Increased anxiety and depression after menstruation

Adriel Gerard, MD

How would you handle this case?

Answer the challenge questions at **MDedge.com/psychiatry** and see how your colleagues responded

Ms. C, age 29, has bipolar disorder and generalized anxiety disorder. Her anxiety and depressive symptoms worsen each month after menstruating. How can you best help her?

CASE Increased anxiety and depression

Ms. C, age 29, has bipolar II disorder (BD II) and generalized anxiety disorder. She presents to her outpatient psychiatrist seeking relief from chronic and significant dips in her mood from Day 5 to Day 15 of her menstrual cycle. During this time, she says she experiences increased anxiety, insomnia, frequent tearfulness, and intermittent suicidal ideation.

Ms. C meticulously charts her menstrual cycle using a smartphone app and reports having a regular 28-day cycle. She says she has experienced this worsening of symptoms since the onset of menarche, but her mood generally stabilizes after Day 14 of her cycle–around the time of ovulation–and remains euthymic throughout the premenstrual period.

HISTORY Depression and a change in medication

Ms. C has a history of major depressive episodes and has experienced hypomanic episodes that lasted 1 to 2 weeks and were associated with an elevated mood, high energy, rapid speech, and increased self-confidence. Ms. C says she has chronically high anxiety associated with trouble sleeping, difficulty focusing, restlessness, and muscle tension. When she was receiving care from previous psychiatrists, treatment with lithium, quetiapine, lamotrigine, sertraline, and fluoxetine was not successful, and Ms. C said she had severe anxiety when she tried sertraline and fluoxetine. After several months of substantial mood instability and high anxiety, Ms. C responded well to pregabalin 100 mg 3 times a day, lurasidone 60 mg/d at bedtime, and gabapentin 500 mg/d at bedtime. Over the last 4 months, she reports that her overall mood has been even, and she has been coping well with her anxiety.

Ms. C is married with no children. She uses condoms for birth control. She previously tried taking a combined estrogen/progestin oral contraceptive, but stopped because she said it made her feel very depressed. Ms. C reports no history of substance use. She is employed, says she has many positive relationships, and does not have a social history suggestive of a personality disorder.

What is the next logical step in managing Ms. C's symptoms?

a) Initiate a selective serotonin reuptake inhibitor (SSRI) to be taken daily

b) Initiate an SSRI to be taken only during the days of her menstrual cycle on which she experiences worsening mood symptoms

Discuss this article at www.facebook.com/MDedgePsychiatry

Dr. Gerard is a psychiatrist in private practice, Brooklyn, New York.

Disclosures

The author reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0338

c) Increase the dosage of lurasidone and/or pregabalin
d) Refer her for psychotherapy
e) Recommend that she try again to take an oral contraceptive

The author's observations

Many women report worsening of mood during the premenstrual period (luteal phase). Premenstrual dysphoric disorder (PMDD) involves symptoms that develop during the luteal phase and end shortly after menstruation; this condition impacts ≤5% of women.[1] The etiology of PMDD appears to involve contributions from genetics, hormones such as estrogen and progesterone, allopregnanolone (a progesterone metabolite), brain-derived neurotrophic factor, brain structural and functional differences, and hypothalamic pathways.[2]

Researchers have postulated that the precipitous decline in the levels of progesterone and allopregnanolone in the luteal phase may contribute to the mood symptoms of PMDD.[2] Allopregnanolone is a modulator of gamma-aminobutyric acid type A (GABA-A) receptors and may exert anxiolytic and sedative effects. Women who experience PMDD may be less sensitive to the effects of allopregnanolone.[3] Additionally, early luteal phase levels of estrogen may predict late luteal phase symptoms of PMDD.[4] The mechanism involved may be estrogen's effect on the serotonin system. The HPA axis may also be involved in the etiology of PMDD because patients with this condition appear to have a blunted cortisol response in reaction to stress.[5] Research also has implicated immune activation and inflammation in the etiology of PMDD.[6]

A PMDD diagnosis should be distinguished from a premenstrual exacerbation of an underlying psychiatric condition, which occurs when a patient has an untreated primary mood or anxiety disorder that worsens during the premenstrual period. PMDD is differentiated from premenstrual syndrome by the severity of symptoms.[2] The recommended first-line treatment of PMDD is an SSRI, but if an SSRI does not work, is not tolerated, or is not preferred for any other reason, recommended alternatives include combined hormone oral contraceptive pills, dutasteride, gabapentin, or various supplements.[7,8] PMDD has been widely studied and is treated by both psychiatrists and gynecologists. In addition, some women report experiencing mood instability around ovulation. Kiesner[9] found that 13% of women studied showed an increased negative mood state midcycle, rather than during the premenstrual period.

Postmenstrual syndrome

Postmenstrual mood symptoms are atypical. Postmenstrual syndrome is not listed in DSM-5 or formally recognized as a medical diagnosis. Peer-reviewed research or literature on the condition is scarce to nonexistent. However, it has been discussed by physicians in articles in the lay press. One gynecologist and reproductive endocrinologist estimated that approximately 10% of women experience significant physical and emotional symptoms postmenstruation.[10] An internist and women's health specialist suggested that the cause of postmenstrual syndrome might be a surge in levels of estrogen and testosterone and may be associated with insulin resistance and polycystic ovarian syndrome, while another possible contribution could be iron deficiency caused by loss of blood from menstruation.[11]

TREATMENT Recommending an oral contraceptive

Ms. C's psychiatrist does not prescribe an SSRI because he is concerned it would destabilize her BD II. The patient also had negative experiences in her past 2 trials of SSRIs.

Because the psychiatrist believes it is prudent to optimize the dosages of a patient's

Clinical Point

Some women are sensitive to low levels of allopregnanolone in the follicular phase, which might lead to postmenstrual mood symptoms

Related Resources

- Ray P, Mandal N, Sinha VK. Change of symptoms of schizophrenia across phases of menstrual cycle. Arch Womens Ment Health. 2020;23(1):113-122. doi:10.1007/s00737-019-0952-4
- Raffi ER, Freeman MP. The etiology of premenstrual dysphoric disorder: 5 interwoven pieces. Current Psychiatry. 2017;16(9):20-28.

Drug Brand Names

Drospirenone/ethinyl estradiol • Yasmin
Dutasteride • Avodart
Fluoxetine • Prozac
Gabapentin • Neurontin
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid
Lurasidone • Latuda
Norethindrone • Aygestin
Pregabalin • Lyrica
Progesterone • Prometrium
Quetiapine • Seroquel
Sertraline • Zoloft

Clinical Point

Because research on postmenstrual mood symptoms is scarce, guidance on how to help Ms. C came from research on how to treat PMDD

current medication before starting a new medication or intervention, he considers increasing Ms. C's dosage of lurasidone or pregabalin. The rationale for optimizing Ms. C's current medication regimen is that greater overall mood stability would likely result in less severe postmenstrual mood symptoms. However, Ms. C does not want to increase her dosage of either medication because she is concerned about adverse effects.

Ms. C's psychiatrist discusses the case with 2 gynecologist/obstetrician colleagues. One suggests the patient try a progesterone-only oral contraceptive and the other suggests a trial of Prometrium (a progesterone capsule used to treat endometrial hyperplasia and secondary amenorrhea). Both suggestions are based on the theory that Ms. C may be sensitive to levels of progesterone, which are low during the follicular phase and rise after ovulation; neither recommendation is evidence-based. A low level of allopregnanolone may lead to less GABAergic activity and consequently greater mood dysregulation. Some women are particularly sensitive to low levels of allopregnanolone in the follicular phase, which might lead to postmenstrual mood symptoms. Additionally, Ms. C's previous treatment with a combined estrogen/progestin oral contraceptive may have decreased her level of allopregnanolone.[12] Ultimately, Ms. C's psychiatrist suggests that she take a progesterone-only oral contraceptive.

The author's observations

Guidance on how to treat Ms. C's postmenstrual symptoms came from research on how to treat PMDD in patients who have BD. In a review of managing PMDD in women with BD, Sepede et al[13] presented a treatment algorithm that recommends a combined estrogen/progestin oral contraceptive as first-line treatment in euthymic patients who are already receiving an optimal dose of mood stabilizers. Sepede et al[13] expressed caution about using SSRIs due to the risk of inducing mood changes, but recommended SSRIs for patients with comorbid PMDD and BD who experience a depressive episode.

Another question is which type of oral contraceptive is most effective for treating PMDD. The combined oral contraceptive drospirenone/ethinyl estradiol has the most evidence for efficacy.[14] Combined oral contraceptives carry risks of venous thromboembolism, hypertension, stroke, migraines, and liver complications, and are possibly associated with certain types of

Bottom Line

Some women may experience mood symptoms during the postmenstrual period that are similar to the symptoms experienced by patients who have premenstrual dysphoric disorder (PMDD). This phenomenon has been described as postmenstrual syndrome, and though evidence is lacking, treating it similarly to PMDD may be effective.

cancer, such as breast and cervical cancer.[15] Their use is contraindicated in patients with a history of these conditions and for women age >35 who smoke ≥15 cigarettes/d.

The limited research that has examined the efficacy of progestin-only oral contraceptives for treating PMDD has been inconclusive.[16] However, progesterone-only oral contraceptives are associated with less overall risk than combined oral contraceptives, and many women opt to use progesterone-only oral contraceptives due to concerns about possible adverse effects of the combined formulations. A substantial drawback of progesterone-only oral contraceptives is they must be taken at the same time every day, and if a dose is taken late, these agents may lose their efficacy in preventing pregnancy (and a backup birth control method must be used[17]). Additionally, drospirenone, a progestin that is a component of many oral contraceptives, has antimineralocorticoid properties and is contraindicated in patients with kidney or adrenal gland insufficiency or liver disease. As was the case when Ms. C initially took a combined contraceptive, hormonal contraceptives can sometimes cause mood dysregulation.

OUTCOME Improved symptoms

Ms. C meets with her gynecologist, who prescribes norethindrone, a progestin-only oral contraceptive. Since taking norethindrone, Ms. C reports a dramatic improvement in the mood symptoms she experiences during the postmenstrual period.

Clinical Point

Progesterone-only oral contraceptives have less overall risk than combined oral contraceptives, but must be taken at the same time every day

References

1. Epperson CN, Steiner M, Hartlage SA, et al. Premenstrual dysphoric disorder: evidence for a new category for DSM-5. Am J Psychiatry. 2012;169(5):465-475.
2. Raffi ER, Freeman MP. The etiology of premenstrual dysphoric disorder: 5 interwoven pieces. Current Psychiatry. 2017;16(9):20-28.
3. Timby E, Bäckström T, Nyberg S, et al. Women with premenstrual dysphoric disorder have altered sensitivity to allopregnanolone over the menstrual cycle compared to controls--a pilot study. Psychopharmacology (Berl). 2016;233(11):2109-2117.
4. Yen JY, Lin HC, Lin PC, et al. Early- and late-luteal-phase estrogen and progesterone levels of women with premenstrual dysphoric disorder. Int J Environ Res Public Health. 2019;16(22):4352.
5. Huang Y, Zhou R, Wu M, et al. Premenstrual syndrome is associated with blunted cortisol reactivity to the TSST. Stress. 2015;18(2):160-168.
6. Hantsoo L, Epperson CN. Premenstrual dysphoric disorder: epidemiology and treatment. Curr Psychiatry Rep. 2015; 17(11):87.
7. Tiranini L, Nappi RE. Recent advances in understanding/management of premenstrual dysphoric disorder/premenstrual syndrome. Faculty Rev. 2022:11:(11). doi:10.12703/r/11-11
8. Raffi ER. Premenstrual dysphoric disorder. Current Psychiatry. 2017;16(9). Accessed January 30, 2023. https://www.mdedge.com/psychiatry/article/145089/somatic-disorders/premenstrual-dysphoric-disorder
9. Kiesner J. One woman's low is another woman's high: paradoxical effects of the menstrual cycle. Psychoneuroendocrinology. 2011;36(1):68-76.
10. Alnuweiri T. Feel low after your period? Postmenstrual syndrome could be the reason. Accessed January 30, 2023. https://www.wellandgood.com/pms-after-period/
11. Sharkey L. Everything you need to know about post-menstrual syndrome. Healthline. Published April 28, 2020. Accessed January 30, 2023. https://www.healthline.com/health/post-menstrual-syndrome
12. Santoru F, Berretti R, Locci A, et al. Decreased allopregnanolone induced by hormonal contraceptives is associated with a reduction in social behavior and sexual motivation in female rats. Psychopharmacology (Berl). 2014;231(17):3351-3364.
13. Sepede G, Brunetti M, Di Giannantonio M. Comorbid premenstrual dysphoric disorder in women with bipolar disorder: management challenges. Neuropsychiatr Dis Treatment. 2020;16:415-426.
14. Rapkin AJ, Korotkaya Y, Taylor KC. Contraception counseling for women with premenstrual dysphoric disorder (PMDD): current perspectives. Open Access J Contraception. 2019;10:27-39. doi:10.2147/OAJC.S183193
15. Roe AH, Bartz DA, Douglas PS. Combined estrogen-progestin contraception: side effects and health concerns. UpToDate. Accessed February 1, 2023. https://www.uptodate.com/contents/combined-estrogen-progestin-contraception-side-effects-and-health-concerns
16. Ford O, Lethaby A, Roberts H, et al. Progesterone for premenstrual syndrome. Cochrane Database Sys Rev. 2012;3:CD003415. doi:10.1002/14651858.CD003415.pub4
17. Kaunitz AM. Contraception: progestin-only pills (POPs). UpToDate. Accessed February 1, 2023. https://www.uptodate.com/contents/contraception-progestin-only-pills-pops