Discussion: 'Add-back regimens in patients using a GnRH agonist for premenstrual dysphoric disorder' by Segebladh et al

In the roundtable that follows, clinicians discuss a study published in this issue of the Journal in light of its methodology, relevance to practice, and implications for future research. Article discussed:

Segebladh B, Borgström A, Nyberg S, et al. 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.e1-8.

DISCUSSION QUESTIONS

- What does prior research tell us about premenstrual dysphoric disorder?
- What was the study's objective?
- What are the benefits and limitations of a crossover study design?
- What did you think about the selected add-back regimens?
- How were the data analyzed?
- What do the findings mean?
- What could be done to investigate this topic further?

From the Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO:

Moderator
Emily S. Jungheim, MD
Instructor

Discussants
Jessica J. Kenerson, MD
Second-year resident

Nastaran Foyouzi-Yousefi, PhD
Chief resident

Jenifer E. Allsworth, MD
Assistant professor

Kerri L. Marquard, MD
Fellow

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INTRODUCTION

Premenstrual dysphoric disorder (PMDD) is not uncommon, and symptoms can range from minimal to disabling. The inclusion of specific diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision* (DSM-IV) improved research quality and led to effective treatments, like gonadotropin-releasing hormone (GnRH) agonists.[1,2] Unfortunately, preventing side effects of long-term GnRH agonist use can be complicated, as PMDD patients may have increased sensitivity to conventional estrogen and progesterone add-back regimens.[3] A new study combining strict diagnostic criteria, careful symptom measurement, and novel add-back regimens is a particularly interesting addition to the current literature on PMDD management.[4]

Emily S. Jungheim, MD, and George A. Macones, MD, MSCE, Associate Editor

BACKGROUND

Jungheim: ***Can you explain our current understanding of PMDD, and comment on the use of GnRH agonists in the treatment of PMDD?***

Kenerson: The DSM-IV notes that PMDD is characterized by psychological and physical symptoms that occur cyclically. Over 100 symptoms have been attributed to the disorder, including bloating, breast tenderness, headache, anxiety, irritated or depressed mood, and increased appetite. These occur in the luteal phase of the menstrual cycle and resolve at the completion of menstruation. PMDD, a chronic condition that can negatively impact personal relationships and occupational productivity, is differentiated from premenstrual syndrome (PMS) by its more severe psychological symptoms.

At this time, the pathogenesis of PMDD is not completely understood. Current research suggests that cyclic changes in the interactions between central neurotransmitters and ovarian hormones lead to symptoms. As such, symptoms occur after ovulation. One possible mechanism is based on evidence that changes in the serotonergic system are associated with anxiety, depression, sleep-cycle changes, appetite, food cravings, compulsions, and obsessions. Fluctuation in circulating levels of estrogen and progesterone can alter the baseline function of the serotonin or 5-hydroxytryptamine system in the brain, leading to PMDD symptoms.

The GABAergic system is also affected by changes in progesterone levels. This neurotransmitter system regulates alertness, stress, anxiety, and vigilance. Progesterone alters this system because it is metabolized to allopregnanolone and prenanolone, which modulate the inhibitory effects of GABA in the brain. Research continues to address the role of changing levels of allopregnanolone and altered neuronal sensitivity to neurosteroids in the brain.

Our understanding of the interactions between central neurotransmitters and ovarian hormones is the basis for the use of GnRH agonists as treatment. Simply put, PMDD symptoms do not present during anovulation. GnRH agonists down-regulate pulsatile GnRH secretion, inhibiting the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. Without these hormones, the ovary does not release mature ovum or produce estrogen or progesterone, re-

sulting in a hormonal state similar to menopause. The absence of physical, affective, and behavioral premenstrual symptoms has been confirmed in a few randomized controlled trials (RCTs), although GnRH agonists do not modulate depressive symptoms. Depressive symptoms may continue to occur.

The administration of low-dose estrogen with GnRH agonists may ameliorate the affective and vasomotor symptoms of PMDD while also decreasing the effects of GnRH agonists on bone health. At this time, add-back hormone replacement remains investigational, and there is no consensus to support the use of estrogen alone or estrogen in concert with progesterone as a first-line therapy for PMDD patients using a GnRH agonist. Furthermore, optimal dosing remains elusive and requires additional research.

STUDY DESIGN

Jungheim: ***These points lead us to this study. What was this study's objective?***

Foyouzi-Yousefi: This is a randomized, double-blind, crossover clinical trial with the objective of investigating add-back therapies that may be acceptable to women treated with GnRH agonists for PMDD.

Jungheim: ***Why do you think this objective is important?***

Foyouzi-Yousefi: The objective addresses one of the most challenging issues in women's health. A strong correlation has been demonstrated between PMDD symptom severity and impairment of social and work performance. Women with PMDD are almost 9 times more likely to report more than a week of impairment to partnership and family activities; individual pursuits, such as hobbies; and work productivity. An increase in the use of healthcare resources by this group of women is reflected in a greater number of visits to ambulatory healthcare providers compared with women who do not have PMDD.[5] In the United States, a diagnosis of PMS or PMDD was associated with significantly increased direct costs (costs of medical care) and indirect costs (loss of work productivity equivalent to about $4333 per patient).[6]

As we know, 1 treatment modality for PMDD is ovulation suppression with a GnRH agonist.[7] In 8 of 10 published RCTs, these agents were superior to placebo when used to treat women with PMS or PMDD. A metaanalysis of 5 of these studies indicated that, compared with placebo, GnRH agonists were more likely to improve premenstrual emotional and physical symptoms (odds ratio, 8.66).[7] "Add-back" hormone strategies have been investigated to counteract undesirable consequences of hypoestrogenism resulting from the prolonged anovulation induced by GnRH agonists. Since women with severe PMS and PMDD have an abnormal response to normal hormonal fluctuations, it is not surprising that some women might experience mood and anxiety symptoms from the addition of gonadal steroids. This reaction, of course, reduces the benefit of the replacement strategy.

Jungheim: ***Can you describe the study design?***

Allsworth: As Dr Foyouzi-Yousefi said, the study design was a randomized, double-blind, crossover design. The crossover study is a specialized form of an RCT, wherein each participant receives multiple treatments. In this study, the order in which the treatments were received was randomized in blocks of 6, and the order was unknown to both the participants and the researchers.

Jungheim: ***What are the advantages and disadvantages of crossover studies?***

Allsworth: The primary advantage of using a crossover design is that each woman serves as her own control. As demonstrated in these analyses, the researchers are able to summarize a patient's response to a treatment regimen by comparing it to her response under the control conditions. There are a number of potential disadvantages to this study design. The crossover design assumes no carryover of the treatment effect. That is, the duration of the treatment effect is time-limited and discrete. If there is a carryover effect, researchers may include a washout period before initiating the next treatment. In this study, the first 18 days of each cycle were defined as the washout period. The crossover design also assumes that the order of treatments has no effect. While the sample size is small in this study, it would be conceptually possible to also study whether the order of treatments confounded the findings. Finally, when using the crossover study design, it is not possible to evaluate the long-term side effects of a single treatment regimen, since each participant received multiple treatments.

Jungheim: ***How do the authors attempt to address potential disadvantages of a crossover study in their approach?***

Marquard: The study design involved using repetitive measures within individual subjects, where the patients acted as their own control. To avoid the potential disadvantages of a crossover study in a 28-day cycle where women took add-back hormones or placebo in the last 14 days, the Cyclicity Diagnoser (CD) scale was used during the last 10 days of each treatment cycle. The first 18 days of the treatment cycle served as a washout period. Despite this washout phase, the negative mood symptom ratings were found to have significant crossover effects. The women in the group that used the 1.5-mg estradiol transdermal gel with the 400-mg vaginal progesterone as the first add-back therapy had higher negative mood ratings for the remainder of the study. Based on this, the authors decided to only use the first treatment cycles for findings pertaining to negative mood symptoms, thus limiting the number of patients in this group.

Jungheim: ***We will further discuss how the authors accounted for this in their analysis. In the meantime, could you comment on the authors' choice of add-back regimens?***

Foyouzi-Yousefi: The authors used continuous daily transdermal estradiol gel with vaginal progesterone or placebo during the last 14 days of each treatment cycle. There were 3 arms in this study. In 1, patients were treated with high-dose estradiol gel, 1.5 mg once daily, in combination with vaginal progesterone, 400 mg once daily, during the last 14 days of the cycle. The second arm consisted of patients who were on transdermal estradiol gel, 1.5 mg, in combination with a

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