AN OVERVIEW ON PREMENSTRUAL SYNDROME

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ABSTRACT

In the weeks leading up to menstruation, the majority of women of reproductive age experience some physical discomfort or distress. Although symptoms are frequently not severe enough to interfere significantly with daily activities, they can be. Thus, severe premenstrual syndrome (PMS) affects 5–8% of women; the majority of these individuals also match the criteria for premenstrual dysphoric disorder (PMDD). The most bothersome symptoms are those that affect mood and behaviour, such as irritability, tension, depression, weepiness, and mood swings, however physical issues like breast soreness and bloating can also be a concern. We discuss two basic treatments for severe PMS: one that targets the hypothalamus-pituitary-ovary axis and the other that targets brain serotonergic synapses. We also present theories regarding the underlying causes of severe PMS. The symptoms are caused by fluctuations in gonadal hormone levels, hence treatments that stop ovarian cyclicity, such as long-acting analogues of gonadotropin-releasing hormone (GnRH) or oestradiol (given as patches or implants), can successfully diminish the symptoms. It is also widely known that serotonin reuptake inhibitors, whether used continuously or just during luteal stages, are helpful.

Keywords: *PMS, Premenstrual syndrome, premenstrual disorder, premenstrual dysphoric disorder*

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INTRODUCTION

In the premenstrual stage of the menstrual cycle, the majority of women of reproductive age experience one or more physical or emotional symptoms. Although the symptoms are minor, 5- 8% of people also experience significant distress or functional impairment along with their moderate to severe symptoms. Clinically significant premenstrual symptoms were referred to as premenstrual tension (PMT) or premenstrual syndrome in early medical publications on this subject (PMS). The term "premenstrual tension syndrome" is listed under the category "Diseases of the Genitourinary Tract" in the WHO International Classification of Diseases (ICD). However, because it is not defined by certain criteria and does not identify severity, this description, like PMS and PMT, is not helpful for clinical diagnosis, drug labelling, or research.

Premenstrual syndrome (PMS) is a term for a condition in which a woman complains of repeated psychological and/or physical symptoms that only arise during the luteal phase of the menstrual cycle and frequently go away by the end of menstruation. Additionally, the symptoms may last even while bleeding (for details of psychological, behavioural, and physical symptoms commonly reported in women with PMS). Significant premenstrual syndrome RCTs have different definitions of severe PMS, however in recent research, premenstrual dysphoric disorder, one form of severe PMS, has been diagnosed using standardised criteria (PMDD). The criteria are based on at least five symptoms, one of which must be one of the four fundamental psychological symptoms (chosen from a list of 17 physical and psychological symptoms) and must be severe prior to the onset of menstruation and mild or nonexistent following it. Depression, feeling helpless or guilty, anxiety/ tension, mood swings, irritability/ persistent anger, decreased interest, poor concentration, fatigue, food cravings or increased appetite, sleep disturbance, feeling out of control or overwhelmed, poor coordination, headache, aches, swelling/ bloating/ weight gain, cramps, and breast tenderness are among the 17 symptoms.

Commonly reported symptoms in women with premenstrual syndrome

Psychological symptoms	Irritability, depression, crying/ tearfulness, anxiety, tension, mood swings, lack of concentration, confusion, forgetfulness, unsociableness, restlessness, temper outbursts/ anger, sadness/ blues, loneliness
Behavioural symptoms	Fatigue, dizziness, sleep/ insomnia, decreased efficiency, accident prone, sexual interest changes, increased energy, tiredness
Physical symptoms: Pain	Headache/ migraine, breast tenderness/ soreness/ pain/ swelling (collectively known as premenstrual mastalgia), back pain, abdominal cramps, general pain
Physical symptoms: Bloatedness and Swelling	Weight gain, abdominal bloating or swelling, oedema of arms and legs, water retention
Appetite symptoms	Increased appetite, food cravings, nausea

AETIOLOGY AND PATHOPHYSIOLOGY

A certain amount of discomfort during the luteal phase should generally be regarded as natural rather than harmful as the majority of women of reproductive age suffer at least modest premenstrual symptoms. In terms of evolution, luteal mood alterations may be relics of the oestrous cycle-related behavioural fluctuations displayed by lower species with the initial goal of encouraging reproduction: when oestrogen levels are high before ovulation, sexual receptivity is raised and aggression is decreased. Even if irritation and anger in people

may not exactly be the same as aggression in mice and other animals, such cycle-related variations in behaviour are likely to be connected to cycle-related variations in behaviour in women.

Historically, prolonged amenorrhea was caused by recurrent pregnancies, lactation, or malnutrition; however, this condition has altered as a result of improvements in nutrition and our ability to manage reproduction. As a result, premenstrual symptoms and cyclic changes in oestrogen and progesterone in women now last for significantly longer periods of time.

Researchers have long hypothesised that gonadal steroids are involved in the pathophysiology of PMS because the relationship between symptom presentation and menstrual cyclicity is the most distinctive aspect of the condition. According to this theory, symptoms are absent during an ovulatory cycles, eliminated by ovarian surgery or ovulation inhibitor therapy, and restored by the injection of exogenous hormones.

However, it is still unclear how modifications in sex steroid synthesis result in luteal symptoms. Many researchers contend that the decline in progesterone levels in the late luteal phase triggers premenstrual symptoms and connects this to changes in CNS neurotransmitters such as aminobutyric acid (GABA). However, the fact that many women experience symptoms that begin during ovulation and during the early luteal phase—i.e., before the fall in progesterone has begun— contradicts this notion.

Additionally, daily progesterone injection for a month caused symptoms (with some delay) in women whose endogenous hormonal cyclicity had been eliminated by pre-treatment with an agonist of gonadotropin-releasing hormone (GnRH), despite hormone concentrations remaining steady. Additionally, if a luteal decline in progesterone was the cause of the condition, progesterone delivery during this phase would be a successful treatment, but it is not. Thus, it is more plausible that symptoms are brought on by either the preovulatory peak in oestradiol or the postovulatory rise in progesterone, or both. However, this explanation is unable to explain why symptoms for some women start at ovulation while they do not for others until late in the luteal phase.

It is also uncertain how much progesterone, as opposed to oestrogen, contributes to symptom onset. Progesterone , rather than oestrogen, may be the cause of dysphoria, according to post menopausal women on sequential hormone replacement treatment; oestrogen also has an antidepressant impact on perimenopausal depressed women. Notably, the days of the cycle when symptoms are most likely to manifest are those when progesterone outweighs oestrogen. However, oestradiol has been shown to be just as efficient as gestagen at eliciting PMS-like symptoms, and the oestrogen in hormone replacement treatment can amplify the misery brought on by gestagen. Additionally, luteal administration of an oestrogen antagonist lessens premenstrual mastalgia while luteal administration of oestrogen has been shown to exacerbate premenstrual symptoms.

The generation of gonadal steroids appears to be similar in women with and without PMS, suggesting that PMS may instead be related to increased responsiveness to normal, changing hormone concentrations. In line with this, exogenous gonadal steroids administered to women with PMS but not to controls caused PMS-like symptoms after pretreatment with an ovulation inhibitor.

According to twin studies, there may be a heritable component to the increased propensity for disphoria caused by the effects of sex hormones on the brain. Stress, stressful situations, and a high body mass index are additional potential risk factors for PMS.

Thyroid indices are said to be more variable in PMS-affected women than in controls when it comes to hormones other than sex steroids. Additionally, PMS has been linked to abnormalities in circadian rhythms, just as anxiety and mood disorders. Accordingly, some studies contend that although the timing of certain hormones' excretion may be atypical in PMS-affected women, their absolute levels—including those of melatonin, cortisol, thyroid-stimulating hormone, and prolactin—are not altered.

PATHOPHYSIOLOGY OF SOMATIC SYMPTOMS

Premenstrual somatic sensations, such as breast tenderness, bloating, joint and muscle pain, are still not well understood. It is still unknown if they are caused by changes in peripheral hormone-responsive tissues or by a diminished tolerance for pain when in a dysphoric mental state. Additionally, drugs that aim to control brain neurotransmission, like SRIs, have at least a palliative effect on somatic symptoms. However, studies have not been able to show that women who report these symptoms have fluid retention or breast growth. On the other

hand, bromocriptine or chasteberry, a dopamine D2 receptor agonist that lowers serum prolactin concentrations but not mood symptoms, are effective treatments for premenstrual mastalgia. Danazol or an oestrogen-receptor antagonist may also have a specific impact on premenstrual mastalgia when administered luteally.

Early research findings suggest that aldosterone or deoxycorticosterone, an aldosterone agonist and progesterone metabolite, play a role in the pathogenesis of premenstrual bloating. Significant stomach bloating can occur without weight gain, calling into question any explanation that involves water retention. Premenstrual headache, migraine, and epilepsy are conditions that many individuals believe should be treated independently from PMS rather than as components of it.

Notably, SRIs have no effect on premenstrual headache. Even though menopausal symptoms, endometriosis, and painful menstrual bleeding (dysmenorrhoea) are commonly confused for PMS, they must be distinguished from one another in research and clinical settings.

TREATMENT

Women with suspected PMS should have their medical histories checked for illnesses like depression, dysthymic disorder, anxiety disorders, and hypothyroidism before considering medication. A history that evaluates the prevalence of these characteristics, as well as domestic violence, should be collected in light of the potential linkages between PMS and sexual abuse, as well as with post-traumatic stress disorder. Even though alcohol and illegal drugs can cause or make anxiety and dysphoria worse, some people with anxiety and mood disorders, including PMS,try to manage their symptoms by using them. Therefore, during the review, the potential usage of such substances should be covered.

The Daily Record of Severity of Problems is one of several tools that have been developed for this purpose. PMS and PMDD diagnoses (per ACOG criteria) need daily documenting of symptoms across two menstrual cycles. However, a lady with significant symptoms might not be prepared to put up with the medical delay brought on by such recording. The advantage for the patient and the doctor is that it allows for a clear diagnostic differentiation between PMS/ PMDD on the one hand, and premenstrual exacerbation of an underlying psychiatric problem, or a condition without a connection to the menstrual cycle, on the other.

Few PMS treatment plans are backed by clinical data, despite the fact that many of them have been promoted as successful. A unique effect on a single symptom may be obscured by using summary measures that evaluate change in multiple symptoms since successful therapies do not always diminish all symptoms equally. Treatment should be customised based on the symptom profile, as some drugs may be more effective for specific symptoms.

SEROTONIN REUPTAKE INHIBITORS (SRIs)

The effectiveness of SRIs in managing PMS/ PMDD has been demonstrated in numerous clinical trials, with response rates for active treatment typically ranging from 60 to 90% compared to 30 to 40% for placebo. Clomipramine, a serotonergic tricyclic antidepressant, the selective SRIs citalopram, escitalopram, fluoxetine, paroxetine, and sertraline, as well as the serotonin and noradrenaline reuptake inhibitor venlafaxine, have all been proven to be effective. SRIs increase quality of life and social functioning while reducing physical and emotional symptoms. SRIs are frequently recognised as the first line of treatment for PMS patients who have significant mood disorders.

SRIs are more successful for treating PMS than antidepressants that primarily target noradrenergic transmission, suggesting that their impact on the condition extends beyond that of an antidepressant. This idea is further bolstered by the fact that, in contrast to antidepressants, the positive effect of SRIs for PMS starts working right away. Due to PMS's quick onset of action, intermittent therapy from midcycle to menses is a viable substitute for continuous therapy. According to data, even shorter active treatment durations are superior to placebo.

According to clinical evidence, the majority of PMS-afflicted women choose intermittent over continuous treatment. However, intermittent SRI administration appears to be less helpful for treating somatic symptoms than for treating mood symptoms, as well as, it is less beneficial for treating somatic symptoms than continuous administration.

SRI side effects are typically not severe. During the first few days of treatment, nausea is extremely common but quickly goes away. Even with intermittent therapy, it typically does not come back. Reduced libido and anorgasmia are not rare and frequently last the entire course of therapy, but they do not exist during the drug-free periods of intermittent therapy. SRIs are not addictive, although many people have withdrawal symptoms when they abruptly stop taking their drug. Discontinuation symptoms are rarely a problem when SRIs are used occasionally, indicating that a 2-week exposure duration is insufficient to cause withdrawal symptoms. SRIs are permitted in the USA, Canada, and Australia for the treatment of PMDD, but not in Europe. The European Agency for the Evaluation of Medicinal Products (EMEA) cancelled the current licence for Fluoxetine in four European countries due to the lack of a European consensus on diagnostic criteria and terminology for PMS/PMDD (including the UK). They stated that there is no clear distinction between moderate PMS and PMDD and that the approval of an SRI for PMDD could result in the over prescription of medication in circumstances when it is not necessary. They also noted that as PMDD is a chronic disorder, it would be necessary to do long-term studies to gauge how well it will be tolerated over the long term. These same reasons, however, might be used to other chronic disorders that SRIs are licensed for in Europe, such as generalised anxiety disorder, social phobia, and dysthymic disorder, for which it is equally true that there is no clear distinction between mild and severe forms.

Other CNS-acting medications tried for PMS do not appear to be very efficient. Buspirone, a serotonergic 5-HT1A agonist, has only marginally positive effects whereas lithium and non- serotonergic antidepressants have been utterly unsuccessful. Alprazolam, a high-affinity benzodiazepine, has inconsistent efficacy data, but it can be a helpful supplementary treatment for women who list premenstrual sleeplessness or extreme anxiety as significant complaints. Due to the possibility of dependence, treatment with alprazolam should be closely watched, especially ifthe patient has a history of substance misuse.

HORMONAL INTERVENTIONS

Many people believe that medications that target these hormones are the most logical strategy for lowering premenstrual complaints because sex steroids have a role in the initiation of premenstrual symptoms. We stress, however, that there is no evidence to support the widely-held theory that progesterone insufficiency causes PMS. As a result, attempts to treat PMS with progesterone (or with oestrogen) in the luteal phase have failed. Despite this, progesterone is still used as a first-line treatment for PMS by many general practitioners in the UK. It is typically administered in the form of pessaries. The goal of hormonal treatment for PMS is therefore to stop the natural hypothalamic-pituitary-gonadal cyclicity that is causing the symptoms, not just to repair ahormonal aberration. Giving a long-acting GnRH agonist can accomplish this. There is strong evidence to support the effectiveness of these preparations. However, because they cause a "medical menopause," which is accompanied by normal menopausal symptoms, including flushing, and a risk of osteoporosis if the therapy is prolonged, they are relatively invasive. Oestrogen replacement therapy paired with a gestagen to prevent oestrogen-induced endometrial hyperplasia can stop these side effects, which are totally caused by oestrogen shortage. Even though some patients claim that gestagens cause their symptoms to resurface, a meta-analysis indicates that this alternative is frequently practical. Combining a GnRH agonist with tibolone, a synthetic oestrogen, progestogen, and androgen receptor agonist, continuously is a potential approach. Levonorgestrel-releasing intrauterine system is another method of avoiding gestagen-induced symptom recurrence; systemic hormone concentrations via this route of delivery are minimal once the endometrium has undergone atrophic transformation. Although there is a great deal of clinical experience, there is just a very small amount of evidence to support this method.

PMS is also eliminated by other ways to limit ovarian cyclicity, such as bilateral oophorectomy surgery (which can be done laparoscopically). Oophorectomy necessitates hormonal add-back with oestrogen plus gestagens, just like treatment with long-acting GnRH agonists. Oestrogen can be taken alone if bilateral oophorectomy and hysterectomy are coupled.

Most PMS patients find surgical intervention to be an excessively intrusive treatment. However, patients who need a hysterectomy for a different gynaecological disease typically need to think about having their ovaries

removed or preserved. In younger women, preservation of the ovaries is almost usually recommended; however, if a patient has severe PMS, preservation of the ovaries may be contraindicated, and the woman may want to have her ovaries removed. Although there is no research to back this up, taking a GnRH agonist for two to three months before surgery will make the patient more aware of the potential consequences of having her ovaries removed and may help her make a more informed choice. One of the simplest methods to successfully eliminate PMS symptoms is to administer oestrogen at amounts that suppress ovulation. It has been suggested that oestrogen be supplied as a transdermal patch or subcutaneous implant rather than oral medication, which is often not advocated. The doses needed for patches could be 100, 150, or 200 g; these are often higher than those needed for hormone replacement therapy but lower than those needed for the oral contraceptive pill. To stop endometrial hyperplasia, the patient will require progestogen unless she underwent a hysterectomy. Unless it is administered within a progesterone-releasing levonorgestrel-containing intrauterine device, this could cause PMS to flare up again in certain patients. Evidence for the efficacy of this combination as a treatment for PMS is limited, despite the fact that there is no doubt that oestrogen inhibits ovulation and symptoms and that the intrauterine system prevents hyperplasia.

Oral contraceptives are frequently prescribed by doctors to treat PMS, however, there have not been many positive placebo-controlled studies. Oral contraceptives with few hormone-free days may also be helpful for PMS since women using them may experience more hormone-related symptomsduring the 7-day hormone-free interval than during hormone consumption, and because decreasingthe hormone-free interval minimises such complaints. Studies support this by demonstrating the efficacy of a novel oral contraceptive that requires a 4-day hormone-free gap rather than a 7-day interval. The therapeutic effectiveness of this oral contraceptive may, however, in part be attributable to the anti-aldosterone and antiandrogen effects of the gestagen component, drospirenone.

When used at dosages that prevent ovulation, the synthetic androgen and gonadotropin inhibitor danazol is helpful for treating PMS; nevertheless, hirsutism and the possibility of teratogenicity prevent its usage as a first-line treatment. Danazol, when used in small dosages just during the luteal phase of the cycle, has few undesirable side effects and is useful in treating mastalgia but not the general symptoms of PMS. An oestrogen receptor antagonist administered luteally also lessens mastalgia.

Bright light therapy may be beneficial for treating moderate to severe PMS due to potential changes in circadian rhythmicity. This strategy appears to be beneficial according to one controlled trial, but it is unclear how long the potential therapeutic effects will last. Although there is debate over the relationship between premenstrual somatic symptoms and water retention, the aldosterone antagonist spironolactone appears to be useful for PMS symptoms of bloating and breast pain.

Numerous methodological flaws were present in the majority of trials evaluating the therapeutic effects of vitamin B6 (pyridoxine) in PMS, including the absence of prospective ratings. Although it is impossible to draw firm conclusions on efficacy, a quantitative review revealed that B6 is superior to a placebo. Calcium supplements and Vitex agnus-castus (chasteberry), which is said to have anti-prolactin properties, may be beneficial for women with PMS. Evening primrose oil has gained popularity, however it does not seem to work very well. Numerous studies have evaluated the therapeutic advantage of magnesium therapy, and some—but not all—of them have found it to be successful. These trials, however limited, are not conclusive, and magnesium may not be well tolerated.

Although limiting sugar intake and having several small meals throughout the day are recommended in books and magazine articles written for the general audience, there is no evidence to back-up these tactics. On the other hand, studies on diets that increase the proportion of complex carbohydrates in the diet reveal benefits, which may be related to improved tryptophan transport into the brain, which causes a brief rise in the synthesis of this transmitter. Exercise and cognitive behavioural therapy have both been touted as helpful.

Other PMS treatments have been evaluated, however they cannot yet be classified as evidence-based due to the fact that the trials were not controlled, had flaws, or had their results not been duplicated. They include the opioid receptor blocker naltrexone, the non-steroidal anti- inflammatory drugs mefenamic acid and naproxen, and others.

CONCLUSION

There is strong empirical evidence to suggest that severe premenstrual disorders can significantly impede one's ability to function. About 5% of all women of reproductive age consistently report having severe PMS. PMS management is difficult. It is critical to obtain a clear diagnosis earlier on rather than relying solely on the patient's diagnosis. Preferably, this assessment should be carried out by the general practitioner before referral to a gynaecologist or a psychiatrist. It is necessary to distinguish PMS/ PMDD from other diagnoses, including depression and anxiety disorders, premenstrual exacerbation of another disorder, and mild physiological symptoms requiring no more than reassurance. The best way to diagnose a condition is to rate its symptoms on a daily basis for at least one menstrual cycle. Clinicians can either ask patients to choose their worst symptoms and record their severity on a daily basis, or they can use a validated scale like the Daily Record of Severity of Problems. The key to diagnosis is the absence of symptoms following menstruation. The symptoms of PMS appear to be brought on by changes in these hormones rather than aberrant amounts of sex steroids, with sufferers being more sensitive to these oscillations than controls. The transmitters, serotonin and GABA have been linked to the fundamental process of brain function. Treatments that prevent ovulation, such as SRIs, GnRH analogues, oestrogen, and some modern oral contraceptives—which some institutions classify as first-line medicines in individuals with severe symptoms—all of them successfully alleviate the symptoms.

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