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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Brexanolone for Postpartum Depression: Promising, but Will It Deliver?

By Nicole Cirino, MD, CST, IF

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Dr. Cirino reports no financial relationships relevant to this field of study.

SYNOPSIS: In two double-blind, randomized, placebo-controlled, Phase III trials of brexanolone, a new medicine for postpartum depression, researchers found a significant reduction in symptoms at 60 hours of infusion compared to placebo.

SOURCE: Meltzer-Brody S, et al. Brexanolone injection in post-partum depression: Two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet* 2018;392:1058-1070.

Brexanolone (Zulresso), a proprietary agent developed by Sage Pharmaceuticals, is chemically identical to the endogenous neuroactive steroid allopregnanolone. It is slated to be the first FDA-approved compound for the treatment of postpartum depression (PPD).

Meltzer-Brody and colleagues conducted two large, multicenter, randomized, controlled trials (RCTs) at 30 clinical sites. Previously, they published results of an open-label trial and a prior RCT on this agent.[1,2] They included the results from the first RCT of brexanolone (BRX) in the analysis in this current article. The three RCTs were conducted using a similar protocol but varied in dose and severity of depression. Inclusion criteria were ambulatory female patients 18-45 years of age with moderate to severe depression as measured by the Hamilton Rating Scale for Depression (HAM-D). Patients had qualifying HAM-D total scores of ≥ 26 for study 1 (severe depression) and 20-25 for study 2 (moderate depression). Women had to be less than six months postpartum and had to agree to cease breastfeeding at the start of the infusion and for four days after the infusion ended. Onset of depression had to occur between the third trimester of pregnancy and four weeks after delivery. Women taking prescribed psychiatric medication had to be at a stable dose 14 days prior to screening until completion of the 72-hour assessment post-infusion.

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This CME activity is intended for the OB/GYN. It is in effect for 36 months from the date of the publication.

Welcome

I am extremely excited to announce a new contributor, Nicole Cirino, MD, CST, IF. Dr. Cirino is an associate professor of obstetrics and gynecology and psychiatry at the Oregon Health & Science University (OHSU) School of Medicine and is the director of mental health at the OHSU Center for Women's Health. Dr. Cirino is a reproductive psychiatrist with expertise in perinatal mood and anxiety disorders and other hormonal-related mood disorders, including premenstrual dysphoric disorder, menopause, and other related issues. She is the course director of the reproductive psychiatry course at OHSU and the director of the Perinatal Mental Health Training Clinic in the Center for Women's Health that trains residents, fellows, and students. She is an expert in sexual medicine, is an AASECT-certified sex therapist, and teaches female sexual dysfunction to medical students and residents. Dr. Cirino will provide new expertise in an important area of women's health. Her first commentary appears in this issue. Please join me in welcoming Dr. Cirino. *— Jeffrey T. Jensen, MD, MPH, Editor*

Exclusion criteria were active psychosis, alcohol or drug abuse in the prior year, attempted suicide in the current episode, and medical history of schizophrenia, bipolar disorder, renal failure, or anemia.

The researchers screened 375 women with moderate to severe PPD, 246 of whom were assigned. Patients in study 1 were randomized 1:1:1 to BRX 90 mcg/kg per hour, BRX 60 mcg/kg per hour (BRX90 and BRX60), or placebo, respectively, for 60 continuous hours in a medically supervised setting. The entire medically supervised period was 72 hours. Patients in study 2 were randomized 1:1 to either BRX90 or placebo. The patients, study team, site staff (with the exception of pharmacists), and the principal investigator were masked to treatment allocations, and all infusion bags were identical in appearance.

The primary endpoint was change in baseline HAM-D scores at 60 hours after the start of the infusion. Blinded onsite raters were trained to administer HAM-D to enable consistent scoring. A blinded onsite rater scored all participants, and a separate independent, blinded central reviewer recorded and scored the HAM-D assessment in 50% of the patients. Scores were assessed at hours 0, 2, 4, 8, 12, 24, 48, 60, and 72 and at days 7 and 30. Other secondary outcome measures were Edinburgh Postnatal Depression Scale (EPDS), Patient Health Questionnaire-9, Generalized Anxiety Disorder 7-item scale, and Clinical Global Impression scale-improvement subscale.

Demographics and baseline characteristics were well balanced across treatment groups. Twenty-two percent of patients were taking antidepressants at baseline. When analyzed using a mixed effects model, there were no statistically significant differences in response between the women who had been taking an antidepressant vs. those who had not. Women receiving BRX had a greater reduction in HAM-D scores compared to placebo at the primary endpoint of 60 hours and at many, but not all, endpoints between two hours and 30 days. Notably, however, the placebo arm also showed a rapid and robust response. At no point did the drug perform worse than placebo. In study 1, at 60 hours, the mean reduction in HAM-D total score from baseline was -19.5 points in the BRX60 group and -17.7 points in the BRX90 group compared with -14.0 points in the placebo group (difference, -5.5; 95% confidence interval [CI], -8.8 to -2.2; $P = 0.0013$ for the BRX60 group; and -3.7; 95% CI, -6.9 to -0.5; $P = 0.0252$ for the BRX90 group). In study 2, at 60 hours, the mean reduction in HAM-D total score from baseline was -14.6 points in the BRX90 group compared with -12.1 points for the placebo group (difference -2.5; 95% CI, -4.5 to -0.5; $P = 0.0160$).

A more familiar and clinically relevant tool, the EPDS also was administered and analyzed. These data were included in the supplementary appendix of the article. The EPDS revealed statistical and clinically significant results at 30 days for BRX60 only. The mean change at 30 days in EPDS score from baseline was -9.2 points in the placebo group. The BRX60 group demonstrated a -12.8 point change in EPDS scores from baseline to day 30, or 3.7 points greater reduction than placebo, which was found to be a significant difference ($P = 0.0290$). In contrast, the BRX90 group demonstrated a -11.0 point change in EPDS scores (baseline to day 30), representing a non-statistically significant difference from placebo (-1.8 points difference; $P = 0.2701$).

The most common adverse events in both studies were headache (15-18% BRX vs. 11-16% placebo), dizziness (10-16% BRX vs. 2-8% placebo), and somnolence (5-18% BRX vs. 4-7% placebo). One BRX60 subject in study 1 had two serious adverse events (suicidal ideation and intentional overdose) following

infusion, and one BRX90 subject in study 2 had two serious adverse events (altered state of consciousness and syncope). Although total adverse effects were similar in BRX and placebo arms, dizziness and somnolence were particularly evident in patients receiving BRX injections. Sedation effects reversed within 15 minutes of cessation of infusion and resolved within 90 minutes.

■ COMMENTARY

I have been following the emergence of this drug since its inception, as it has generated significant interest in the reproductive psychiatry community. It is perplexing that it has taken this long to find an effective "hormonal treatment" for PPD given the robust evidence showing that hormonal factors play a key role in etiology. Our patients routinely request hormonal treatment for perinatal mood and anxiety disorders, but none are available. BRX is novel in its approach, yet quite simple in its mechanism of action, as it is chemically equivalent to allopregnanolone. We know plasma concentrations of allopregnanolone increase during pregnancy and decrease substantially after childbirth in both rodents and humans, and fluctuations in allopregnanolone affect anxiety and depression in animal models.[3] Dosing of this agent was developed to mimic allopregnanolone levels in the third trimester.

The neuroactive properties of allopregnanolone are due to its effect as a positive allosteric modulator of GABA type A ($GABA_A$) receptors, which are the major inhibitory transmitter receptors in the brain and the site of action of benzodiazepines, barbiturates, neuroactive steroids, anesthetics, and convulsants.[4] It is no surprise that the most common adverse effects were dizziness and somnolence, which resolved when the infusion was discontinued. The antianxiety effect of the $GABA_A$ mechanism of action also likely plays a role in response rates.

The trial was well-designed and well-executed. The placebo response rate was high, as the authors noted, but this is not unusual in neurobehavioral interventions. I suspect that the intensity of treatment, as well as the removal of the patient from the role of primary caregiver and cessation of breastfeeding, may play a role in response in both the placebo and treatment groups.

The other novel characteristic of this new compound is the rapidity of response for depression symptoms. In this study and in most depression literature, depressive symptom response is defined as a 50% reduction in HAM-D score. Typically, antidepressants take two weeks or longer for response. In this study by Meltzer-Brody et al, response rates separated from placebo within 24 hours. For the BRX60 group, the depressive symptom response rate separated from placebo at 24, 36, 60, and 72 hours and at day 30. In the integrated BRX90 data from all three RCTs, the response rate was significant compared to placebo at hours 24, 48, 60, and 72 and at days 7 and 30.

Remission rates are another important feature to consider in antidepressants trials and are worth paying attention to in this trial. Typically in depression literature, remission is defined as HAM-D score < 7 for a prolonged period, often up to four to six months.[5] There is inconsistency in the depression literature regarding the length of time required for a patient to be asymptomatic before the participant is "in remission." Meltzer-Brody et al defined remission as a HAM-D score ≤ 7 at any given time. This would signify that the patient is symptom-free from depression for that point in time only. Fifty-one percent of BRX60 patients achieved "remission" of symptoms at 60 hours vs. 16% in the placebo arm in study 1; and 61% vs. 38% placebo achieved remission at 60 hours in study 2. The integrated data from all three RCTs of BRX90 showed remission rates of 50% vs. 28% placebo at 60 hours. Of the patients who had a response at 60 hours, 94% did not relapse at day 30. We do not know if this effect can be sustained for more than 30 days or will require maintenance infusions for full remission of PPD. Since PPD has a different etiology than typical unipolar depression and the mechanism of action and delivery are novel for BRX, it may be that response rates for PPD are more rapid than response rates for depression in other periods of the female reproductive life cycle.

The most significant limitation with this treatment option is the 60-hour infusion, which likely will require overnight hospitalization until the issues around safety have been explored fully. Most psychiatric inpatient units are not equipped to administer any intravenous infusions, and psychiatric inpatient bed shortages are already at crisis levels nationally. The cost of a 60-hour infusion with 72-hour medical monitoring will be prohibitive, particularly in the field of mental health, where basic services often are denied or underinsured for many patients. Sage Pharmaceuticals has announced it is working on injectable and oral forms of a similar agent. Thus, the very real barrier to the successful launch of this product is not in the science behind it, but the ability to navigate the healthcare delivery system to be able to provide it. The FDA initially announced a priority review of this product for Dec. 19, 2018, but postponed the review for three months to March 19, 2019, to allow time to develop a Risk Evaluation and Mitigation Strategy with Elements to Assure Safe Use.[6]

Clinically, the first-line treatment for moderate to severe PPD will remain selective-serotonin reuptake inhibitors (SSRIs) combined with psychosocial interventions. Pending FDA approval and accessibility in the healthcare system, BRX will present a strong alternative to SSRIs for first-line treatment of PPD because of its rapid onset of action, robust response rate, and low side effect profile. I hope further research will explore its efficacy in perinatal bipolar depression and perinatal anxiety disorders. ■

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SPECIAL FEATURE

Perimenopausal Depression

By Chiara Ghetti, MD

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Dr. Ghetti reports no financial relationships relevant to this field of study.

In November 2018, the American College of Obstetricians and Gynecologists published an update to the 2015 Committee Opinion: Screening for Perinatal Depression.[1] Perinatal depression affects up to one in seven women, and more than half of women with depression before pregnancy have depression during pregnancy.[2] As OB/GYNs, we strive to screen women for perinatal depression both in pregnancy and postpartum. Although depression frequently affects reproductive-age women, it is common in women throughout the lifespan. Women are at elevated risk for depression during several reproductive periods of increased vulnerability. These periods correspond to adolescence, pregnancy, postpartum period, and the menopausal transition. So, what do we really know about depression in perimenopausal women?

In 2018, Maki et al, on behalf of the Board of Trustees for the North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers, published the Guidelines for the Evaluation and Treatment of Perimenopausal Depression.[3] I will briefly discuss the authors' key recommendations and explore the role of OB/GYNs in the evaluation and treatment of depression.

The guidelines are consensus recommendations for the evaluation and management of perimenopausal depression. An expert panel developed these recommendations through systematic review of existing literature. The guidelines pertain specifically to depression in women in the menopausal transition (including early through late transition and early postmenopause), which is considered a time of vulnerability for both depressive symptoms and major depressive episodes. The authors reviewed the evidence relating to epidemiology, clinical presentation, therapeutic effects of antidepressant medications, effects of hormone therapy, and the efficacy of other therapies.

The main reported finding is that similar to depression during other reproductive phases, the majority of women who experience a major depressive episode in the perimenopausal period have experienced previous episodes. Although depression during the midlife period presents with the classic defined symptoms of depression (feeling down or sad, little interest in doing things, changes in sleeping habits, decreased energy, change in appetite, difficulty concentrating, having thoughts of hurting oneself), often, it is interwoven with menopausal vasomotor symptoms and sleep disturbances. These menopausal symptoms can complicate its evaluation and treatment. Diagnosis of perimenopausal depression requires the determination of the appropriate reproductive stage, alongside the assessment of the coexisting menopausal and psychiatric conditions, as well as an awareness of the psychosocial factors that commonly affect midlife women. The menopausal transition may coincide with numerous psychosocial stressors, which may include children leaving the home, dealing with aging parents, illness and death of parents or a significant other, medical illnesses, and changes in marital status. Each of these may affect a woman's psychological well-being.

Providers should attempt to develop a thorough differential diagnosis and use validated screening tools to diagnose their patients accurately. A simple validated tool is the PHQ-9,[4] a self-administered measure that assesses depressive symptom severity over the prior two weeks and correlates highly with the diagnosis of major depression by the *Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders*. Regarding treatment, to date, there have been no large randomized trials of antidepressants in a well-defined population of perimenopausal and postmenopausal women with major depressive disorder. The main therapeutic options for this midlife population correspond to the accepted therapies for depression, including pharmacotherapy and psychotherapy. While estrogen therapy is not approved for the treatment of perimenopausal depression, it has demonstrated antidepressant effects in perimenopausal women and, in particular, those experiencing vasomotor symptoms.

THE ROLE OF THE OB/GYN IN EVALUATING AND TREATING DEPRESSION

OB/GYNs are in the unique position of seeing women throughout their lifespan and through many vulnerable reproductive and life course periods. Patients frequently consider OB/GYNs their primary care providers, and we often see ourselves as primary care providers.[5] In addition, many conditions OB/GYNs treat are risk factors for (or highly associated with) depressive symptoms or major depressive episodes.

Although most OB/GYNs view mental health issues as important, significant variations have been reported in screening and treatment practices among providers. In 2003, LaRocco et al surveyed 282 obstetricians and found that less than half screened patients for depression regardless of symptoms.[6] In 2018, Fedock et al reported from a random national sample of obstetric providers and found that providers employed universal postpartum screening but had significantly lower screening rates in pregnant patients.[7]

La Rocco et al reported that providers find depression screening difficult to carry out in everyday practice, and some providers are unsure as to whether screening improves outcomes.[6] Leddy et al found that OB/GYNs are not confident in their abilities to diagnose mental health conditions and frequently express concern about the adequacy of their training in screening and treatment of these conditions.[8]

Several abstracts addressing depression screening were presented at the annual meeting of the 2018 American College of Obstetricians and Gynecologists. Hadley et al reported that although a large number of providers regularly screen for postpartum depression and anxiety, only a subset of these feel confident treating these conditions.[9] Lau et al found that while OB/GYN and family medicine providers employed near-universal screening in postpartum patients after a didactic session on perinatal depression, only three-fourths of those who screened positive were referred to a behavioral health specialist and only 18% were treated with medications.[10]

Several authors have recommended supplemental training in mental health topics for OB/GYNs. In addition to more training, other models may aid us in better serving women's mental health needs. In 2014, Melville et al reported a randomized trial of a collaborative depression care intervention in an OB/GYN clinic compared to usual care.[5] Collaborative care models use an embedded team of mental health specialists who work with clinicians to help manage symptoms. Melville et al demonstrated that the subjects randomized to the collaborative care intervention had a greater improvement in depressive symptoms and improved functioning compared to the usual care group. Their findings make a strong case for mental health care integrated into healthcare settings for women. In 2017, Bhat et al eloquently presented the dramatic effect that OB/GYNs can have on women's well-being by adopting a clinical paradigm that involves regular depression screening and early treatment in the phases of adolescence, pregnancy, peripartum, and the menopausal transition.[11] Although a collaborative care model may not be accessible to all of us, we are in a unique position to significantly affect women's lives. ■

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ABSTRACT & COMMENTARY

Ripples From Original WHI Study Results Continue: Is This Appropriate?

By Robert W. Rebar, MD

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Dr. Rebar reports no financial relationships relevant to this field of study.

SYNOPSIS: Recommendations for menopausal hormone therapy were widely publicized and adopted following the original publication of the results of the Women's Health Initiative and affected both initiation and continuation of estrogen therapy through at least 2013.

SOURCE: Crawford SL, et al. Menopausal therapy trends before versus after 2002: Impact of the Women's Health Initiative study results. *Menopause* 2018; Dec. 21. doi: 10.1097/GME.0000000000001282. [Epub ahead of print].

To better appreciate how to educate patients and providers about menopausal hormone therapy (MHT; generally regarded as estrogen plus progesterone in women with a uterus and as estrogen alone in women without a uterus), Crawford et al analyzed survey data from up to 14 approximately annual visits collected between 1996 and 2013 from 3,018 participants in the NIH's multicenter Study of Women's Health Across the Nation (SWAN). The investigators wished to determine the effect of the initial 2002 report[1] of data from the Women's Health Initiative (WHI), which involved administration of estrogen-progestin therapy to postmenopausal women and was halted prematurely because of significant concerns about safety on initiation and continuation of MHT. SWAN included women of diverse ethnicities 42-52 years of age with an intact uterus and one or two ovaries to examine the changes that occur longitudinally across the menopausal transition.

MHT initiation fell from 8.6% before publication of the WHI results to 2.8% post-WHI ($P < 0.0001$), with a decrease in continuation as well from 84.0% to 62.0% ($P < 0001$). Although the magnitude of the decreased initiation and continuation varied among ethnic groups, it occurred in all and tended to be greater in women who might be expected to benefit more from MHT based on current guidelines, specifically younger women with severe vasomotor flushes. More frequent vasomotor symptoms were associated with greater initiation of MHT both pre- and post-WHI ($P < 0.001$ for both), but the largest decrease (9.4% decline) occurred in women who had the most frequent hot flashes. Similarly, young postmenopausal women were less apt to begin MHT and were more likely to discontinue use despite current guidelines. Reasons for initiating MHT changed after publication of WHI, with the largest declines for use among those who wished to reduce the risk of osteoporosis and heart disease. The largest reasons for discontinuing MHT were for media reports and provider advice.

■ COMMENTARY

The initial report that the WHI was being terminated early because of safety concerns changed our views on MHT forever. MHT should not be used for prevention of coronary heart disease, breast cancer, or dementia. Despite subsequent studies and guidelines promoting appropriate use of MHT in certain symptomatic postmenopausal women, providers who are not gynecologists are significantly less likely to recommend use of MHT (as noted in this report), regardless of patient symptomatology. I know that I have been frustrated when patients who clearly would benefit from MHT were advised not to begin or to discontinue therapy after seeing another provider. Yet, as Dr. Jensen reviewed in the January issue of *OB/GYN Clinical Alert*, another large cohort study, this time from Denmark, documented that long-term follow-up (median 17.6 years) of almost 30,000 women representing 7% of the Danish female population enrolled between 1993 and 1997 between the ages of 50 and 64 years showed no association of MHT and overall mortality.[2] This squares with a recent reanalysis of the data from the WHI documenting the safety of MHT when begun within five years of menopause and documenting no increase in all-cause mortality.[3]

American women have had their reproductive lives turned topsy-turvy three times in the last 50 years. In the 1960s, they witnessed the publicity surrounding combination oral contraceptive agents and the increased risks for several significant diseases, including deep venous thrombosis, stroke, and myocardial infarction. The far greater risks of pregnancy compared to the use of oral contraceptives were not emphasized in the press releases. Many women discontinued use of this form of contraception only to suffer unintended pregnancies. Then followed the debacle related to the Dalkon Shield intrauterine device (IUD), which resulted in a dramatic decline in IUD usage in the United States; today, this usage is still lower than in most other industrialized countries. More recently, women were subjected to incompletely analyzed findings from the WHI, which has decreased use of MHT even when it is indicated.

As Dr. Jensen noted in his review of the Danish study, the take-home message for clinicians counseling women on the risks and benefits of MHT should be positive. We need to emphasize to patients and less-informed providers that MHT is extremely useful in improving quality of life and is warranted for women with vasomotor flushes,[4] plays a role in protection against fracture risk,[5] and can improve sexual function.[6] Moreover, we have long known that MHT is warranted to prevent coronary heart disease,[7] as well as to prevent symptoms associated with estrogen deficiency following bilateral oophorectomy in premenopausal women and in those with premature menopause.[8]

Both the North American Menopause Society and the Endocrine Society have guidelines for the use of MHT.[9,10] Both effectively agree that MHT is the most effective therapy for vasomotor symptoms and the genitourinary syndrome of menopause (GSM) and can prevent bone loss. Both emphasize the need to individualize therapy based on clinical factors and patient preference and note that benefits may exceed risks for the majority of women younger than 60 years of age. Both note that low-dose vaginal estrogen therapy is effective for treatment of GSM in women without indications for systemic MHT. For those not desiring local estrogen, a variety of vaginal moisturizers and lubricants are available. Neither guideline recommends a firm age by which MHT must be discontinued, focusing on shared decision-making with the patient. All women should embrace healthy lifestyle measures. It is these recommendations that we must emphasize in counseling patients and in educating other providers. ■

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ABSTRACT & COMMENTARY

Should Two-Dose Methotrexate Be the Standard of Care for Ectopic Pregnancy?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she receives grant/research support from Bayer and is a consultant for Merck.

SYNOPSIS: In this meta-analysis, the two-dose methotrexate treatment protocol was associated with higher odds of treatment success and a shorter treatment period compared to the single-dose protocol.

SOURCE: Alur-Gupta S, et al. Two-dose versus single-dose of methotrexate for treatment of ectopic pregnancy: A meta-analysis. *Am J Obstet Gynecol* 2019; Jan 7. pii: S0002-9378(19)30004-3. doi: 10.1016/j.ajog.2019.01.002. [Epub ahead of print].

In this systematic review and meta-analysis, the study population included women with an ectopic pregnancy diagnosed by transvaginal ultrasound, and interventions included single-dose, two-dose, and multi-dose protocols of methotrexate. Alur-Gupta et al searched PubMed, Embase, and the Cochrane Library from inception to July 2018 for randomized, controlled trials for which the full text in English could be accessed. They collected data from each study, including year of study, number of subjects, location of recruitment, mean age of subjects, mean body mass index of subjects, pretreatment hCG, pretreatment adnexal mass diameter, randomization and blinding processes, inclusion and exclusion criteria, description of methotrexate protocols used, definition of outcomes measured including treatment success, length of follow-up, side effects, and surgery for tubal rupture. The primary outcome measured was treatment success (as defined by the individual studies) overall and for the following subgroups: high hCG levels (> 3,000-5,500 mIU/mL) and large adnexal mass (> 2-3.5 cm). Secondary outcomes included side effects (nausea, diarrhea, mucositis, abdominal pain, lab abnormalities), surgery for tubal rupture, and length of follow-up in days.

Seven publications met inclusion criteria for the meta-analysis. None of the studies were performed in the United States. The study size ranged from 70 to 160 patients. Only half the studies reported side effects or length of follow-up, and only five reported rates of surgery for tubal rupture. There were four single-dose vs. two-dose trials and three single-dose vs. multidose trials. For the four single-dose vs. two-dose trials, treatment success was defined variably: hCG < 5 mIU/mL, hCG < 200 mIU/mL, or hCG < 15 mIU/mL within six weeks without surgery or repeat dose. For the primary outcome of treatment success, the two-dose protocol was associated with 1.84 greater odds of success compared to single dose (95% confidence interval [CI], 1.13-3.00). Side effects were 1.53 times more likely in the two-dose compared to the single-dose protocol (95% CI, 1.01-2.30). Odds of surgery for tubal rupture were lower, but not statistically significant (odds ratio [OR], 0.65; 95% CI, 0.26-1.63), and the length of follow up was shorter by 7.9 days (95% CI, 3.5-12.2 days) in the two-dose compared to the single-dose protocol. Women in the high hCG group had 3.23 greater odds of treatment success with two-dose compared to single-dose protocols (95% CI, 1.53-6.84). Similarly, women with larger adnexal masses had more success with the two-dose compared to single-dose regimens (OR, 2.92; 95% CI, 1.23-6.93).

■ COMMENTARY

Despite advances in detection and treatment, ectopic pregnancy remains a significant cause of maternal morbidity and mortality in the United States.[1] The fallopian tubes are the most common site of ectopic pregnancy. Once tubal ectopic pregnancy is diagnosed, treatment includes expectant management (reserved for asymptomatic patients with low initial hCG values), medical management with methotrexate, or surgery (salpingostomy or salpingectomy). Candidates for medical management include women with confirmed or high clinical suspicion for tubal ectopic pregnancy who are hemodynamically stable with an unruptured mass and who do not have absolute contraindications to methotrexate (e.g., intrauterine pregnancy, breastfeeding, clinically significant liver or renal

disease, blood dyscrasias, peptic ulcer disease, immunodeficiency, and active pulmonary disease).[2] Women initiating methotrexate treatment must agree to close surveillance in case treatment fails and surgical intervention is warranted.

There are single-dose, two-dose, and multidose protocols for methotrexate treatment. The main difference between the single-dose and two-dose protocols are that the two-dose protocol requires administering a second dose of 50 mg/m^2 of methotrexate on day 4. Neither regimen requires rescue doses of folinic acid (leucovorin) that are required in the multidose protocols.[1] Therefore, both the single-dose and two-dose regimens are simple to follow, and in both protocols, the patient returns on day 4 anyway for an hCG level. Although more exposure to methotrexate increases the risk of side effects, these generally are mild (nausea, vomiting, mucositis) and do not require hospitalization. It is also acknowledged that the single-dose protocol typically requires a second dose of methotrexate in 25% of cases for inadequate declines in hCG values.[1] Therefore, the two-dose regimen is seen as a compromise of convenience and efficacy between the single-dose and multidose regimens.

To date, the optimal methotrexate regimen has been debated within the American College of Obstetricians and Gynecologists, which stated that the choice should be guided by the initial hCG level and a discussion with the patient regarding the benefits and risks of each approach.[1] Similarly, the American Society for Reproductive Medicine does not favor one approach over another.[2] This meta-analysis has several strengths, including stringent criteria for study entry (high-quality randomized, controlled trials only) and the inclusion of more recent studies than past meta-analyses that did not reach the same conclusions.[3,4] Alur-Gupta et al made a strong case for using two-dose methotrexate protocols as first-line for the treatment of tubal ectopic pregnancy. Besides the increased success in all women, even in those with higher hCG levels and larger adnexal masses, the shorter treatment duration makes this a compelling argument. Women definitely would appreciate shorter follow-up periods and fewer blood draws. Adopting the two-dose regimen as standard of care also may expand the population that is offered medical management to include women with a higher initial HCG level that typically has been a relative contraindication to methotrexate therapy (> 5,000 mIU/mL). ■

REFERENCES

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CME/CE QUESTIONS

1. **According to Meltzer-Brody et al, which of the following is true about brexanolone (BRX) treatment compared to placebo?**
   a. Response rates were not seen in BRX60 or BRX90 until 60 hours of infusion.
   b. Rash and nausea were the most common adverse events.
   c. Participants receiving BRX60 and BRX90 had a greater reduction in HAM-D scores at 60 hours.
   d. Bipolar patients showed more rapid response rates than unipolar depression.
3. **Which statement is true regarding perimenopausal depression?**
   a. It is less common in women who have previously suffered depression.
   b. It is a side effect of vasomotor symptoms.
   c. It often coexists with vasomotor symptoms, sleep disturbances, and psychosocial factors.
   d. It is a normal part of the menopausal transition and should not be screened for.
2. **Two-dose methotrexate treatment for ectopic pregnancy was more successful than single-dose treatment in which of the following subgroups?**
   a. Women with ruptured tubal ectopic pregnancies
   b. Women with larger adnexal masses (> 2 cm to 3.5 cm)
   c. Women with ectopic pregnancies with fetal heart tones
   d. Women with gestational sac diameters < 4 cm