they may be relevant to some individual somatic symptoms, for instance cyclic mastalgia or water retention [13].

Many genetic and epigenetic factors influence the neuroendocrine threshold of premenstrual symptoms according to the biopsychosocial model. Severity of mood symptoms and associated distress should guide clinical judgement [8,13]. However, both HCPs and women have their personal view of the set point of such threshold, explaining variable epidemiology of PMS/PMDD symptoms [23]. If the diagnostic threshold is too high, clinically relevant premenstrual symptoms may be underestimated and PMS/PMDD remain untreated. If it is too low, paraphysiologic variations in menstrual cycle-related well-being can be over-treated (Figure 2). The central nervous system (CNS) is one of the main target tissues for reproductive hormones but it is also a source of neurosteroids, which are involved throughout genomic and non-genomic mechanisms in a vast array of CNS functions [45–47] far beyond the scope of the present overview. Here, we report the key concepts relevant to the current understanding of pathophysiology and potential treatment targets of PMS/PMDD.

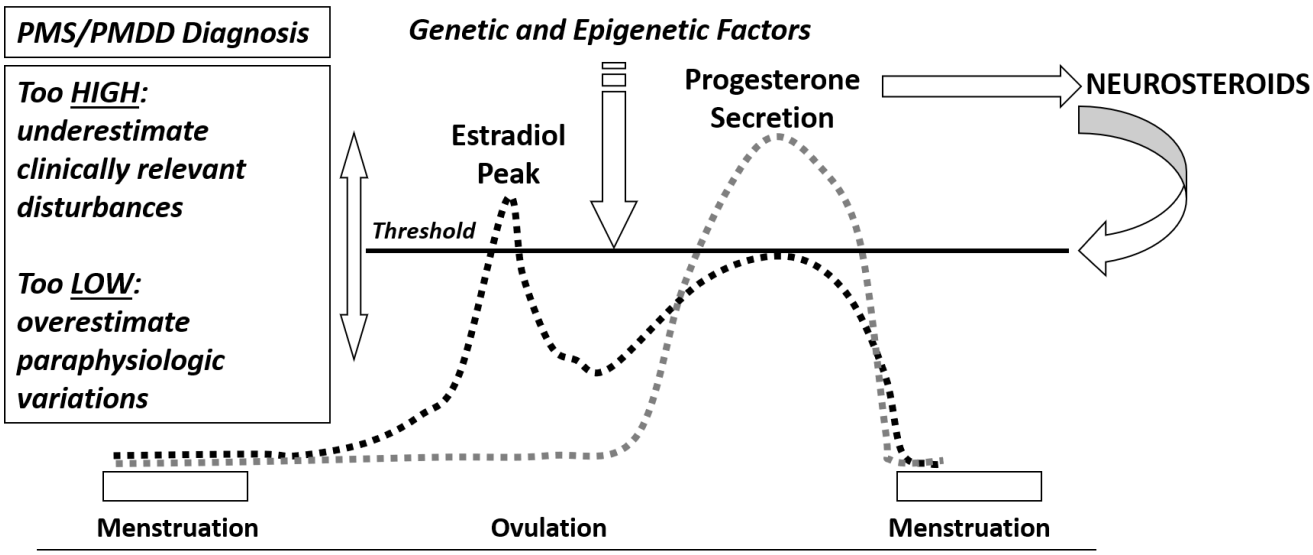

Figure 2. Neuroendocrine threshold and PMS/PMDD diagnosis.

Estrogens and Progesterone

Hormonal transitions are associated with reproductive mood disorders, whereas premenarchal girls and postmenopausal women do not experience PMS/PMDD in the absence of gonadal steroid fluctuations. The same is true when gonadal steroids are high and rather stable, as occurs in pregnancy [48]. In addition, premenstrual symptoms do not occur during anovulatory cycles and disappear in chemically and/or surgically castrated women [9]. Several mechanisms involving estrogen receptors polymorphisms may explain the vulnerability to reproductive mood disorders [49]. Fluctuations of gonadal steroids, in particular progesterone produced by the corpus luteum, are key factors for PMS/PMDD [42], given the synchrony with post-ovulatory phase and the reinstatement of symptoms during GnRH agonist treatment when add-back progesterone is administered [50]. However, many women experience premenstrual symptoms immediately after ovulation and during the early luteal phase, while others report an exacerbation only a few days before menstruation, irrespective of progesterone fluctuations [9]. Therefore, the importance of the progesterone to estrogens ratio has been also investigated, because estrogens may exert an antidepressant effect [51], and women with PMS/PMDD and healthy women have similar progesterone serum concentrations [42,52]. A recent study prospectively evaluated estrogen and progesterone levels in both early and late luteal phases in women with PMDD and the association of these levels with PMDD symptom severity [53]. In women with PMDD, estrogen levels were lower than the controls during the early luteal phase and displayed a significant interaction with early luteal progesterone, suggesting that low estrogen level could moderate the severity of PMDD symptoms following exposure to progesterone [53]. On the other hand, estradiol administration may provoke PMS-like complaints, similarly to progesterone administration alone or together with estrogens [50,54]. Moreover, PMS-like symptoms often persist after anovulation has been induced with COCs, suggesting that both the dose of estrogens and the type of progestins may be relevant to mood symptoms in vulnerable women [55]. Finally, postmenopausal women receiving combined hormonal replacement therapy (HRT) may experience PMS-like complaints despite stable levels of estradiol and progesterone [56]. Of note, administration of mifepristone, a progesterone receptor antagonist, did not reduce physical, emotional and/or behavioral manifestation of PMS or change the timing of these symptoms [57,58]. More recently, ulipristal acetate (UPA), a second-generation SPRM already employed for emergency contraception and for the treatment of uterine fibroids [59], was tested as a suitable option to ameliorate symptoms in women with PMDD. The first proof-of-concept randomized controlled trial on UPA at low chronic dosing (5 mg/day) showed improvement in emotional and behavioral symptoms of PMDD [60]. Interestingly, brain-imaging studies demonstrated a specific sensitivity

to gonadal steroids, confirmed at the cellular level in women with PMDD [61,62], that appeared regulated by UPA in response to behavioral stimuli [63]. Whether UPA displays a positive effect on PMDD by blocking the progesterone receptor-mediated signaling or by preventing ovulation with more stable levels of gonadal steroids remains to be determined.

At present, the most commonly prescribed hormonal treatment for the management of both physical and affective symptoms of PMS is CHC, with the rationale of suppressing ovulation [13]. Temporary chemical castration with gonadotropin releasing hormone (GnRH) agonists also appeared to be an effective treatment in the management of PMS/PMDD, more on physical than psychological symptoms [64]. However, add-back therapies using a combination of estrogen and progestogen to minimize negative effects of prolonged low estrogenic state in fertile women may restore symptoms in PMDD women who are intolerant especially to progestogens [65].

5. Allopregnanolone and GABAergic System

Progesterone plays a crucial role within the CNS because of its metabolite allopregnanolone. The enzymes 5alpha-reductase and 3alpha-hydroxysteroid-dehydrogenase form this neuroactive steroid, which is a strong positive modulator of the gamma-aminobutyric acid (GABA) receptor and, therefore, has the ability to increase both synaptic and extrasynaptic cortical inhibition. Allopregnanolone binds to an allosteric site on the GABAA receptor and increases its sensitivity to GABA. As an inhibitory neurotransmitter, GABA is an important regulator of stress, anxiety, vigilance and seizures [47,66,67]. Allopregnanolone increases after ovulation and is secreted into circulation from both ovarian and adrenal tissues. Its deficiency has been a potential explanation for emotional and behavioral premenstrual symptoms, but not all studies have shown a lower concentration of progesterone metabolites in women with PMS compared to controls under basal or stimulated conditions [68–71]. Moreover, the duration of exposure to allopregnanolone could play a critical role. Indeed, in the pseudopregnancy rat model, allopregnanolone acute withdrawal resulted in an anxiety-like reaction [72]. Studies on mood effects of oral progesterone treatment revealed an inverted U-shaped bimodal relation between negative mood severity and allopregnanolone concentration. For instance, postmenopausal women treated with different doses of oral progesterone showed the highest negative mood scores when allopregnanolone concentration was equal to physiological luteal phase concentration; on the other hand, mood deterioration was less evident at lower and higher allopregnanolone concentrations [73]. A recent randomized controlled trial (RCT) showed that dutasteride, a 5alpha-reductase inhibitor, blocking the conversion of progesterone to allopregnanolone, significantly decreased symptoms (i.e., irritability, anxiety, sadness, food cravings and bloating) in women with PMDD, with no effect in healthy controls [74]. On the other hand, it is likely that, at high concentration, allopregnanolone can cause sedation by activating the GABA receptor, but also paradoxical reactions with adverse mood in susceptible women [75]. CHC exerts neurobiological effects, including an alteration of allopregnanolone action, which is mostly related to a specific class of progestins that displays some androgenic properties [76]. However, in healthy women without underlying mood or anxiety disorder, this finding did not translate into adverse mood changes, despite lowering serum allopregnanolone levels [77]. Of note, a low estrogen pill containing the anti-androgenic progestogen drospirenone, which also displays anti-mineralcorticoid properties, could help treating premenstrual symptoms [78] even if such COC induced a decrease in anxiolytic steroids, such as allopregnanolone [79]. The effect of CHC on mood is highly variable and depends not only on the biochemical characteristics of exogenous steroids but also on the type and severity of symptoms. Indeed, there is generally a poor response in women with a history of mood affective disorders or PMDD [80,81]. Hormonal regimens reducing the estrogen-free interval or suppressing menstruation have been proposed as better choices [82,83], but more accurate studies are needed to effectively select suitable women in clinical practice.

Considering the ovarian cycle-related plasticity of GABA-A receptor (namely, changes in subunit composition and pharmacological properties) in the animal model [84], abnormal response to allopregnanolone may be prevented by the blockade of its action on GABA-A receptor. Indeed, allopregnanolone's effect can be antagonized by its endogenous isomer isoallopregnanolone (Sepranolone, UC1010), a GABA-A receptor modulating steroid antagonist (GAMSA) [85]. In a randomized, double-blind study of sepranolone in PMDD, the subcutaneous injection (10 mg) every 48 h during the 14 premenstrual days of 10 mg dose significantly attenuated symptoms, impairment, and distress. The drug was well tolerated and no safety concerns were identified, including menstrual cycle disturbances [86].

6. Opioid System

Early data indicated a transient premenstrual fall of plasma beta-endorphin in patients with PMS [87] and a reduced threshold of both the RIII reflex (Tr) and the psychophysical threshold for pain (Tp) during the luteal phase, especially in women reporting higher PMS scores [88]. Low central opioid tone during the mid-luteal phase, as also indicated by the loss of luteinizing-hormone (LH) and cortisol response to naloxone, supported a failure of adaptation in women with PMS who also displayed transient disturbances of their hypothalamus–pituitary–adrenal (HPA) axis [89,90]. In addition, the reduction in opioid inhibition was responsible for the increased frequency and reduced amplitude of LH pulses and consequent progesterone pattern of secretion in PMS patients, further supporting the notion that PMS is a neuroendocrine disorder [91].

7. Serotoninergic System

Women with PMS/PMDD displayed a serotoninergic dysregulation with atypical transmission, lower density of transporter receptors, decreased plasmatic serotonin levels in the luteal phase and higher serotonin responsiveness in follicular rather than in luteal phase [92]. Gonadal steroids significantly modulated serotoninergic system at multiple levels of the CNS, affecting mood and behavior [93]. Estrogens increased degradation of MAO, an enzyme involved in serotonin catabolism, resulting in a higher serotonin availability in the CNS, whereas progesterone potentiated MAO activity decreasing serotonin [94]. Moreover, a consistent finding in PMDD patients was the increased amygdala reactivity during the luteal phase [52]. Serotonin terminals strongly influenced this brain area processing emotions such anxiety and aggression under the modulation of gonadal steroids [9]. Interestingly, an interaction between serotonin and the GABAergic system was present through direct activation of the enzyme 3alpha-hydroxysteroid-deidrogenase, involved in the production of allopregnanolone [95]. Given the pivotal role of serotonin in modulating mood and behavior, serotonin reuptake inhibitors (SSRIs), i.e., fluoxetine, paroxetine, sertraline, escitalopram, and citalopram, are effective in reducing the symptoms of PMS/PMDD, whether taken only in the luteal phase or continuously. However, SSRIs' side effects may compromise compliance [96]. Even serotonin and norepinephrine reuptake inhibitors SNRIs (i.e., venlafaxine) have shown efficacy for treatment of PMS/PMDD, while antidepressants that predominantly affect noradrenergic or dopaminergic transmission do not significantly improve symptoms of PMS/PMDD [97]. At present, SSRIs are the first-line treatment for severe PMS/PMDD and their use, alone or in combination with cognitive behavioral therapy, has reached a consensus [8,13].

8. Other Trends in Neuroinflammation

Novel trends in neuroendocrinology link inflammatory processes to psychiatric and somatic disorders sharing common features with PMS/PMDD [98]. Estradiol and progesterone have anti-inflammatory and anti-oxidative properties, and their decline in the late luteal phase leads to increased endometrial oxidative stress and synthesis of pro-inflammatory prostaglandins, cytokines, chemokines and matrix metalloproteinases [99]. Specific chemokines predict more severe PMS symptoms, thus underlying a possible link between uterus and brain function through the uterine–chemokine–brain axis [100]. In

addition, some studies have found elevated levels of pro-inflammatory factors in women with PMS [101] and a positive relationship between C-reactive protein (CRP) levels with PMS symptom severity, especially mood, behavior and pain symptomatology [102]. However, further data are needed to validate the role of inflammation, oxidative stress, and antioxidant status in the pathophysiology of PMS [103]. Interestingly, circulating levels of brain-derived neurotrophic factor (BDNF), a regulator of neurogenesis in response to gonadal steroids, were reduced in women with PMS [104]. Other interesting perspectives point to neuroinflammation expressed via the GABAergic system as an etiological factor for PMS/PMDD [105], as well as to the potential influence of the gut–brain axis in mediating the severity of premenstrual symptoms due to progesterone-dependent changes of gut microbiota [106].

9. Conclusions

PMS and PMDD are very common disorders in women of reproductive age and generate a significant burden in daily life activities and relationships. They are centrally based disorders with an involvement of several neuroendocrine pathways. An altered brain sensitivity to allopregnanolone, a metabolite of progesterone produced after ovulation potentiating GABA activity, along with an impairment of opioid and serotoninergic systems, may justify the occurrence of emotional and behavioral symptoms. Chronic inflammation may represent the link between peripheral symptoms and central integrated responses to stressors with significant modulation by gonadal steroids. At present, therapeutic strategies address both the suppression of ovulatory function and the biochemistry of neural systems to manage PMS/PMDD. Promising approaches include the use of neuroactive molecules as the interface between brain and gonadal functions.

Author Contributions: R.E.N. writing, editing and supervision; L.C. writing and revision of the relevant literature; D.B., A.R., F.B., P.M., G.S., M.P. and R.R., revision of the scientific literature; L.T. writing, editing and supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We dedicate this manuscript to the commitment of Paola Vallarino who devoted great energy and time to the National Association PMS/PMDD in Italy in order to increase awareness, knowledge and education (https://itapms.org/, 23 January 2022).

Conflicts of Interest: R.E.N. had past financial relationships (lecturer, member of advisory boards and/or consultant) with Boehringer Ingelheim, Ely Lilly, Endoceutics, Gedeon Richter, HRA Pharma, Merck Sharpe & Dohme, Procter & Gamble Co, TEVA Women's Health Inc and Zambon SpA. At present, she has ongoing relationship with Astellas, Bayer HealthCare AG, Exceltis, Fidia, Novo Nordisk, Organon & Co, Palatin Technologies, Pfizer Inc, Shionogi Limited and Theramex. None of these companies are relevant to the present work. Other authors declare no conflicts of interest.

References

1. Critchley, H.O.; Babayev, E.; Bulun, S.E.; Clark, S.; Garcia-Grau, I.; Gregersen, P.K.; Kilcoyne, A.; Kim, J.-Y.J.; Lavender, M.; Marsh, E.E.; et al. Menstruation: Science and society. *Am. J. Obstet. Gynecol.* **2020**, *223*, 624–664. [CrossRef] [PubMed]
2. Roeder, H.J.; Leira, E.C. Effects of the Menstrual Cycle on Neurological Disorders. *Curr. Neurol. Neurosci. Rep.* **2021**, *21*, 34. [CrossRef] [PubMed]
3. Pinkerton, J.V.; Guico-Pabia, C.J.; Taylor, H.S. Menstrual cycle-related exacerbation of disease. *Am. J. Obstet. Gynecol.* **2010**, *202*, 221–231. [CrossRef] [PubMed]
4. Barrington, D.J.; Robinson, H.J.; Wilson, E.; Hennegan, J. Experiences of menstruation in high income countries: A systematic review, qualitative evidence synthesis and comparison to low- and middle-income countries. *PLoS ONE* **2021**, *16*, e0255001. [CrossRef]

5. Matteson, K.A.; Zaluski, K.M. Menstrual Health as a Part of Preventive Health Care. *Obstet. Gynecol. Clin. N. Am.* **2019**, *46*, 441–453. [CrossRef]
6. Tassorelli, C.; Greco, R.; Allena, M.; Terreno, E.; Nappi, R.E. Transdermal Hormonal Therapy in Perimenstrual Migraine: Why, When and How? *Curr. Pain Headache Rep.* **2012**, *16*, 467–473. [CrossRef]
7. Shulman, L.P. Gynecological Management of Premenstrual Symptoms. *Curr. Pain Headache Rep.* **2010**, *14*, 367–375. [CrossRef]
8. Ismaili, E.; Consensus Group of the International Society for Premenstrual Disorders; Walsh, S.; O'Brien, P.M.S.; Bäckström, T.; Brown, C.; Dennerstein, L.; Eriksson, E.; Freeman, E.W.; Ismail, K.M.K.; et al. Fourth consensus of the International Society for Premenstrual Disorders (ISPMD): Auditable standards for diagnosis and management of premenstrual disorder. *Arch. Women's Ment. Health* **2016**, *19*, 953–958. [CrossRef]
9. Yonkers, K.A.; O'Brien, P.S.; Eriksson, E. Premenstrual syndrome. *Lancet* **2008**, *371*, 1200–1210. [CrossRef]
10. American College of Obstetricians and Gynecologists. *Guidelines for Women's Health Care: A Resource Manual*, 4th ed.; American College of Obstetricians and Gynecologists: Washington, DC, USA, 2014; pp. 607–613.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American College of Obstetricians and Gynecologists: Washington, DC, USA, 2013.
12. Hofmeister, S.; Bodden, S. Premenstrual Syndrome and Premenstrual Dysphoric Disorder. *Am. Fam. Physician* **2016**, *94*, 236–240.
13. Stute, P.; Bodmer, C.; Ehlert, U.; Eltbogen, R.; Ging, A.; Streuli, I.; Von Wolff, M. Interdisciplinary consensus on management of premenstrual disorders in Switzerland. *Gynecol. Endocrinol.* **2017**, *33*, 342–348. [CrossRef] [PubMed]
14. Epperson, C.N.; Steiner, M.; Hartlage, S.A.; Eriksson, E.; Schmidt, P.J.; Jones, I.; Yonkers, K.A. Premenstrual Dysphoric Disorder: Evidence for a New Category for DSM-5. *Am. J. Psychiatry* **2012**, *169*, 465–475. [CrossRef] [PubMed]
15. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*, 11th ed.; WHO: Geneva, Switzerland, 2019.
16. Studd, J.; Nappi, R.E. Reproductive depression. *Gynecol. Endocrinol.* **2012**, *28*, 42–45. [CrossRef] [PubMed]
17. Studd, J. Severe premenstrual syndrome and bipolar disorder: A tragic confusion. *Menopause Int.* **2012**, *18*, 82–86. [CrossRef]
18. Slyepchenko, A.; Minuzzi, L.; Frey, B.N. Comorbid Premenstrual Dysphoric Disorder and Bipolar Disorder: A Review. *Front. Psychiatry* **2021**, *12*, 719241. [CrossRef]
19. Hall, E.; Steiner, M. Psychiatric Symptoms and Disorders Associated with Reproductive Cyclicity in Women: Advances in Screening Tools. *Women's Health* **2015**, *11*, 399–415. [CrossRef]
20. Steiner, M.; MacDougall, M.; Brown, E. The premenstrual symptoms screening tool (PSST) for clinicians. *Arch. Women's Ment. Health* **2003**, *6*, 203–209. [CrossRef]
21. Mortola, J.F.; Girton, L.; Beck, L.; Yen, S.S. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: The calendar of premenstrual experiences. *Obstet. Gynecol.* **1990**, *76*, 302–307. [CrossRef]
22. Sattar, K. Epidemiology of Premenstrual Syndrome, A Systematic Review and Meta-Analysis Study. *J. Clin. Diagn. Res.* **2014**, *8*, 106–109. [CrossRef]
23. Yonkers, K.A.; Simoni, M.K. Premenstrual disorders. *Am. J. Obstet. Gynecol.* **2018**, *218*, 68–74. [CrossRef]
24. Pilver, C.E.; Kasl, S.; Desai, R.; Levy, B.R. Health advantage for black women: Patterns in pre-menstrual dysphoric disorder. *Psychol. Med.* **2011**, *41*, 1741–1750. [CrossRef] [PubMed]
25. Rapkin, A.J.; Winer, S.A. Premenstrual syndrome and premenstrual dysphoric disorder: Quality of life and burden of illness. *Expert Rev. Pharm. Outcomes Res.* **2009**, *9*, 157–170. [CrossRef] [PubMed]
26. Gao, M.; Gao, D.; Sun, H.; Cheng, X.; An, L.; Qiao, M. Trends in Research Related to Premenstrual Syndrome and Premenstrual Dysphoric Disorder From 1945 to 2018: A Bibliometric Analysis. *Front. Public Health* **2021**, *9*, 596128. [CrossRef]
27. Potter, J.; Bouyer, J.; Trussell, J.; Moreau, C. Premenstrual Syndrome Prevalence and Fluctuation over Time: Results from a French Population-Based Survey. *J. Women's Health* **2009**, *18*, 31–39. [CrossRef] [PubMed]
28. Sander, B.; Gordon, J.L. Premenstrual Mood Symptoms in the Perimenopause. *Curr. Psychiatry Rep.* **2021**, *23*, 73. [CrossRef]
29. de Wit, A.E.; de Vries, Y.A.; de Boer, M.K.; Scheper, C.; Fokkema, A.; Janssen, C.A.; Giltay, E.J.; Schoevers, R.A. Efficacy of combined oral contraceptives for depressive symptoms and overall symptomatology in premenstrual syndrome: Pairwise and network meta-analysis of randomized trials. *Am. J. Obstet. Gynecol.* **2021**, *225*, 624–633. [CrossRef]
30. Choi, S.H.; Hamidovic, A. Association Between Smoking and Premenstrual Syndrome: A Meta-Analysis. *Front. Psychiatry* **2020**, *11*, 575526. [CrossRef]
31. Bertone-Johnson, E.R.; Hankinson, S.E.; Willett, W.C.; Johnson, S.R.; Manson, J.E. Adiposity and the Development of Premenstrual Syndrome. *J. Women's Health* **2010**, *19*, 1955–1962. [CrossRef]
32. Fernández, M.D.M.; Saulyte, J.; Inskip, H.; Takkouche, B. Premenstrual syndrome and alcohol consumption: A systematic review and meta-analysis. *BMJ Open* **2018**, *8*, e019490. [CrossRef]
33. Pearce, E.; Jolly, K.; Jones, L.; Matthewman, G.; Zanganeh, M.; Daley, A. Exercise for premenstrual syndrome: A systematic review and meta-analysis of randomised controlled trials. *BJGP Open* **2020**, *4*, 25. [CrossRef]
34. Perkonigg, A.; Yonkers, K.A.; Pfister, H.; Lieb, R.; Wittchen, H.-U. Risk Factors for Premenstrual Dysphoric Disorder in a Community Sample of Young Women: The role of traumatic events and posttraumatic stress disorder. *J. Clin. Psychiatry* **2004**, *65*, 1314–1322. [CrossRef] [PubMed]
35. Pereira, D.; Pessoa, A.R.; Madeira, N.; Macedo, A.; Pereira, A.T. Association between premenstrual dysphoric disorder and perinatal depression: A systematic review. *Arch. Women's Ment. Health* **2021**, *25*, 61–70. [CrossRef] [PubMed]

36. Osborn, E.; Brooks, J.; O'Brien, P.M.S.; Wittkowski, A. Suicidality in women with Premenstrual Dysphoric Disorder: A systematic literature review. *Arch. Women's Ment. Health* **2021**, *24*, 173–184. [CrossRef]
37. Nobles, C.J.; Thomas, J.J.; Valentine, S.E.; Gerber, M.; Ba, A.S.V.; Marques, L. Association of premenstrual syndrome and premenstrual dysphoric disorder with bulimia nervosa and binge-eating disorder in a nationally representative epidemiological sample. *Int. J. Eat. Disord.* **2016**, *49*, 641–650. [CrossRef] [PubMed]
38. Nappi, R.E.; Nappi, G. Neuroendocrine aspects of migraine in women. *Gynecol. Endocrinol.* **2012**, *28*, 37–41. [CrossRef] [PubMed]
39. Amital, D.; Herskovitz, C.; Fostick, L.; Silberman, A.; Doron, Y.; Zohar, J.; Itsekson, A.; Zolti, M.; Rubinow, A.; Amital, H. The Premenstrual Syndrome and Fibromyalgia—Similarities and Common Features. *Clin. Rev. Allergy Immunol.* **2010**, *38*, 107–115. [CrossRef] [PubMed]
40. Graziottin, A. The shorter, the better: A review of the evidence for a shorter contraceptive hormone-free interval. *Eur. J. Contracept. Reprod. Health Care* **2016**, *21*, 93–105. [CrossRef] [PubMed]
41. Stahl, S.M. Estrogen Makes the Brain a Sex Organ. *J. Clin. Psychiatry* **1997**, *58*, 421–422. [CrossRef]
42. Backstrom, T.; Sanders, D.; Leask, R.; Davidson, D.; Warner, P.; Bancroft, J. Mood, Sexuality, Hormones, and the Menstrual Cycle. II. Hormone Levels and Their Relationship to the Premenstrual Syndrome. *Psychosom. Med.* **1983**, *45*, 503–507. [CrossRef]
43. Soares, C.N.; Zitek, B. Reproductive hormone sensitivity and risk for depression across the female life cycle: A continuum of vulnerability? *J. Psychiatry Neurosci.* **2008**, *33*, 331–343.
44. Wise, D.D.; Felker, A.; Stahl, S.M. Tailoring treatment of depression for women across the reproductive lifecycle: The importance of pregnancy, vasomotor symptoms, and other estrogen-related events in psychopharmacology. *CNS Spectr.* **2008**, *13*, 647–662. [CrossRef] [PubMed]
45. Genazzani, A.; Gastaldi, M.; Bidzinska, B.; Mercuri, N.; Nappi, R.; Segre, A.; Petraglia, F. The brain as a target organ of gonadal steroids. *Psychoneuroendocrinology* **1992**, *17*, 385–390. [CrossRef]
46. Bernardi, F.; Pluchino, N.; Stomati, M.; Pieri, M.; Genazzani, A.R. CNS: Sex Steroids and SERMs. *Ann. N. Y. Acad. Sci.* **2003**, *997*, 378–388. [CrossRef] [PubMed]
47. Giatti, S.; Diviccaro, S.; Serafini, M.M.; Caruso, D.; Garcia-Segura, L.M.; Viviani, B.; Melcangi, R.C. Sex differences in steroid levels and steroidogenesis in the nervous system: Physiopathological role. *Front. Neuroendocr.* **2019**, *56*, 100804. [CrossRef] [PubMed]
48. Schweizer-Schubert, S.; Gordon, J.L.; Eisenlohr-Moul, T.A.; Meltzer-Brody, S.; Schmalenberger, K.M.; Slopien, R.; Zietlow, A.-L.; Ehlert, U.; Ditzen, B. Steroid Hormone Sensitivity in Reproductive Mood Disorders: On the Role of the GABAA Receptor Complex and Stress During Hormonal Transitions. *Front. Med.* **2021**, *7*, 479646. [CrossRef]
49. McEvoy, K.; Osborne, L.; Nanavati, J.; Payne, J.L. Reproductive Affective Disorders: A Review of the Genetic Evidence for Premenstrual Dysphoric Disorder and Postpartum Depression. *Curr. Psychiatry Rep.* **2017**, *19*, 94. [CrossRef]
50. Schmidt, P.J.; Nieman, L.K.; Danaceau, M.A.; Adams, L.F.; Rubinow, D.R. Differential Behavioral Effects of Gonadal Steroids in Women with and in Those without Premenstrual Syndrome. *N. Engl. J. Med.* **1998**, *338*, 209–216. [CrossRef]
51. Studd, J.W. A guide to the treatment of depression in women by estrogens. *Climacteric* **2011**, *14*, 637–642. [CrossRef]
52. Bixo, M.; Johansson, M.; Timby, E.; Michalski, L.; Bäckström, T. Effects of GABA active steroids in the female brain with a focus on the premenstrual dysphoric disorder. *J. Neuroendocr.* **2018**, *30*, e12553. [CrossRef]
53. Yen, J.-Y.; Lin, H.-C.; Liu, T.-L.; Long, C.-Y.; Ko, C.-H. Early- and Late-Luteal-Phase Estrogen and Progesterone Levels of Women with Premenstrual Dysphoric Disorder. *Int. J. Environ. Res. Public Health* **2019**, *16*, 4352. [CrossRef]
54. Bäckström, T.; Andreen, L.; Birzniece, V.; Björn, I.; Johansson, I.-M.; Nordenstam-Haghjo, M.; Nyberg, S.; Poromaa, I.S.; Wahlström, G.; Wang, M.; et al. The Role of Hormones and Hormonal Treatments in Premenstrual Syndrome. *CNS Drugs* **2003**, *17*, 325–342. [CrossRef] [PubMed]
55. Oinonen, K.A.; Mazmanian, D. To what extent do oral contraceptives influence mood and affect? *J. Affect. Disord.* **2002**, *70*, 229–240. [CrossRef]
56. Schmidt, P.J.; Rubinow, D.R. Sex Hormones and Mood in the Perimenopause. *Ann. N. Y. Acad. Sci.* **2009**, *1179*, 70–85. [CrossRef] [PubMed]
57. Chan, A.F.; Mortola, J.F.; Wood, S.H.; Yen, S.S. Persistence of premenstrual syndrome during low-dose administration of the pro-gesterone antagonist RU 486. *Obstet. Gynecol.* **1994**, *84*, 1001–1005.
58. Schmidt, P.J.; Nieman, L.K.; Grover, G.N.; Muller, K.L.; Merriam, G.R.; Rubinow, D.R. Lack of Effect of Induced Menses on Symptoms in Women with Premenstrual Syndrome. *N. Engl. J. Med.* **1991**, *324*, 1174–1179. [CrossRef] [PubMed]
59. Critchley, H.O.D.; Chodankar, R.R. 90 YEARS OF PROGESTERONE: Selective progesterone receptor modulators in gynaecological therapies. *J. Mol. Endocrinol.* **2020**, *65*, T15–T33. [CrossRef] [PubMed]
60. Comasco, E.; Kallner, H.K.; Bixo, M.; Hirschberg, A.L.; Nyback, S.; de Grauw, H.; Epperson, C.N.; Sundström-Poromaa, I. Ulipristal Acetate for Treatment of Premenstrual Dysphoric Disorder: A Proof-of-Concept Randomized Controlled Trial. *Am. J. Psychiatry* **2021**, *178*, 256–265. [CrossRef]
61. Baller, E.B.; Wei, S.-M.; Kohn, P.D.; Rubinow, D.R.; Alarcón, G.; Schmidt, P.J.; Berman, K.F. Abnormalities of Dorsolateral Prefrontal Function in Women with Premenstrual Dysphoric Disorder: A Multimodal Neuroimaging Study. *Am. J. Psychiatry* **2013**, *170*, 305–314. [CrossRef]

62. Wei, S.-M.; Baller, E.B.; Martinez, P.E.; Goff, A.C.; Li, H.J.; Kohn, P.D.; Kippenhan, J.S.; Soldin, S.J.; Rubinow, D.R.; Goldman, D.; et al. Subgenual cingulate resting regional cerebral blood flow in premenstrual dysphoric disorder: Differential regulation by ovarian steroids and preliminary evidence for an association with expression of ESC/E(Z) complex genes. *Transl. Psychiatry* **2021**, *11*, 206. [CrossRef]
63. Kaltsouni, E.; Fisher, P.M.; Dubol, M.; Hustad, S.; Lanzenberger, R.; Frokjaer, V.G.; Wikström, J.; Comasco, E.; Sundström-Poromaa, I. Brain reactivity during aggressive response in women with premenstrual dysphoric disorder treated with a selective progesterone receptor modulator. *Neuropsychopharmacology* **2021**, *46*, 1460–1467. [CrossRef]
64. Wyatt, K.M.; Dimmock, P.W.; O'Brien, P.S.; Ismail, K.M.; Jones, P.W. The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: A meta analysis. *BJOG Int. J. Obstet. Gynaecol.* **2004**, *111*, 585–593. [CrossRef] [PubMed]
65. Segebladh, B.; Borgström, A.; Nyberg, S.; Bixo, M.; Sundström-Poromaa, I. Evaluation of different add-back estradiol and progesterone treatments to gonadotropin-releasing hormone agonist treatment in patients with premenstrual dysphoric disorder. *Am. J. Obstet. Gynecol.* **2009**, *201*, 139.e1–139.e8. [CrossRef] [PubMed]
66. Rupprecht, R.; Holsboer, F. Neuroactive steroids: Mechanisms of action and neuropsychopharmacological perspectives. *Trends Neurosci.* **1999**, *22*, 410–416. [CrossRef]
67. Zorumski, C.F.; Paul, S.M.; Covey, D.F.; Mennerick, S. Neurosteroids as novel antidepressants and anxiolytics: GABA-A receptors and beyond. *Neurobiol. Stress* **2019**, *11*, 100196. [CrossRef]
68. Rapkin, A.J.; Morgan, M.; Goldman, L.; Brann, D.W.; Simone, D.; Mahesh, V.B. Progesterone metabolite allopregnanolone in women with premenstrual syndrome. *Obstet. Gynecol.* **1997**, *90*, 709–714. [CrossRef]
69. Monteleone, P.; Luisi, S.; Tonetti, A.; Bernardi, F.; Genazzani, A.D.; Luisi, M.; Petraglia, F.; Genazzani, A.R. Allopregnanolone concen-trations and premenstrual syndrome. *Eur. J. Endocrinol.* **2000**, *142*, 269–273. [CrossRef]
70. Lombardi, I.; Luisi, S.; Quirici, B.; Monteleone, P.; Bernardi, F.; Liut, M.; Casarosa, E.; Palumbo, M.; Petraglia, F.; Genazzani, A.R. Adrenal response to adrenocorticotropic hormone stimulation in patients with premenstrual syndrome. *Gynecol. Endocrinol.* **2004**, *18*, 79–87. [CrossRef]
71. Hantsoo, L.; Epperson, C.N. Allopregnanolone in premenstrual dysphoric disorder (PMDD): Evidence for dysregulated sensitivity to GABA-A receptor modulating neuroactive steroids across the menstrual cycle. *Neurobiol. Stress* **2020**, *12*, 100213. [CrossRef]
72. Smith, S.S.; Gong, Q.H.; Li, X.; Moran, M.H.; Bitran, D.; Frye, C.A.; Hsu, F.-C. Withdrawal from 3α-OH-5α-Pregnan-20-One Using a Pseudopregnancy Model Alters the Kinetics of Hippocampal GABAA-Gated Current and Increases the GABAAReceptor α4 Subunit in Association with Increased Anxiety. *J. Neurosci.* **1998**, *18*, 5275–5284. [CrossRef]
73. Andreen, L.; Sundström-Poromaa, I.; Bixo, M.; Nyberg, S.; Bäckström, T. Allopregnanolone concentration and mood—a bimodal association in postmenopausal women treated with oral progesterone. *Psychopharmacology* **2006**, *187*, 209–221. [CrossRef]
74. Martinez, P.E.; Rubinow, D.R.; Nieman, L.K.; Koziol, D.E.; Morrow, A.L.; Schiller, C.E.; Cintron, D.; Thompson, K.D.; Khine, K.K.; Schmidt, P.J. 5α-Reductase Inhibition Prevents the Luteal Phase Increase in Plasma Allopregnanolone Levels and Mitigates Symptoms in Women with Premenstrual Dysphoric Disorder. *Neuropsychopharmacology* **2016**, *41*, 1093–1102. [CrossRef] [PubMed]
75. Andréen, L.; Nyberg, S.; Turkmen, S.; van Wingen, G.; Fernandez, G.; Bäckström, T. Sex steroid induced negative mood may be explained by the paradoxical effect mediated by GABAA modulators. *Psychoneuroendocrinology* **2009**, *34*, 1121–1132. [CrossRef] [PubMed]
76. Porcu, P.; Serra, M.; Concas, A. The brain as a target of hormonal contraceptives: Evidence from animal studies. *Front. Neuroendocr.* **2019**, *55*, 100799. [CrossRef] [PubMed]
77. Rapkin, A.J.; Morgan, M.; Sogliano, C.; Biggio, G.; Concas, A. Decreased neuroactive steroids induced by combined oral contraceptive pills are not associated with mood changes. *Fertil. Steril.* **2006**, *85*, 1371–1378. [CrossRef]
78. Lopez, L.M.; A Kaptein, A.; Helmerhorst, F.M. Oral contraceptives containing drospirenone for premenstrual syndrome. *Cochrane Database Syst. Rev.* **2012**, *15*, CD006586. [CrossRef]
79. Paoletti, A.M.; Lello, S.; Fratta, S.; Orrù, M.; Ranuzzi, F.; Sogliano, C.; Concas, A.; Biggio, G.; Melis, G.B. Psychological effect of the oral contraceptive formulation containing 3 mg of drospirenone plus 30 μg of ethinyl estradiol. *Fertil. Steril.* **2004**, *81*, 645–651. [CrossRef]
80. Bengtsdotter, H.; Lundin, C.; Danielsson, K.G.; Bixo, M.; Baumgart, J.; Marions, L.; Brynhildsen, J.; Malmborg, A.; Lindh, I.; Poromaa, I.S. Ongoing or previous mental disorders predispose to adverse mood reporting during combined oral contraceptive use. *Eur. J. Contracept. Reprod. Health Care* **2018**, *23*, 45–51. [CrossRef]
81. Fruzzetti, F.; Fidecicchi, T. Hormonal Contraception and Depression: Updated Evidence and Implications in Clinical Practice. *Clin. Drug Investig.* **2020**, *40*, 1097–1106. [CrossRef]
82. Rapkin, A.J.; Korotkaya, Y.; Taylor, K.C. Contraception counseling for women with premenstrual dysphoric disorder (PMDD): Current perspectives. *Open Access J. Contracept.* **2019**, *10*, 27–39. [CrossRef]
83. Coffee, A.L.; Kuehl, T.J.; Willis, S.; Sulak, P.J. Oral contraceptives and premenstrual symptoms: Comparison of a 21/7 and extended regimen. *Am. J. Obstet. Gynecol.* **2006**, *195*, 1311–1319. [CrossRef]
84. Maguire, J.; Stell, B.; Rafizadeh, M.; Mody, I. Ovarian cycle–linked changes in GABAA receptors mediating tonic inhibition alter seizure susceptibility and anxiety. *Nat. Neurosci.* **2005**, *8*, 797–804. [CrossRef] [PubMed]
85. Bäckström, T.; Das, R.; Bixo, M. Positive GABA $_{A}$ receptor modulating steroids and their antagonists: Implications for clinical treatments. *J. Neuroendocr.* **2021**, *34*, e13013. [CrossRef] [PubMed]

86. Bäckström, T.; Ekberg, K.; Hirschberg, A.L.; Bixo, M.; Epperson, C.N.; Briggs, P.; Panay, N.; O'Brien, S. A randomized, double-blind study on efficacy and safety of sepranolone in premenstrual dysphoric disorder. *Psychoneuroendocrinology* **2021**, *133*, 105426. [CrossRef] [PubMed]
87. Facchinetti, F.; Martignoni, E.; Petraglia, F.; Sanees, M.G.; Nappi, G.; Genazzani, A.R. Premenstrual fall of plasma β-endorphin in patients with premenstrual syndrome. *Fertil. Steril.* **1987**, *47*, 570–573. [CrossRef]
88. Tassorelli, C.; Sandrini, G.; Cecchini, A.P.; Nappi, R.E.; Sances, G.; Martignoni, E. Changes in Nociceptive Flexion Reflex Threshold Across the Menstrual Cycle in Healthy Women. *Psychosom. Med.* **2002**, *64*, 621–626. [CrossRef]
89. Rabin, D.S.; Schmidt, P.J.; Campbell, G.; Gold, P.W.; Jensvold, M.; Rubinow, D.R.; Chrousos, G.P. Hypothalamic-Pituitary-Adrenal Function in Patients with the Premenstrual Syndrome. *J. Clin. Endocrinol. Metab.* **1990**, *71*, 1158–1162. [CrossRef]
90. Facchinetti, F.; Fioroni, L.; Martignoni, E.; Sances, G.; Costa, A.; Genazzani, A.R. Changes of opioid modulation of the hypothalamo-pituitary-adrenal axis in patients with severe premenstrual syndrome. *Psychosom. Med.* **1994**, *56*, 418–422. [CrossRef]
91. Facchinetti, F.; Genazzani, A.D.; Martignoni, E.; Fioroni, L.; Nappi, G.; Genazzani, A.R. Neuroendocrine changes in luteal function in patients with premenstrual syndrome. *J. Clin. Endocrinol. Metab.* **1993**, *76*, 1123–1127. [CrossRef]
92. Halbreich, U.; Tworek, H. Altered Serotonergic Activity in Women with Dysphoric Premenstrual Syndromes. *Int. J. Psychiatry Med.* **1993**, *23*, 1–27. [CrossRef]
93. Barth, C.; Villringer, A.; Sacher, J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. *Front. Neurosci.* **2015**, *9*, 37. [CrossRef]
94. Rapkin, A.J.; Akopians, A.L. Pathophysiology of premenstrual syndrome and premenstrual dysphoric disorder. *Menopause Int.* **2012**, *18*, 52–59. [CrossRef] [PubMed]
95. Griffin, L.D.; Mellon, S.H. Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 13512–13517. [CrossRef] [PubMed]
96. Marjoribanks, J.; Brown, J.; O'Brien, P.M.S.; Wyatt, K. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst. Rev.* **2013**, *2013*, CD001396. [CrossRef] [PubMed]
97. di Scalea, T.L.; Pearlstein, T. Premenstrual Dysphoric Disorder. *Med. Clin. N. Am.* **2019**, *103*, 613–628. [CrossRef]
98. Bertone-Johnson, E.R. Chronic Inflammation and Premenstrual Syndrome: A Missing Link Found? *J. Women's Health* **2016**, *25*, 857–858. [CrossRef]
99. Jabbour, H.N.; Kelly, R.W.; Fraser, H.M.; Critchley, H.O.D. Endocrine Regulation of Menstruation. *Endocr. Rev.* **2006**, *27*, 17–46. [CrossRef]
100. Roomruangwong, C.; Sirivichayakul, S.; Carvalho, A.F.; Maes, M. The uterine-chemokine-brain axis: Menstrual cycle-associated symptoms (MCAS) are in part mediated by CCL2, CCL5, CCL11, CXCL8 and CXCL10. *J. Affect. Disord.* **2020**, *269*, 85–93. [CrossRef]
101. Bertone-Johnson, E.R.; Ronnenberg, A.G.; Houghton, S.; Nobles, C.; Zagarins, S.E.; Takashima-Uebelhoer, B.B.; Faraj, J.L.; Whitcomb, B.W. Association of inflammation markers with menstrual symptom severity and premenstrual syndrome in young women. *Hum. Reprod.* **2014**, *29*, 1987–1994. [CrossRef]
102. Gold, E.B.; Wells, C.; Rasor, M.O. The Association of Inflammation with Premenstrual Symptoms. *J. Women's Health* **2016**, *25*, 865–874. [CrossRef]
103. Granda, D.; Szmidt, M.; Kaluza, J. Is Premenstrual Syndrome Associated with Inflammation, Oxidative Stress and Antioxidant Status? A Systematic Review of Case–Control and Cross-Sectional Studies. *Antioxidants* **2021**, *10*, 604. [CrossRef]
104. Cubeddu, A.; Bucci, F.; Giannini, A.; Russo, M.; Daino, D.; Russo, N.; Merlini, S.; Pluchino, N.; Valentino, V.; Casarosa, E.; et al. Brain-derived neurotrophic factor plasma variation during the different phases of the menstrual cycle in women with premenstrual syndrome. *Psychoneuroendocrinology* **2011**, *36*, 523–530. [CrossRef] [PubMed]
105. Bannister, E. There is increasing evidence to suggest that brain inflammation could play a key role in the aetiology of psychiatric illness. Could inflammation be a cause of the premenstrual syndromes PMS and PMDD? *Post Reprod. Health* **2019**, *25*, 157–161. [CrossRef] [PubMed]
106. Roomruangwong, C.; Carvalho, A.F.; Geffard, M.; Maes, M. The menstrual cycle may not be limited to the endometrium but also may impact gut permeability. *Acta Neuropsychiatr.* **2019**, *31*, 294–304. [CrossRef] [PubMed]