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CASE REPORT

A Patient's Significant Clinical Improvement from Transdermal Progesterone Cream for Premenstrual Syndrome: A Case Report

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ABSTRACT

Background: Premenstrual syndrome (PMS) is a prevalent global condition characterized by physical and distressing psychological symptoms during the luteal phase. Its etiology is linked to hormonal fluctuations and abnormal allopregnanolone metabolism, leading to impaired gamma-aminobutyric acid-A (GABA-A) receptor sensitivity and an altered stress response. While selective serotonin reuptake inhibitors are frequently used, transdermal progesterone cream (TPC) offers a physiological alternative by avoiding first-pass hepatic metabolism and facilitating steady neurosteroid conversion in the central nervous system.

Case Report: A 45-year-old woman with a history of developmental trauma, depression, and postpartum anxiety presented with severe premenstrual mood lability, irritability, and associated physical symptoms that caused marked interpersonal strain. The patient was prescribed a cyclical regimen of TPC (20 mg applied daily on days 12 to 26 of her menstrual cycle) combined with specific natural health products, including a B-complex and magnesium bisglycinate. At her first follow-up two months later, the patient reported an 80% improvement in her overall condition, highlighted by a resolution of acute anxiety episodes and premenstrual mood fluctuations. Long-term correspondence confirmed sustained emotional baseline stability and life-changing clinical well-being. The protocol was well-tolerated without adverse events.

Conclusion: This case demonstrates that TPC is a safe, effective, and pathophysiologically sound intervention for women suffering from severe PMS. By stabilizing the estrogen-to-progesterone ratio and normalizing GABAergic signaling, TPC can provide profound emotional and physical stability.

Keywords: Allopregnanolone; Gamma-Aminobutyric Acid-A Receptor Sensitivity; Mood Lability; Neurosteroidogenesis; Natural Health Products; Premenstrual Syndrome

INTRODUCTION

Premenstrual syndrome (PMS) is a complex condition marked by psychological and physical symptoms that occur approximately two weeks before menstruation (Farahmand et al., 2017), which are linked to the luteal phase of the female menstrual cycle, and resolve when menstruation ceases (Freeman, 2003). Globally, the pooled prevalence of PMS involving females of reproductive age is 47.8% (Gudipally & Sharma, 2023). Common psychological symptoms of PMS include irritability, crying, mood swings, and anxiety, whereas physical symptoms include headaches, breast tenderness, abdominal pain, and changes in appetite (Gudipally & Sharma, 2023).

The etiology of PMS involves hormonal fluctuations during the monthly menstrual cycle accompanied by reductions in estradiol and progesterone (Modzelewski et al., 2024).

The progesterone metabolite allopregnanolone (ALLO), an allosteric modulator of the gamma-aminobutyric acid (GABA) receptor, has broad effects on the central nervous system (CNS), which explains its role in reducing PMS symptoms (Modzelewski et al., 2024). The role of ALLO in PMS is complex because it parallels the rise and fall of progesterone and peaks in the luteal phase (Modzelewski et al., 2024). ALLO acts specifically on GABA-A receptors, facilitating the inhibition of signaling in the brain, leading to the suppression of corticotopin-releasing hormone (CRH) from the hypothalamus, thus blunting the stress response and attenuating anxiety (Toufexis et al., 2004). Females with PMS have an abnormal stress response characterized by an inability to return to baseline following a stressor, and insufficient production of ALLO and/or reduced sensitivity of the GABA-A receptor to ALLO (di Scalea & Pearlstein, 2019). The abnormal stress response and associated ALLO dynamics underlie mood instability, anxiety, and other emotional symptoms (di Scalea & Pearlstein, 2019). Further complicating matters, women with PMS may exhibit elevated baseline ALLO levels or abnormal progesterone conversion. As blocking ALLO synthesis reduces these symptoms, altered ALLO metabolism likely plays a key role in symptom development (Modzelewski et al., 2024).

Based on the aforementioned data, it seems clinically plausible that treatment aimed at modulating ALLO production may facilitate improved sensitivity of the GABA-A receptor, thus helping with PMS symptoms. This is the precise reason why selective serotonin reuptake inhibitors (SSRIs) have been used to treat the more severe form of PMS – known as premenstrual dysphoric disorder – since SSRIs increase ALLO levels, assist in the restoration of normal GABAergic function, and augment stress resilience (di Scalea & Pearlstein, 2019).

Transdermal progesterone cream (TPC) should also be considered for reproductive-aged females experiencing PMS. Theoretically, TPC may facilitate baseline allopregnanolone (ALLO) production, mitigate issues associated with abnormal ALLO metabolism, and improve GABA-A receptor sensitivity to ALLO. This case report details a reproductive-aged female with severe PMS symptoms who experienced significant symptom alleviation following a combined regimen of TPC and micronutrients. Although micronutrients were utilized, clinical observations and patient feedback strongly suggested that TPC was the primary driver of therapeutic improvement.

PATIENT HISTORY AND BACKGROUND

A 45-year-old woman presented to my clinical practice on September 20, 2023, with a history of panic attacks and depression. Her medical history was notable for developmental trauma experienced during childhood and adolescence, stemming from the caregiving demands of her father's cancer diagnosis. She had previously consulted a therapist for several years approximately 10 to 15 years prior, at which time psychiatric medication was prescribed but never initiated. Instead, she managed her symptoms through lifestyle modification.

The patient also reported a history of postpartum anxiety following the delivery of her baby girl during the coronavirus disease 2019 pandemic. Upon returning home, pandemic-related lockdown measures left the patient and her husband to care for the newborn without external support.

CURRENT SYMPTOMATOLOGY AND ASSESSMENT

Over the last several years, the patient experienced seasonal depression, energy challenges, and significant mood fluctuations coinciding with her menstrual cycles. She reported episodes of acute anxiety triggered by her daughter's distress, during which she practiced cognitive detachment ("checking out") to maintain composure and remain available to assist her child.

Her menstrual cycles occurred every 28-30 days, with an occasional missed period every 4-5 cycles attributed to stress. Premenstrually, her mood was described as highly labile, accompanied by irritability, breast tenderness, backaches, and cravings for salt and sugar. These premenstrual changes precipitated interpersonal challenges, which increased in severity following the birth of her daughter. The family history was non-contributory to these presenting symptoms. Her medical history was significant for a diagnosis of polycystic ovarian syndrome.

BASELINE LIFESTYLE AND INTERVENTIONS

The patient was not taking any prescribed medications. Her baseline regimen consisted of natural health products (NHPs), including:

Vitamin D3: 2000 IU daily

Vitamin B1: 100 mg occasionally

Prenatal supplement: A comprehensive multiple vitamin and mineral formula

She reported no use of cannabis or other recreational substances, and rare alcohol consumption. Her energy level was rated between 4 and 8 out of 10 (with 10 being the best), showing frequent diurnal fluctuations. She typically retired to bed around 9:00 PM and achieved sleep onset

within 10 min. However, sleep architecture was fragmented due to nocturnal childcare duties, with awakenings at 12:00 AM, 2:00 AM, and 5:00 AM. The final morning awakening occurred between 5:30 and 7:30 AM. She reported a highly supportive marriage and high relationship satisfaction.

DIAGNOSIS AND MANAGEMENT PLAN

The patient was diagnosed with premenstrual syndrome (PMS). The initial treatment plan advised continuing the prenatal multiple vitamin and mineral supplement and vitamin D3, with additional NHPs, hormonal, and lifestyle interventions:

B-complex: 1 capsule daily

Magnesium bisglycinate: 400 mg at bedtime

TPC: 20 mg applied daily on days 12 to 26 of each menstrual cycle

Physical activity: Recommended exercise for approximately 20 minutes, 1 to 2 times weekly

CLINICAL PROGRESS AND FOLLOW-UP

First Follow-Up (November 15, 2023)

At her first follow-up appointment, the patient reported an 80% improvement in her overall condition, noting that her social circle had observed a positive behavioral shift. Her premenstrual mood swings had ameliorated, and acute anxiety episodes occurred only a few times since initiating treatment.

The therapeutic plan was adjusted as follows:

Omega-3 essential fatty acids: Added to provide 750 mg eicosapentaenoic acid (EPA) and 500 mg docosahexaenoic acid (DHA) daily.

B-complex: Increased to two capsules daily.

Final Follow-Up (January 17, 2024)

At the final evaluation, the patient demonstrated approximately 80% adherence to the recommended NHP protocol. She reported an improved capacity for cognitive regulation, allowing her to navigate challenging mental states with greater ease without reverting to previous negative cycle patterns. She observed that missing doses of her NHPs or TPC correlated with a recurrence of negative mood states, reinforcing adherence.

The patient achieved a significant and satisfactory resolution of her previously distressing PMS symptoms. Her self-reported emotional baseline was calm and content, reflecting an overall improvement in her clinical well-being. She expressed high satisfaction with the treatment outcomes and appeared in good spirits. Given her clinical improvement, the patient deemed further follow-up appointments unnecessary.

LONG-TERM PATIENT PERSPECTIVE

In a subsequent correspondence dated June 11, 2026, regarding the documentation of her case and response to TPC, the patient provided the following reflections:

> Following the birth of my child, I found myself having challenging mood swings and fatigue. In Sept 2023, Dr. Prousky introduced me to bioidentical progesterone cream to help manage these symptoms. The PMS related stress began to mellow after a few months. The changes became profoundly life-changing, leading to a stability that I haven't experienced before.

DISCUSSION

TPC has demonstrated clinical utility in alleviating PMS symptoms in reproductive-aged women (Lee, Hanley & Hopkins, 1999). Lee, Hanley and Hopkins (1999) attribute these benefits to the correction of progesterone deficiency, which offsets relative estrogen dominance and counteracts stress-induced cortisol production. Although this hypothesis is clinically plausible, TPC may offer distinct neurosteroidogenic advantages. By bypassing first-pass hepatic metabolism, TPC avoids the rapid, sharp spikes in systemic ALLO associated with oral administration, which can paradoxically trigger mood symptoms in sensitive individuals. In contrast, TPC provides a sustained pool of parent progesterone for steady, localized ALLO conversion within the CNS, optimizing GABA-A receptor sensitivity. Consequently, TPC lessens affective PMS symptoms via stable GABAergic modulation, while simultaneously mitigating physical symptoms such as mastalgia, abdominal distress, and cephalgia by rebalancing the estrogen-to-progesterone ratio. This hormonal rebalancing also counteracts luteal water retention and bloating symptoms arising from increased plasma renin and aldosterone system activation in PMS, resulting from progesterone's diuretic properties that facilitate renal sodium excretion (Rosenfeld et al., 2008).

Testing of serum progesterone levels before treatment was not necessary. I prescribe TPC empirically based on the clinical presentation and diagnosis of the patient. I have administered this treatment to many premenopausal, perimenopausal, menopausal, and postmenopausal patients. To my knowledge, I have had only one case in which TPC surprisingly worsened a patient's mood. This patient was previously diagnosed with a mood disorder, was stable

although her mood was low, and was not on any prescribed medication. She was also postmenopausal, for which her progesterone level would obviously be very low or deficient compared to her premenopausal level. Her mood worsened within a few weeks of taking 20 mg of TPC daily except on Sundays. Upon discontinuation of TPC, her mood returned to its low baseline state. Other than this patient, I cannot recall a single case of any patient worsening on TPC treatment.

If testing is clinically indicated, saliva testing would be the most accurate since the serum level is unreliable when determining the bioavailable progesterone level (Lee, 2003; Lee, Hanley & Hopkins, 1999). Saliva testing, on the other hand, reflects the tissue-active free progesterone value and shows an increase from regular TPC administration (Lee, 2003; Lee, Hanley & Hopkins, 1999). Once TPC is applied, the levels increase over the course of 3-4 hours, are maintained for another 3-4 hours, and then drop gradually over the course of another 3-4 hours (Lee, Hanley & Hopkins, 1999). Should saliva testing be desired, the approximate optimal range is between 0.3 and 0.5 ng/ml although 2 ng/ml can be considered the upper limit (Lee, Hanley & Hopkins, 1999). To date, I have not requisitioned any saliva testing at baseline or beyond when prescribing TPC and have not found it necessary when providing this treatment.

The route of administration is important. According to Lee, Hanley and Hopkins (1999), large doses of oral progesterone (i.e., often in the range of 100-400 mg per day) provide a very small amount (approximately 10%) of circulating "real" progesterone (p. 356). In contrast, TPC at doses of 15-40 mg per day, provides a more physiological dose since progesterone passes through the skin and into the subcutaneous fat, gradually restoring progesterone levels to normal over the course of several months (Lee, Hanley & Hopkins, 1999). The correct dose of TPC is the dose that works for the patient (Lee, Hanley & Hopkins, 1999), but 20 mg/day often provides sufficient benefit although I have sometimes needed to increase the dose to 40 mg/day for symptom amelioration. In women of reproductive age, TPC is applied daily, usually 14-15 days prior to expected menses. I usually have my patients apply TPC at bedtime because it can assist with restorative sleep. Although TPC is usually devoid of adverse effects, in premenopausal women who have been progesterone deficient for many years, the application of TPC can sometimes cause water retention, cephalgia, breast engorgement and mastalgia. These unpleasant symptoms will abate in 2 weeks, sometimes lasting as long as 2-3 months, due to the temporary increased estrogen receptor sensitivity that can happen when progesterone deficiency is being corrected (Lee, Hanley & Hopkins, 1999).

Published evidence evaluating the clinical efficacy of progesterone in PMS is lacking. A Cochrane review included only two studies for analysis, which encompassed 280 patients between 18 and 45 years of age (Ford et al., 2012). The progesterone dose and delivery methods were different, which meant that the studies could not be combined for the meta-analysis. Based on the limited data, the trial results could not prove or disprove the clinical efficacy of progesterone as a treatment for PMS. However, none of the published studies included in the analysis used TPC as a treatment for PMS.

While there are many evidence-based orthomolecular and herbal medicine options for PMS, such as vitamin B1 (Abdollahifard et al., 2014), vitamin B6 (Ebrahimi et al., 2012; Retallick-Brown et al., 2020; Wyatt et al., 1999), magnesium (Facchinetti et al., 1991; Fathizadeh et al., 2010), calcium (Arab et al., 2020; Shobeiri et al., 2017), potassium (Okeahialam, 2017; Takacs, 1998), broad-spectrum micronutrients (Retallick-Brown et al., 2020), chasteberry extract (Csupor et al., 2019), and saffron extract (Mohammadi & Karimi, 2026), I assert that TPC is the most etiological treatment for PMS given its positive impact on ALLO dynamics, luteal phase optimization, and balancing the estrogen-to-progesterone ratio.

LIMITATIONS

The positive effects of TPC may have worked synergistically with the other recommended treatments. Since the patient had been taking micronutrients before working with me, it is more likely that the noted benefits were a consequence of TPC treatment. It is also impossible to generalize the positive benefits noted here for other patients struggling with PMS. While a significant criticism is the absence of randomized controlled trials (RCTs) evaluating TPC for PMS, the comprehensive work of the late Dr. Lee, MD., has shown this treatment to be both efficacious and safe when prescribed to patients struggling with disabling PMS symptoms. In one of Dr. Lee's earliest volumes on natural progesterone, he reported on its clinical efficacy:

> More than a decade ago, after reading of the work of of Dr. Katherina Dalton in London, who defined PMS and found success using high-dose progesterone administered as rectal suppositories, I decided to add natural progesterone cream to my treatment of patients with PMS. The results were most impressive. The majority (but not all) of these patients reported remarkable improvement in their symptoms, including the elimination of their premenstrual water retention and weight gain. I have received hundreds of phone calls and letters from

women and their doctors over the past few years who report that PMS has been alleviated with the use of natural progesterone (1996, p. 231).

CONCLUSION

While I hope that a well-constructed RCT on TPC for PMS is conducted in the future, the positive outcome in this case is quite ordinary given my clinical experience with this treatment. TPC is safe and often effective in treating PMS. The benefits, as noted by the patient in this case, improved her PMS symptoms by 80% and afforded her life-changing stability. For interested clinicians, all references referring to the late Dr. John R. Lee, MD., is a recommended resource (Lee, 1996; Lee, 2003; Lee, Hanley & Hopkins, 1999), as is his website (https://www.johnleemd.com/).

ETHICS STATEMENT

This case report was prepared in accordance with the CARE Case Report Guidelines. Written informed consent was obtained from the patient for publication of this de-identified case report. All identifying information has been removed or altered to protect patient privacy.

CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest related to this case report.

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AUTHOR CONTRIBUTIONS

Dr. Jonathan Prousky conceived the clinical intervention, managed the case, and prepared the manuscript.

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