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Courtesy Drew Buchanan

STI CARE

Achieving a 'new sexual health paradigm' means expanding care

BY TARA HAELLE

A vital aspect of expanding access and care for sexually transmitted infections (STIs) in the United States is broadening responsibility for this care across the health care system and other community resources, according to an article published online in Clinical Infectious Diseases (2021 Jul 6. doi: 10.1093/cid/ciab609). This expansion and decentralization of care are central to adopting the "new sexual health paradigm" recommended by a National Academies report that was published in March.

"STIs represent a sizable, longstanding, and growing public health challenge," write Vincent Guilamo-Ramos, PhD, MPH, dean and professor at the Duke University School of Nursing and director of the Center for Latino Adolescent and Family Health (CLAFH) at Duke University, both in Durham, N.C., and his colleagues. Yet the limitations on the current STI workforce and limited federal funding and support for STI prevention and care mean it will take clinicians of all types from across the health care spectrum to meet the challenge, they explain.

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PREGNANCY LOSS

Survey exposes rates twice as high for female surgeons

BY MARCIA FRELLICK

Nearly half of female surgeons (42%) who were recently surveyed have had a miscarriage or stillbirth – twice the rate of women aged 30-40 years in the general population – according to an article published online in JAMA Surgery (2021 Jul 28.doi: 10.1001/jamasurg.2021.3301).

The authors, led by Erika L. Rangel, MD, division of general and gastrointestinal surgery, department of surgery, Brigham and Women's Hospital, Boston, found that after the losses the women took little or no time off.

Of 692 surgeons surveyed, 347 female surgeons had experienced a pregnancy loss. Of those, 244 had a miscarriage at less than 10 weeks' gestation, 92 had a miscarriage between 10 and 20 weeks' gestation, and 11 had a stillbirth (loss at 20 weeks or later).

Most took no time off after miscarriage

After a miscarriage, 225 of 336 women (75%) took no time off work, and after a stillbirth, 5 of 11 (45%) took off 1 week or less, the authors found.

The study addressed an issue that people have talked about anecdotally or on social media, Dr. Rangel told this news organization.

"This was finally an opportunity to do a study of enough magnitude to show that there is a very quantifiable difference in complication rate,

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Commentary

Dr. Lindsay Dale, Dr. Patricia Black, and Dr. Eve Espey call for the end of the mifepristone REMS for medication abortions.

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Specific COVID-19 antibodies found in breast milk of vaccinated women

BY JALEESA BAULKMAN
FROM JAMA NETWORK OPEN

The breast milk of women who had received Pfizer's COVID-19 vaccine contained specific antibodies against the infectious disease, new research found.

"The COVID-19 pandemic has raised questions among individuals who are breastfeeding, both because of the possibility of viral transmission to infants during breastfeeding and, more recently, of the potential risks and benefits of vaccination in this specific population," researchers wrote.

In August, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, and most recently, the Centers for Disease Control and Prevention, recommended that pregnant people receive the COVID-19 vaccine.

The study, published Aug. 11 in JAMA Network Open (2021. doi:10.1001/jamanetworkopen.2021.20575), adds to a growing collection of research that has found COVID-19 antibodies in the breast milk of women who were vaccinated against or have been infected with the illness.

Study author Erika Esteve-Palau, MD, PhD, and her colleagues collected blood and milk samples from 33 people who were on average 37 years old and who were on average 17.5 months post partum to examine the correlation of the levels of immunoglobulin G antibodies against the spike protein (S1 subunit) and against the nucleocapsid (NC) of SARS-CoV-2.

Blood and milk samples were taken from each study participant at three time points – 2 weeks after receiving the first dose of the vaccine, 2 weeks after receiving the second dose, and 4 weeks after the second dose. No participants had confirmed SARS-CoV-2 infection prior to vaccination or during the study period.

Researchers found that, after the second dose of the vaccine, IgG(S1) levels in breast milk increased and were positively associated with corresponding levels in the blood samples. The median range of IgG(S1) levels for serum-milk pairs at each time point were 519 to 1 arbitrary units (AU) per mL 2 weeks after receiving the first dose of the vaccine, 8,644 to 78 AU/mL 2 weeks after receiving the second dose, and 12,478 to 50.4 AU/mL 4 weeks after receiving the second dose.

Lisette D. Tanner, MD, MPH, FACOG, who was not involved in the study, said she was not surprised by the findings as previous studies have shown the passage of antibodies in breast milk in vaccinated women. One 2021 study published in JAMA (doi: 10.1001/jama.2021.5782) found SARS-CoV-2–specific IgA and IgG antibodies in breast milk for 6 weeks after vaccination. IgA secretion was evident as early as 2 weeks after vaccination followed by a spike in IgG after 4 weeks (a week after the second vaccine). Meanwhile, another 2021 study published in mBio (doi: 10.1128/mBio.03192-20) found that breast milk produced by parents with COVID-19 is a source of SARS-CoV-2 IgA and IgG antibodies and can neutralize COVID-19 activity.

The median range of IgG(S1) levels for serum-milk pairs at each time point were 519 to 1 arbitrary units per mL 2 weeks after receiving the first dose of the vaccine and **12,478 to 50.4 AU/mL 4 weeks after receiving the second dose.**

"While the data from this and other studies is promising in regards to the passage of antibodies, it is currently unclear what the long-term effects for children will be," said Dr. Tanner of the department of gynecology and obstetrics at Emory University, Atlanta. "It is not yet known what level of antibodies is necessary to convey protection to either neonates or children. This is an active area of investigation at multiple institutions."

Dr. Tanner said she wished the study "evaluated neonatal cord blood or serum levels to better understand the immune response mounted by the children of women who received vaccination."

Researchers of the current study said larger prospective studies are needed to confirm the safety of SARS-CoV-2 vaccination in individuals who are breastfeeding and further assess the association of vaccination with infants' health and SARS-CoV-2–specific immunity.

Dr. Palau and Dr. Tanner had no relevant financial disclosures.

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References: 1. Blatt AJ, et al. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. Cancer Cytopathol. 2015;123(5):282-288. doi:10.1002/ cncy.21544 (Study included ThinPrep, SurePath and Hybrid Capture 2 assay). **2.** Austin RM, et al. Enhanced detection of cervical cancer and precancer through use of imaged liquid-based cytology in routine cytology and HPV cotesting. Am J Obstet Gynecol. 2018;150(5):385-392. doi:10.1093/ajcp/aqy114 (Study included ThinPrep Pap test, ThinPrep imaging, Digene HPV, Cervista HPV and Aptima HPV).

Maternal headache tied to higher risk of SGA babies

BY JENNIE SMITH
FROM CEPHALALGIA

Pregnant women who experience migraine with aura – and also the far more common tension-type headache – are at increased risk for giving birth to small-for-gestational-age (SGA) babies, according to results from an observational study.

Migraine during pregnancy has been associated in previous studies with hypertensive pregnancy complications including preeclampsia; however, little is known about other headache types and their effects on pregnancy and birth outcomes.

For their research, published online in Cephalalgia (2021 Jul 20. doi: 10.1177/03331024211029236), Isabella Neri, MD, PhD, and colleagues at Hospital Policlinico of Modena, Italy, looked at headache status for 515 consecutive pregnant women evaluated during their first trimester and followed through childbirth.

Altogether 224 women, or 43.5% of the cohort, were diagnosed with migraine without aura (n = 72), migraine with aura (n = 27), or tension-type headache (n = 125). The authors did not report on the severity or frequency of headaches.

> "I would want to see that association replicated in another study before I thought that I needed to warn women with tension-type headache about this potential outcome. **There's lot of uncertainty here about the magnitude of the risk.**"

Women with migraine with aura and tension-type headache saw higher rates of SGA infants (25.9% and 10.4% of births, respectively) compared with 5.5% for women without headache. Women presenting with tension-type headache saw elevated risk for SGA infants (odds ratio, 4.19; $P = .004$) as did women with migraine with aura (OR, 5.37; $P = .02$).

Admission to neonatal intensive care was significantly higher in all the headache groups. However, the authors found no statistically significant associations between headaches and any other perinatal outcome investigated in the study, including gestational diabetes, placental abruption, gestational hypertension, and preterm delivery.

A previous study conducted by the same research group had reported a relationship between migraine and gestational hypertension. The authors cited the small sample size of the migraine groups in the current study, "the diverse features of the population," and the popularity of low-dose aspirin administration as potentially affecting that outcome.

Interpret findings with caution

Asked by this news organization to comment on the research, two headache neurologists praised Dr. Neri and colleagues' research for focusing on an understudied topic – but also said that the results would not change their practice unless replicated in larger studies.

Elizabeth W. Loder, MD, MPH, chief emeritus of the division of headache at Brigham and Women's Faulkner Hospital in Boston, urged caution in interpreting the findings, particularly with regard to tension-type headache. "This study adds to information suggesting that pregnancy complications probably are higher in women who have migraine with aura, and there's biological plausibility for that," Dr. Loder said. "Having aura means you may have some vascular abnormalities and things that logically might be associated with an increased risk of small-for-gestational age infants." But the small size of the migraine-with-aura group in this study – 27 women – and the fact that other perinatal outcomes measured in the study did not reach significance, allows for the possibility that the SGA findings were due to chance, Dr. Loder noted.

With tension-type headache, a biological rationale for SGA risk is more elusive, Dr. Loder said. "I would want to see that association replicated in another study before I thought that I needed to warn women with tension-type headache about this potential outcome. There's lot of uncertainty here about the magnitude of the risk."

While Dr. Neri and colleagues described the instruments used in their study to diagnose migraine and migraine with aura, they did not explain how tension-type headache was diagnosed.

Tension-type headache, while common, is still not well characterized, Dr. Loder noted, and may represent a heterogeneous condition or the milder end of a biological continuum that includes migraine with aura. Also, the group in the study had a higher prevalence of smoking, and though the authors made statistical adjustments for smoking status, "smokers are systematically different than people who aren't in other ways that could be associated with these outcomes," Dr. Loder said.

While the authors of the study suggested that interventions might be indicated for women with tension-type headache in pregnancy, "showing an association doesn't necessarily mean that intervening would make a difference" on pregnancy outcomes, Dr. Loder said.

Amaal J. Starling, MD, of the Mayo Clinic in Phoenix, said in an interview that she, too, appreciated that this study looked at pregnancy outcomes in the setting of headache disorders. "Unfortunately even though headache disorders and especially migraine affect women so much, we still know very little about migraine in pregnancy," she said.

Dr. Starling noted that many women with migraine are discouraged by their health care providers from becoming pregnant, because of the false belief that migraine cannot be managed in pregnancy. In her own practice, she said, she treats many patients with severe headache who become pregnant and who require pharmacological intervention during pregnancy.

baona/Getty Images

This does not mean she regards headache in pregnancy as innocent. "I want patients to be on high alert for changes in headache symptoms in pregnancy. If someone has worsening of headache or migraine or aura in the setting of pregnancy, we consider that a red flag," potentially indicating complications such as high blood pressure, gestational hypertension, or a blood clot.

Like Dr. Loder, Dr. Starling said she was not surprised by Dr. Neri and colleagues' finding that migraine with aura might impact pregnancy outcomes. "We know that migraine with aura has a lot of vascular abnormalities that underlie the pathogenesis," she said.

Dr. Starling found the findings related to tension-type headache less convincing, not least because the diagnostic criteria for tension-type headache was not made clear in the study. "I view this as an exploratory study that says maybe there's a signal here. A larger epidemiological study would need to be done to confirm or refute this data," Dr. Starling said. Until the findings can be replicated, "this study would not affect my clinical practice in any way."

Dr. Neri and colleagues described no outside funding for their research or financial conflicts of interest. Dr. Starling has received consulting fees from pharmaceutical manufacturers but reported no financial disclosures relevant to the study discussed. Dr. Loder reported no financial conflicts of interest.

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COVID-19 disease may actually cause preeclampsia

BY TARA HAELLE
FROM THE JOURNAL OF OBSTETRICS AND GYNECOLOGY

New evidence strongly suggests that COVID-19 disease causes an increased risk of preeclampsia and preterm birth in those who have an infection while pregnant, according to a retrospective observational study published in the American Journal of Obstetrics and Gynecology (2021 Aug 26. doi: 10.1016/j.ajog.2021.08.020). Though the study was observational, its primary finding was a dose-response relationship between the severity of COVID-19 disease and the likelihood of preeclampsia or preterm birth, fulfilling a key criterion for establishing causality in an association.

"The fact that 43% (13/30) of the cases of preeclampsia diagnosed after SARS-CoV-2 infection were preterm preeclampsia (<37 weeks) suggests that COVID-19 may be a cause for medically indicated preterm birth that contributes to the excess preterm birth delivery rate previously reported," wrote Jonathan Lai, MD, of the Fetal Medicine Research Institute of King's College Hospital, London, and colleagues. The study also found an increased likelihood of COVID-19 disease in those who had preeclampsia before their infection. "Whether preeclampsia can predispose COVID-19 some cases, or that the two conditions may co-occur because they share similar risk factors requires further investigation," the authors wrote.

It's also unclear whether the increased risk of preeclampsia is contributing to the higher preterm birth risk, according to Linda Eckert, MD, a professor of Ob.Gyn. at the University of Washington, Seattle who specializes in maternal immunization.

"COVID is linked to preeclampsia in this study, and COVID is linked to preterm birth," Dr. Eckert said in an interview. "The question of whether preeclampsia leading to preterm birth is also linked to infection is not possible to tease out in this study as all the factors are likely interrelated. There is a relationship between COVID and preterm birth absent preeclampsia."

The researchers retrospectively examined data from 1,223 pregnant women who tested positive for SARS-CoV-2 between February 2020 and March 2021 at any of 14 National Health Service maternity hospitals in the United Kingdom. The researchers compared the severity of disease among the women with their risk of preeclampsia as a primary outcome, followed by the outcomes of preterm birth and gestational age at delivery.

COVID-19 infections were classified as asymptomatic, mild illness (lacking shortness of breath, dyspnea, or abnormal chest imaging), moderate illness (evidence of lower respiratory disease but an oxygen saturation of at least 94%), and severe illness (requiring "high dependency or intensive care secondary to respiratory impairment/failure or multiorgan dysfunction").

The researchers adjusted their analysis of preeclampsia to account for prior risk of preeclampsia based on maternal characteristics and medical history. Analysis of preterm birth risk included adjustment for maternal age, weight, height, race, method of conception, chronic hypertension, smoking, and diabetes.

Preeclampsia occurred in 4.2% of the women, and 17.6% of the women had a preterm birth. In addition, 1.3% of the cohort had a miscarriage, and there were 10 (0.81%) fetal deaths. Since 21 cases of preeclampsia occurred before the women tested positive, the researchers removed those cases from the analysis. Among the remaining 30 cases, 13 women had preterm preeclampsia and 17 had term preeclampsia.

When the researchers compared the study population's risk of preeclampsia with that of a separate population with similar risk factors, they found a dose-response increased risk in those with COVID-19 infections. While 1.9% of asymptomatic patients had preeclampsia, incidence was 2.2% in patients with mild disease, 5.7% in those with moderate disease, and 11.1% in those with severe disease. Women with severe COVID-19 tended to be older and to have a higher body mass index.

After adjustments, women were nearly five times more likely to develop preeclampsia if they had severe COVID-19 compared with women with asymptomatic infection (adjusted relative risk, 4.9). Those with moderate or severe disease had triple the risk of preeclampsia compared to those with mild or asymptomatic infection (aRR, 3.3).

To investigate whether having preeclampsia predisposes women to develop COVID-19 disease, the researchers compared the women who had preeclampsia before their infection with women in the study who never developed preeclampsia. Although they found a trend toward higher risk of moderate or severe COVID-19 following preeclampsia, the association was not significant before or after adjustment.

After adjustments, **women were nearly five times more likely to develop preeclampsia** if they had severe COVID-19 compared with women with asymptomatic infection.

The researchers also found a dose-response relationship in risk of preterm birth. While 11.7% of asymptomatic patients had preterm birth, the incidence was 12.8% in those with mild COVID-19, 29.9% in those with moderate disease, and 69.4% in those with severe disease. Women with severe disease were more than five times more likely to have a preterm birth than were women with an asymptomatic infection (aRR, 5.64), and the risk of preterm birth was 2.5 times greater in women with moderate disease (aRR, 2.47).

"Moreover, there was a dose-response relationship between gestational age at delivery and the severity of SARS-CoV-2 infection," the authors reported. Mean gestational age at delivery was 38.7 weeks in asymptomatic women compared to 37.5 weeks for those with moderate disease and 33 weeks in those with severe disease ($P < .001$).

"The more severe the infection with SARS-CoV-2, the greater the risk of preeclampsia and preterm birth," the authors wrote. "SARS-CoV-2 infection can lead to endothelial dysfunction, intravascular inflammation, proteinuria, activation of thrombin, and hypertension, which are all features of preeclampsia. Therefore, a causal relationship must be considered."

A dose-response association is only one criterion for causality, however; so it's still premature to say definitively that a causal relationship exists, Dr. Eckert said.

"More investigation in different populations across different ethnicities is needed before causality can be confidently assured," she said.

Anthony Sciscione, DO, director of maternal-fetal medicine and the ob.gyn. residency at ChristianaCare in Newark, Del., agreed that the precise relationship between the two remains unresolved.

"We don't know what causes preeclampsia," but "we strongly suspect it has to do with a placental dysfunction, or endothelial dysfunction, and it's really clear that women who get COVID have a much higher risk of preeclampsia," Dr. Sciscione said in an interview. It's possible that no real relationship exists between the two (or that greater surveillance of women with COVID-19 is picking up the relationship) but it's more likely that one of two other situations is happening, Dr. Sciscione said. Either COVID-19 involves a syndrome that looks like preeclampsia in pregnant women, or the disease "leads to the cascade that causes preeclampsia," he said.

One clear clinical implication of these findings is that "women who have severe COVID early in pregnancy may need to be watched more closely for signs of developing preeclampsia" and that "women with severe COVID are more likely to have preterm births," Dr. Eckert said. "This absolutely lends support to the need for pregnant individuals to receive a COVID vaccine."

Dr. Sciscione said his experience counseling pregnant patients about the vaccine has made it clear that patients generally want to do what's safest for their babies and may feel uneasiness about the safety of the vaccine. "The truth is, now there's mounting evidence that there are fetal effects, not just maternal effects" from COVID-19 disease. He added that preterm birth is associated with a variety of long-term adverse outcomes, such as cerebral palsy and learning disabilities.

"At this time it's critically important that women be offered and get the vaccine because we know that people that are vaccinated don't get as sick," Dr. Sciscione said.

The research was funded by the Fetal Medicine Foundation and the National Institutes of Health. The authors and Dr. Eckert have no disclosures. Dr. Sciscione is the associate editor of the American Journal of Obstetrics and Gynecology, where the study appeared.

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72.1% and **71.2%** in LIBERTY 1 and 2 vs **16.8%** and **14.7%** for placebo, respectively (*P* <0.0001)[1]

- **Myfembree was studied in LIBERTY 1 and 2,** which were 2 replicate, 24-week, randomized, double-blind, placebo-controlled clinical trials that enrolled premenopausal women with heavy menstrual bleeding associated with uterine fibroids[1]
- Response rate was the primary endpoint, defined as the proportion of women receiving Myfembree who achieved menstrual blood loss volume <80 mL ***and*** ≥50% reduction in menstrual blood loss volume from baseline over the last 35 days of treatment. Mean menstrual blood loss volume (± standard deviation) at baseline was 231 mL (± 156)[1]

INDICATION

Myfembree is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

Limitations of Use: Use of Myfembree should be limited to 24 months due to the risk of continued bone loss which may not be reversible.

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BOXED WARNING: THROMBOEMBOLIC DISORDERS AND VASCULAR EVENTS

- **Estrogen and progestin combination products, including Myfembree, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in women at increased risk for these events.**
- **Myfembree is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension.**

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Myfembree is contraindicated in women with any of the following: high risk of arterial, venous thrombotic, or thromboembolic disorder; pregnancy; known osteoporosis; current or history of breast cancer or other hormone-sensitive malignancies; known hepatic impairment or disease; undiagnosed abnormal uterine bleeding; known hypersensitivity to components of Myfembree.

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders: Discontinue immediately if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs or is suspected. Discontinue at least 4 to 6 weeks before surgery associated with an increased risk of thromboembolism, or during periods of prolonged immobilization, if feasible. Discontinue immediately if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis as these have been reported with estrogens and progestins.

Bone Loss: Myfembree may cause a decrease in bone mineral density (BMD) in some patients, which may be greater with increasing duration of use and may not be completely reversible after stopping treatment. Consider the benefits and risks in patients with a history of low trauma fracture or risk factors for osteoporosis or bone loss, including medications that may decrease BMD. Assessment of BMD by dual-energy X-ray absorptiometry (DXA) is recommended at baseline and periodically thereafter. Consider discontinuing Myfembree if the risk of bone loss exceeds the potential benefit.

Hormone-Sensitive Malignancies: Discontinue Myfembree if a hormone-sensitive malignancy is diagnosed. Surveillance measures in accordance with standard of care, such as breast examinations and mammography are recommended. Use of estrogen alone or estrogen plus progestin has resulted in abnormal mammograms requiring further evaluation.

Depression, Mood Disorders, and Suicidal Ideation: Promptly evaluate patients with mood changes and depressive symptoms including shortly after initiating treatment, to determine whether the risks of continued therapy outweigh the benefits. Patients with new or worsening depression, anxiety, or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior and reevaluate the benefits and risks of continuing Myfembree.

Hepatic Impairment and Transaminase Elevations: Steroid hormones may be poorly metabolized in these patients. Instruct women to promptly seek medical attention for symptoms or signs that may reflect liver injury, such as jaundice or right upper abdominal pain. Acute liver test abnormalities may necessitate the discontinuation of Myfembree use until the liver tests return to normal and Myfembree causation has been excluded.

Common adverse events and discontinuation rates vs placebo[1]

- Discontinuation rates due to adverse events (3.9%) were similar to placebo (4.3%)
- The most common adverse events occurring at ≥3% and at a greater incidence than placebo were hot flush/hyperhidrosis/night sweats; abnormal uterine bleeding; alopecia; and decreased libido. These are not all the possible side effects of Myfembree

Learn more at MyfembreeHCP.com

Gallbladder Disease or History of Cholestatic Jaundice: Discontinue Myfembree if signs or symptoms of gallbladder disease or jaundice occur. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, assess the risk-benefit of continuing therapy. Studies among estrogen users suggest a small increased relative risk of developing gallbladder disease.

Elevated Blood Pressure: For women with well-controlled hypertension, monitor blood pressure and stop Myfembree if blood pressure rises significantly.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy: Advise women to use non-hormonal contraception during treatment and for one week after discontinuing Myfembree. Avoid concomitant use of hormonal contraceptives. Myfembree may delay the ability to recognize pregnancy because it alters menstrual bleeding. Perform testing if pregnancy is suspected and discontinue Myfembree if pregnancy is confirmed.

Risk of Early Pregnancy Loss: Myfembree can cause early pregnancy loss. Exclude pregnancy before initiating and advise women to use effective non-hormonal contraception.

Uterine Fibroid Prolapse or Expulsion: Advise women with known or suspected submucosal uterine fibroids about the possibility of uterine fibroid prolapse or expulsion and instruct them to contact their physician if severe bleeding and/or cramping occurs.

Alopecia: Alopecia, hair loss, and hair thinning were reported in phase 3 trials with Myfembree. Consider discontinuing Myfembree if hair loss becomes a concern. Whether the hair loss is reversible is unknown.

Effects on Carbohydrate and Lipid Metabolism: More frequent monitoring in Myfembree-treated women with prediabetes and diabetes may be necessary. Myfembree may decrease glucose tolerance and result in increased blood glucose concentrations. Monitor lipid levels and consider discontinuing if hypercholesterolemia or hypertriglyceridemia worsens.

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations in triglycerides levels leading to pancreatitis. Use of Myfembree is associated with increases in total cholesterol and LDL-C.

Effect on Other Laboratory Results: Patients with hypothyroidism and hypoadrenalism may require higher doses of thyroid hormone or cortisol replacement therapy. Use of estrogen and progestin combinations may raise serum concentrations of binding proteins (e.g., thyroid-binding globulin, corticosteroid-binding globulin), which may reduce free thyroid or corticosteroid hormone levels. Use of estrogen and progestin may also affect the levels of sex hormone-binding globulin, and coagulation factors.

Hypersensitivity Reactions: Immediately discontinue Myfembree if a hypersensitivity reaction occurs.

ADVERSE REACTIONS: Most common adverse reactions for Myfembree (incidence ≥3% and greater than placebo) were hot flush/hyperhidrosis/night sweats, abnormal uterine bleeding, alopecia, and decreased libido. These are not all the possible side effects of Myfembree.

DRUG INTERACTIONS: P-gp Inhibitors: Avoid use of Myfembree with oral P-gp inhibitors. If use is unavoidable, take Myfembree first, separate dosing by at least 6 hours, and monitor patients for adverse reactions. **Combined P-gp and Strong CYP3A Inducers:** Avoid use of Myfembree with combined P-gp and strong CYP3A inducers.

LACTATION: Advise women not to breastfeed while taking Myfembree.

Please see Brief Summary of the full Prescribing Information including BOXED WARNING on the following pages

Reference: 1. Myfembree [Prescribing Information]. Brisbane, CA: Myovant Sciences, Inc. May 2021.

MYFEMBREE® (relugolix, estradiol, and norethindrone acetate) tablets, for oral use

Brief Summary of the Full Prescribing Information

Rx Only

WARNING: THROMBOEMBOLIC DISORDERS AND VASCULAR EVENTS

- **Estrogen and progestin combination products, including MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism (PE), deep vein thrombosis (DVT), stroke and myocardial infarction (MI), especially in women at increased risk for these events.**
- **MYFEMBREE is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension.**

1. INDICATIONS AND USAGE

MYFEMBREE is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

Limitations of Use

Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss which may not be reversible.

4. CONTRAINDICATIONS

MYFEMBREE is contraindicated in women:

- With a high risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include women over 35 years of age who smoke, and women who are known to have:
  - current or history of deep vein thrombosis or pulmonary embolism
  - vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral vascular disease)
  - thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
  - inherited or acquired hypercoagulopathies
  - uncontrolled hypertension
  - headaches with focal neurological symptoms or migraine headaches with aura if over 35 years of age
- Who are pregnant. Exposure to MYFEMBREE early in pregnancy may increase the risk of early pregnancy loss.
- With known osteoporosis, because of the risk of further bone loss.
- With current or history of breast cancer or other hormone-sensitive malignancies, and with increased risk for hormone-sensitive malignancies.
- With known hepatic impairment or disease.
- With undiagnosed abnormal uterine bleeding.
- With known anaphylactic reaction, angioedema, or hypersensitivity to MYFEMBREE or any of its components. Anaphylactoid reactions have been reported.

5. WARNINGS AND PRECAUTIONS

5.1. Thromboembolic Disorders and Vascular Events

MYFEMBREE is contraindicated in women with current or history of thrombotic or thromboembolic disorders and in women at increased risk for these events.

Discontinue MYFEMBREE immediately if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs or is suspected. Discontinue MYFEMBREE at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization, if feasible.

Discontinue MYFEMBREE immediately if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis as these have been reported in patients receiving estrogens and progestins.

Estrogen and progestin combinations, including the estradiol/norethindrone acetate component of MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders, including pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, especially in women at high risk for these events. In general, the risk is greatest among women over 35 years of age who smoke, and women with uncontrolled hypertension, dyslipidemia, vascular disease, or obesity.

In Phase 3 placebo-controlled clinical trials in 1066 women treated with MYFEMBREE for another indication, 2 thromboembolic events (DVT and PE) occurred in 1 woman with risk factors of obesity and a preceding knee injury and one case was reported for a woman treated with relugolix monotherapy in the postmarketing period.

5.2. Bone Loss

MYFEMBREE is contraindicated in women with known osteoporosis. Consider the benefits and risks of MYFEMBREE treatment in patients with a history of a low trauma fracture or risk factors for osteoporosis or bone loss, including taking medications that may decrease bone mineral density (BMD) (e.g., systemic or chronic inhaled corticosteroids, anticonvulsants, or chronic use of proton pump inhibitors).

Assessment of BMD by dual-energy X-ray absorptiometry (DXA) is recommended at baseline and periodically thereafter. Consider discontinuing MYFEMBREE if the risk associated with bone loss exceeds the potential benefit of treatment. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation for patients with inadequate dietary intake may be beneficial. MYFEMBREE may cause a decrease in BMD in some patients. BMD loss may be greater with increasing duration of use and may not be completely reversible after stopping treatment. The impact of BMD decreases on long-term bone health and future fracture risk in premenopausal women is unknown.

In Phase 3 clinical trials, women treated with MYFEMBREE for up to 52 weeks had a decline in lumbar spine BMD of 0.80%.

5.3. Hormone-Sensitive Malignancies

MYFEMBREE is contraindicated in women with current or a history of hormone-sensitive malignancies (e.g., breast cancer) and in women at increased risk for hormone-sensitive malignancies. Discontinue MYFEMBREE if a hormone-sensitive malignancy is diagnosed.

Surveillance measures in accordance with standard of care, such as breast examinations and mammography are recommended. The use of estrogen alone or estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

5.4. Depression, Mood Disorders, and Suicidal Ideation

Promptly evaluate patients with mood changes and depressive symptoms including shortly after initiating treatment, to determine whether the risks of continued therapy with MYFEMBREE outweigh the benefits. Patients with new or worsening depression, anxiety, or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing MYFEMBREE if such events occur.

In Phase 3 placebo-controlled clinical trials, as compared to placebo, a greater proportion of women treated with MYFEMBREE reported depression (including depression, mood swings, and depressed mood) (2.4% vs. 0.8%), irritability (2.4% vs. 0%), and anxiety (1.2% vs. 0.8%). Suicidal ideation occurred in women treated with MYFEMBREE in placebo-controlled clinical trials conducted for a different indication.

5.5. Hepatic Impairment and Transaminase Elevations

Contraindication in Patients with Hepatic Impairment

MYFEMBREE is contraindicated in patients with known hepatic impairment or disease. Steroid hormones may be poorly metabolized in patients with impaired liver function.

Transaminase Elevations

Instruct women to promptly seek medical attention for symptoms or signs that may reflect liver injury, such as jaundice or right upper abdominal pain. Acute liver test abnormalities may necessitate the discontinuation of MYFEMBREE use until the liver tests return to normal and MYFEMBREE causation has been excluded.

In Phase 3 placebo-controlled clinical trials, elevations [≥ 3 times the upper limit of the normal (ULN) reference range] in alanine aminotransferase (ALT) occurred in 0.4% (1/254) of women treated with MYFEMBREE compared with no elevations in placebo-treated women. Elevations ≥ 3 times ULN in aspartate aminotransferase (AST) occurred in 0.8% (2/254) of women treated with MYFEMBREE compared with 0.4% (1/256) of placebo-treated women. No pattern in time to onset of these liver transaminase elevations was identified.

5.6. Gallbladder Disease or History of Cholestatic Jaundice

Discontinue MYFEMBREE if signs or symptoms of gallbladder disease or jaundice occur. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, assess the risk-benefit of continuing therapy. Studies among estrogen users suggest a small increased relative risk of developing gallbladder disease.

5.7. Elevated Blood Pressure

MYFEMBREE is contraindicated in women with uncontrolled hypertension. For women with well-controlled hypertension, continue to monitor blood pressure and stop MYFEMBREE if blood pressure rises significantly.

In one of the two Phase 3 clinical trials (Study L1), more women experienced the adverse reaction of new or worsening hypertension with MYFEMBREE as compared to placebo (7.0% vs. 0.8%).

5.8. Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

Exclude pregnancy before initiating MYFEMBREE. Start MYFEMBREE as early as possible after the start of menses but no later than 7 days after menses has started. If MYFEMBREE is initiated later in the menstrual cycle, irregular and/or heavy bleeding may initially occur. Women who take MYFEMBREE may experience amenorrhea or a reduction in the amount, intensity, or duration of menstrual bleeding, which may delay the ability to recognize pregnancy. Perform pregnancy testing if pregnancy is suspected and discontinue MYFEMBREE if pregnancy is confirmed.

Advise women of reproductive potential to use effective non-hormonal contraception during treatment with MYFEMBREE and for one week after the final dose. Avoid concomitant use of hormonal contraceptives with MYFEMBREE. The use of estrogen-containing hormonal contraceptives can increase estrogen levels which may increase the risk of estrogen-associated adverse events and decrease the efficacy of MYFEMBREE.

5.9. Risk of Early Pregnancy Loss

MYFEMBREE is contraindicated for use in pregnancy. Based on findings from animal studies and its mechanism of action, MYFEMBREE can cause early pregnancy loss. However, in both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures about half and approximately 300 times exposures in women at the recommended human dose, respectively.

5.10. Uterine Fibroid Prolapse or Expulsion

Advise women with known or suspected submucosal uterine fibroids about the possibility of uterine fibroid prolapse or expulsion and instruct them to contact their physician if severe bleeding and/or cramping occurs while being treated with MYFEMBREE. In Phase 3 placebo-controlled clinical trials, uterine fibroid prolapse and uterine fibroid expulsion were reported in women treated with MYFEMBREE.

5.11. Alopecia

Consider discontinuing MYFEMBREE if hair loss becomes a concern.

In Phase 3 placebo-controlled clinical trials, more women experienced alopecia, hair loss, and hair thinning (3.5%) with MYFEMBREE, compared to placebo (0.8%). In 3 of the 11 affected women treated with MYFEMBREE across Phase 3 clinical trials, alopecia was reported as moderate. For one MYFEMBREE-treated woman in the extension trial, alopecia was a reason for discontinuing treatment.

No specific pattern of hair loss was described. The majority of affected women completed the study with reported hair loss ongoing. Whether the hair loss is reversible is unknown.

5.12. Effects on Carbohydrate and Lipid Metabolism

More frequent monitoring in MYFEMBREE-treated women with prediabetes and diabetes may be necessary. MYFEMBREE may decrease glucose tolerance and result in increased blood glucose concentrations.

Monitor lipid levels and consider discontinuing MYFEMBREE if hypercholesterolemia or hypertriglyceridemia worsens. In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations in triglycerides levels leading to pancreatitis. Use of MYFEMBREE is associated with increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C).

5.13. Effect on Other Laboratory Results

Patients with hypothyroidism and hypoadrenalism may require higher doses of thyroid hormone or cortisol replacement therapy.

The use of estrogen and progestin combinations may raise serum concentrations of binding proteins (e.g., thyroid-binding globulin, corticosteroid-binding globulin), which may reduce free thyroid or corticosteroid hormone levels.

The use of estrogen and progestin may also affect the levels of sex hormone-binding globulin, and coagulation factors.

5.14. Hypersensitivity Reactions

MYFEMBREE is contraindicated in women with a history of hypersensitivity reactions to relugolix or any component of MYFEMBREE. Immediately discontinue MYFEMBREE if a hypersensitivity reaction occurs.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Thromboembolic Disorders and Vascular Events
- Bone Loss
- Depression, Mood Disorders, and Suicidal Ideation
- Hepatic Impairment and Transaminase Elevation
- Elevated Blood Pressure
- Uterine Fibroid Prolapse or Expulsion.
- Alopecia
- Effects on Carbohydrate and Lipid Metabolism
- Hypersensitivity Reactions

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of MYFEMBREE was evaluated in two placebo-controlled clinical trials, Study L1 (LIBERTY 1) and Study L2 (LIBERTY 2), in women with heavy menstrual bleeding associated with uterine fibroids. In the Phase 3 studies, women received a once daily relugolix 40 mg tablet plus an over encapsulated tablet of E2 1 mg and NETA 0.5 mg (relugolix+E2/NETA), which is equivalent to 1 tablet of MYFEMBREE. Across the two studies, 254 women received MYFEMBREE once daily for 24 weeks. Additionally, 256 women received placebo for 24 weeks, and 258 women received relugolix 40 mg monotherapy once daily for 12 weeks followed by MYFEMBREE for 12 weeks. Of these, 476 women were treated with MYFEMBREE in a 28-week extension trial, Study L3 (LIBERTY Extension), for a total treatment duration of up to 12 months. Demographics were similar across the studies; approximately 43% were White, 51% were Black, and approximately 23% were of Hispanic or Latino ethnicity. The mean age at study entry was approximately 42 years (range 19 to 51 years).

Serious Adverse Reactions

Serious adverse reactions were reported in 3.1% of MYFEMBREE-treated women compared with 2.3% of placebo-treated women in Studies L1 and L2. In MYFEMBREE-treated women, serious adverse drug reactions included uterine myoma expulsion and menorrhagia experienced by one woman, uterine leiomyoma (prolapse), cholecystitis, and pelvic pain reported for one woman each.

Adverse Reactions Leading to Study Drug Discontinuation

In the two placebo-controlled clinical trials (Study L1 and Study L2), 3.9% of women treated with MYFEMBREE discontinued therapy due to adverse reactions, compared with 4.3% receiving placebo. The most common adverse reaction leading to discontinuation of MYFEMBREE was uterine bleeding (1.2%) with onset usually reported within the first 3 months of therapy.

Common Adverse Reactions

The most common adverse reactions reported in at least 3% of women treated with MYFEMBREE and at an incidence greater than placebo during double-blind placebo-controlled treatment are summarized in Table 1.

Table 1: Adverse Reactions Occurring in 3% or More of Women Treated with MYFEMBREE and at a Greater Incidence than Placebo in Studies L1 and L2

Adverse Reaction	MYFEMBREE (N = 254) %	Placebo (N = 256) %
Hot flush, hyperhidrosis, or night sweats	10.6	6.6
Abnormal uterine bleeding[1]	6.3	1.2
Alopecia	3.5	0.8
Libido decreased[2]	3.1	0.4

[1] Includes menorrhagia, metrorrhagia, vaginal haemorrhage, polymenorrhoea, and menstruation irregular.

[2] Includes libido decreased and loss of libido.

In one of the two Phase 3 clinical trials (Study L1), more women experienced the adverse reaction of new or worsening hypertension with MYFEMBREE as compared to placebo (7.0% vs 0.8%).

Less Common Adverse Reactions

Adverse reactions reported in at least 2% and less than 3% of women in the MYFEMBREE group and greater incidence than placebo included irritability, dyspepsia, and breast cyst. Other important adverse reactions reported in women treated with MYFEMBREE included one serious reaction each of uterine myoma expulsion (0.4%) and uterine leiomyoma (prolapse) (0.4%).

The adverse reactions most commonly reported in the extension trial, Study L3, were similar to those in the placebo-controlled trials.

Bone Loss

The effect of MYFEMBREE on BMD was assessed by dual-energy X-ray absorptiometry (DXA). The least squares mean percent change from baseline in lumbar spine BMD at Month 6 in Studies L1 and L2 is presented in Table 2.

Table 2: Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD in Women with Uterine Fibroids at Month 6 in Studies L1 and L2

	Studies L1 and L2 Treatment Month 6	
	Placebo	MYFEMBREE
Number of Subjects	256	254
Percent Change from Baseline (95% CI*)	0.18 (-0.21, 0.58)	-0.23 (-0.64, 0.18)
Treatment Difference, %	-0.42	

*Confidence Interval

In the open-label extension Study L3, continued bone loss was observed with 12 months of continuous treatment with MYFEMBREE. The least squares mean percent change from baseline in lumbar spine BMD at Month 6 and Month 12 for women treated with MYFEMBREE in Studies L1 or L2 and then continued on MYFEMBREE for an additional 28 weeks in Study L3 is presented in Table 3, below.

Table 3: Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD at Month 6 in Studies 1 and 2 and Month 12 in Study 3 in Women with Uterine Fibroids treated with MYFEMBREE

	Study L3 (N = 163)	
	Month 6*	Month 12
Percent Change from Baseline* (95% CI)**	-0.23 (-0.69, 0.24)	-0.80 (-1.36, -0.25)

*Baseline and Month 6 assessments include only those participants from Studies L1 and L2 who participated in Study L3.

**CI = confidence interval.

A separate concurrent prospective observational study enrolled 262 women with uterine fibroids who were age-matched to participants of Studies L1 and L2. These women did not receive treatment for uterine fibroids and underwent DXA scans at Month 6 and Month 12 to monitor for changes in BMD. Mean percent change from baseline (95% CI) in BMD at the lumbar spine at Month 6 and Month 12 was 0.00 (-0.32, 0.31) and -0.41 (-0.77, -0.05), respectively.

A decline in lumbar spine BMD of > 3% was observed in 23% (30/132) of women who had a DXA scan following 12 months of MYFEMBREE treatment in Study L3 and in 17.4% (37/213) of untreated women in the Observational Cohort. A decline of > 8% was seen in 1% (1/132) of women treated with MYFEMBREE who completed a DXA scan at Month 12 and in 0.9% (2/213) of untreated women in the Observational Cohort.

In Studies L1, L2, and L3, 0.6% (4/634) women treated with MYFEMBREE experienced low trauma fractures (defined as a fall from standing height or less). Two of these women were treated with relugolix monotherapy for 12 weeks prior to MYFEMBREE therapy.

Depression, Mood Disorders, and Suicidal Ideation

In the Phase 3, placebo-controlled trials (Studies L1 and L2), MYFEMBREE was associated with adverse mood changes. A greater proportion of women treated with MYFEMBREE compared to placebo reported depression (including depression, mood swings, and depressed mood) (2.4% vs. 0.8%), irritability (2.4% vs. 0%), and anxiety (1.2% vs. 0.8%).

Suicidal ideation was reported for women treated with MYFEMBREE in placebo-controlled clinical trials conducted for a different indication.

Resumption of Menstruation after Discontinuation

Post study menstrual status was available for 35 women in Study L1 and 30 women in Study L2 who were treated with MYFEMBREE and prematurely discontinued the study or did not continue into the long-term extension study. For these women, 100% (35/35) in Study L1 and 93.3% (28/30) in Study L2 resumed menses. The mean time from last dose to occurrence of menses was 36 days in Study L1 and 30.7 days in Study L2. Mean time to occurrence of menses was longer for women who achieved amenorrhea (40.6 days and 41.1 days in Studies L1 and L2, respectively) compared with women without amenorrhea (33.0 days and 26.6 days in Studies L1 and L2, respectively) in the last 35 days of treatment. After 12 months of treatment with MYFEMBREE (Study L1 or Study L2, then Study L3) 93.8% (61/65) of women resumed menses. Mean time from last dose of drug to occurrence of menses was 40.5 days. Mean time to occurrence of menses was longer in women who reported amenorrhea over the last 35 days of treatment compared with women without amenorrhea over the last 35 days of treatment (45.6 days vs. 32.6 days, respectively).

Women who did not have a return to menses included those who had surgery, used alternative medications associated with amenorrhea, entered menopause, and unknown cause.

Increases in Lipids

Lipid levels were assessed at baseline and Week 24/End of Treatment in Study L1 and Study L2. Of the women with normal total cholesterol (< 200 mg/dL) at baseline, increases to > 200-240 mg/dL were seen in 13.7% of women treated with MYFEMBREE as compared to 7.7% of women treated with placebo, and increases to > 240 mg/dL were seen in 1.7% and 0.6% of MYFEMBREE and placebo-treated women respectively. For women with LDL < 130 mg/dL at baseline, increases to 130 to < 160 mg/dL, 160 to < 190 mg/dL and ≥ 190 mg/dL were seen in 9.3%, 1.5%, and 0.5% of women treated with MYFEMBREE as compared to 6.5%, 0.5% and 0% of women treated with placebo, respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of relugolix monotherapy outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: anaphylactoid reaction

Skin and subcutaneous tissue disorders: drug eruption

Neoplasms, benign, malignant and unspecified: uterine leiomyoma degeneration

Respiratory, thoracic and mediastinal disorders: pulmonary embolism

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on MYFEMBREE

P-gp Inhibitors

Co-administration of MYFEMBREE with P-gp inhibitors increases the AUC and maximum concentration (C_{max}) of relugolix and may increase the risk of adverse reactions associated with MYFEMBREE. Avoid use of MYFEMBREE with oral P-gp inhibitors.

If use is unavoidable, take MYFEMBREE first, separate dosing by at least 6 hours, and monitor patients for adverse reactions.

Combined P-gp and Strong CYP3A Inducers

Use of MYFEMBREE with combined P-gp and strong CYP3A inducers decreases the AUC and C_{max} of relugolix, estradiol, and/or norethindrone and may decrease the therapeutic effects of MYFEMBREE. Avoid use of MYFEMBREE with combined P-gp and strong CYP3A inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to MYFEMBREE during pregnancy. Pregnant females exposed to MYFEMBREE and healthcare providers are encouraged to call the MYFEMBREE Pregnancy Exposure Registry at 1-(855) 428-0707.

Risk Summary

MYFEMBREE is contraindicated in pregnancy. Based on findings from animal studies and its mechanism of action, MYFEMBREE may cause early pregnancy loss. Discontinue MYFEMBREE if pregnancy occurs during treatment.

The limited human data with the use of MYFEMBREE in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *[see Data]*.

In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures about half those at the maximum recommended human dose (MRHD) of 40 mg. In both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures about half and approximately 300 times exposures in women at the MRHD, respectively *[see Data]*.

Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to estrogens and progestins before conception or during early pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. There are insufficient data to conclude whether the presence of uterine fibroids reduces the likelihood of achieving pregnancy or increases the risk of adverse pregnancy outcomes. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum recommended human dose (MRHD) of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown.

In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A no observed adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold lower than that in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day.

Commentary

Remove REMS requirements for mifepristone

BY LINDSAY DALE, MD, PATRICIA BLACK, MD, AND EVE ESPEY, MD, MPH

Since evidence shows that medication abortion is extremely safe, why is mifepristone so restricted? And should it be? Mifepristone, used with misoprostol for medication abortion for pregnancies up to 10 weeks' gestation, is highly regulated in the United States. As of 2000, when the Food and Drug Administration approved Mifeprex (brand name of mifepristone), its access was restricted under the FDA Risk Evaluation and Mitigation Strategy.

REMS is an FDA drug safety program, where medications with serious safety concerns are subject to restrictions intended to ensure that the benefits of the medication outweigh its risks. For example, the drug vigabatrin, with a side effect of permanent vision loss, is used to treat epilepsy. The REMS for vigabatrin requires counseling on the risk of vision loss and periodic vision monitoring.

The FDA claims that rare side effects of mifepristone – heavy vaginal bleeding, severe infection, and incomplete abortion – are risks that warrant the REMS, despite the known safety of medication abortion, with less than 1% of patients requiring emergency intervention for heavy vaginal bleeding or infection. The mifepristone REMS requires that the drug is dispensed in a hospital, clinic, or medical office by a certified health care provider and not in a pharmacy as with most prescribed medications, and that patients read and sign the patient agreement form in the presence of the dispensing physician and may not receive counseling via telemedicine.

Since FDA approval, much evidence shows that the REMS is unnecessary and creates a major obstacle to access. Many clinicians cannot meet the REMS requirements; many women must travel great distances to obtain mifepristone or delay their abortion past the acceptable gestational age for medication abortion.

In spring 2020, at the onset of the COVID-19 pandemic, the Centers for Disease Control and Prevention issued general guidance recommending use of telemedicine to limit in-person medical visits to reduce risk of exposure to the SARS-CoV-2 virus, and to ensure access to medication abortion, the ACLU filed a federal lawsuit against the FDA to suspend the requirement for in-person mifepristone dispensing. In July 2020, a Maryland District Judge granted a preliminary injunction, preventing the FDA from enforcing the in-person dispensing requirement for the duration of the declared public health emergency, allowing telemedicine medication abortion using mail or delivery service for administration of mifepristone. All other REMS requirements remained in effect.

In January 2021, the FDA appealed, seeking to reinstate the REMS. The U.S. Supreme Court ruled to reimpose the REMS. Following this decision, a large coalition of reproductive rights groups petitioned the Biden administration to suspend the mifepristone in-person requirement during the pandemic public health emergency. In April 2021, the FDA announced it would use discretion and cease to enforce the in-person dispensing requirement throughout the remainder of the public health emergency.

Dr. Dale is an obstetrics and gynecology specialist in Albuquerque; Dr. Black is an obstetrics and gynecology specialist in Albuquerque, who currently practices at the University of New Mexico Children's Psychiatric Center; and Dr. Espey is professor and chair of the department of ob.gyn. and family planning, and fellowship director at the University of New Mexico, Albuquerque.

We applaud the FDA for taking the advice of numerous scientific and advocacy groups to expand access to mifepristone by at least temporarily nullifying unnecessary and burdensome restrictions that disproportionately affect people of color; young people; and people who live in rural areas, have lower incomes, and are undocumented. We join the voices of numerous colleagues and organizations, including the American College of Obstetricians and Gynecologists, in calling for a permanent end to the mifepristone REMS. ■

Safety, efficacy of telehealth abortions match in-person care

BY JALEESA BAULKMAN
FROM JAMA NETWORK OPEN

Telehealth abortion may be just as safe and effective as in-person care, according to a small study published online in JAMA Network Open (2021 Aug 24. doi: 10.1001/jamanetworkopen.2021.22320).

Of the 110 women from whom researchers collected remote abortion outcome data, 95% had a complete abortion without additional medical interventions, such as aspiration or surgery, and none experienced adverse events. Researchers said this efficacy rate is similar to in-person visits.

"There was no reason to expect that the medications prescribed [via telemedicine] and delivered through the mail would have different outcomes from when a patient traveled to a clinic," study author Ushma D. Upadhyay, PhD, MPH, associate professor in the department of obstetrics, gynecology, and reproductive sciences at the University of California, San Francisco, said in an interview.

Medication abortion, which usually involves taking mifepristone (Mifeprex) followed by misoprostol (Cytotec) during the first 10 weeks of pregnancy, has been available in the United States since 2000. The Food and Drug Administration's Risk Evaluation and Mitigation Strategy requires that mifepristone be dispensed in a medical office, clinic, or hospital, prohibiting dispensing from pharmacies in an effort to reduce potential risk for complications.

In April 2021, the FDA lifted the in-person dispensing requirement for mifepristone for the duration of the COVID-19 pandemic. However, Dr. Upadhyay hopes the findings of her current study will make this suspension permanent.

> "There was no reason to expect that the medications prescribed [via telemedicine] and delivered through the mail would have different outcomes **from when a patient traveled to a clinic.**"

For the study, Dr. Upadhyay and colleagues examined the safety and efficacy of fully remote, medication abortion care. Eligibility for the medication was assessed using an online form that relies on patient history, or patients recalling their last period, to assess pregnancy duration and screen for ectopic pregnancy risks. Nurse practitioners reviewed the form and referred patients with unknown last menstrual period date or ectopic pregnancy risk factors for ultrasonography. A mail-order pharmacy delivered medications to eligible patients. The protocol involved three follow-up contacts: confirmation of medication administration, a 3-day assessment of symptoms, and a home pregnancy test after 4 weeks. Follow-up interactions were conducted by text, secure messaging, or telephone.

Researchers found that, in addition to the 95% of the patients having a complete abortion without intervention, 5% (five) of patients required addition medical care to complete the abortion. Two of those patients were treated in EDs.

Gillian Burkhardt, MD, who was not involved in the study, said Dr. Upadhyay's study proves what has been known all along, that medication is super safe and that women "can help to determine their own eligibility as well as in conjunction with the provider."

"I hope that this will be one more study that the FDA can use when thinking about changing the risk evaluation administration strategy so that it's removing the requirement that a person be in the dispensing medical office," Dr. Burkhardt, assistant professor of family planning in the department of obstetrics & gynecology at the University of New Mexico Hospital, Albuquerque, said in an interview. "I hope it also makes providers feel more comfortable as well, because I think there's some hesitancy among providers to provide abortion without doing an ultrasound or without seeing the patient typically in front of them."

This isn't the first study to suggest the safety of telemedicine abortion. A 2019 study published in Obstetrics & Gynecology (doi: 10.1097/AOG.0000000000003357), which analyzed records from nearly 6,000 patients receiving medication abortion either through telemedicine or in person at 26 Planned Parenthood health centers in four states found that ongoing pregnancy and aspiration procedures were less common among telemedicine patients. Another 2017 study published in BMJ (doi: 10.1136/bmj.j2011) found that women who used an online consultation service and self-sourced medical abortion during a 3-year period were able to successfully end their pregnancies with few adverse events.

Dr. Upadhyay said one limitation of the current study is its sample size, so more studies should be conducted to prove telemedicine abortion's safety.

"I think that we need continued research on this model of care just so we have more multiple studies that contribute to the evidence that can convince providers as well that they don't need a lot of tests and that they can mail," Dr. Upadhyay said.

Dr. Upadhyay and Dr. Burkhardt reported no conflicts of interests.

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Socioeconomic disparities persist in hysterectomy access

BY HEIDI SPLETE
FROM OBSTETRICS & GYNECOLOGY

BLACK WOMEN UNDERGOING hysterectomies were significantly more likely to be treated by low-volume surgeons than high-volume surgeons, and to experience perioperative complications as a result, based on data from more than 300,000 patients.

"Outcomes for hysterectomy, for both benign and malignant disease, are improved when the procedure is performed at high-volume hospitals and by high-volume surgeons," Anne Knisely, MD, of Columbia University, New York, and colleagues wrote.

Historically, Black patients have been less likely to be referred to high-volume hospitals, the researchers noted. Recent efforts to regionalize surgical procedures to high-volume hospitals aim to reduce disparities and improve care for all patients, but the data on disparities in care within high-volume hospitals are limited, they said.

In a study published in Obstetrics & Gynecology (2021 Jul 8. doi: 10.1097/AOG.0000000000004456), the researchers identified 300,586 women who underwent hysterectomy in New York state between 2000 and 2014. The researchers divided surgeons at these hospitals into volume groups based on average annual hysterectomy volume.

The women were treated by 5,505 surgeons at 59 hospitals. Overall, Black women comprised significantly more of the patients treated by low-volume surgeons compared with high-volume surgeons (19.4% vs. 14.3%; adjusted odds ratio, 1.26), and more women treated by low-volume surgeons had Medicare insurance compared with those treated by high-volume surgeons (20.6% vs. 14.5%; aOR, 1.22).

A majority of the patients (262,005 patients) were treated by a total of 1,377 high-volume surgeons, while 2,105 low-volume surgeons treated 2,900 patients. Abdominal hysterectomies accounted for 57.5% of the procedures, followed by laparoscopic (23.9%), vaginal (13.2%), and robotic assisted (5.3%). Approximately two-thirds (64.4%) of the patients were aged 40-59 years; 63.7% were White, 15.1% were Black, and 8.5% were Hispanic.

The overall complication rate was significantly higher in patients treated by low-volume surgeons, compared with high-volume surgeons (31.0% vs. 10.3%), including intraoperative complications, surgical-site complications, medical complications, and transfusions. The perioperative mortality rate also was significantly higher for patients of low-volume surgeons compared with high-volume surgeons (2.2% vs. 0.2%).

Low-volume surgeons were more likely to perform urgent or emergent procedures, compared with high-volume surgeons (26.1% vs 6.4%), and to perform abdominal hysterectomy versus minimally invasive hysterectomy compared with high-volume surgeons (77.8% vs. 54.7%), the researchers added.

The study findings were limited by several factors, including the observational design and possible undercoding of outcomes, inclusion only of New York state patients, lack of data on clinical characteristics such as surgical history and complexity, lack of data on surgeon characteristics, and

Continued on following page ▸

One center's experience delivering monochorionic twins

BY JAKE REMALY
FROM OBSTETRICS & GYNECOLOGY

At a maternal–fetal medicine practice in New York, monochorionic pregnancies were not at increased risk for cesarean delivery, compared with dichorionic pregnancies, a retrospective study shows.

Between 2005 and 2021, mode of delivery of diamniotic twins at this practice did not significantly differ by chorionicity, researchers affiliated with Maternal Fetal Medicine Associates and the department of obstetrics, gynecology, and reproductive science at Icahn School of Medicine at Mount Sinai, New York, reported in Obstetrics & Gynecology (2021 Aug 5. doi: 10.1097/AOG.0000000000004483).


Dr. Krishna

The study supports a recommendation from the American College of Obstetricians and Gynecologists that vaginal delivery "is a reasonable option in well selected diamniotic twin pregnancies, irrespective of chorionicity, and should be considered, provided that an experienced obstetrician is available," said Iris Krishna, MD, assistant professor of maternal-fetal medicine at Emory University, Atlanta.

Of 1,121 diamniotic twin pregnancies included in the analysis, 202 (18%) were monochorionic. The cesarean delivery rate was not significantly different between groups: 61% for monochorionic and 63% for dichorionic pregnancies.

Among women with planned vaginal delivery (101 monochorionic pregnancies and 422 dichorionic pregnancies), the cesarean delivery rate likewise did not significantly differ by chorionicity. Twenty-two percent of the monochorionic pregnancies and 21% of the dichorionic pregnancies in this subgroup had a cesarean delivery.

Among patients with a vaginal delivery of twin A, chorionicity was not associated with mode of delivery for twin B. Combined vaginal-cesarean deliveries occurred less than 1% of the time, and breech extraction of twin B occurred approximately 75% of the time, regardless of chorionicity.

The researchers also compared neonatal outcomes for monochorionic-diamniotic twin pregnancies at or after 34 weeks of gestation, based on the intended mode of delivery (95 women with planned vaginal delivery and 68 with planned cesarean delivery). Neonatal outcomes generally were similar, although the incidence of mechanical ventilation was less common in cases with planned vaginal delivery (7% vs. 21%).

"Our data affirm that an attempt at a vaginal birth for twin pregnancies, without contraindications to vaginal delivery and regardless of chorionicity, is reasonable and achievable," wrote study author Henry N. Lesser, MD, with the department of obstetrics and gynecology at Sinai Hospital in Baltimore, and colleagues.

The patients with planned cesarean delivery had a contraindication to vaginal delivery or otherwise chose to have a cesarean delivery. The researchers excluded from their analysis pregnancies with intrauterine fetal demise of either twin before labor or planned cesarean delivery.

The study's reliance on data from a single practice decreases its external validity, the researchers noted. Induction of labor at this center typically occurs at 37 weeks' gestation for monochorionic twins and at 38 weeks for dichorionic twins, and "senior personnel experienced in intrauterine twin manipulation are always present at delivery," the study authors said.

The study describes "the experience of a single site with skilled obstetricians following a standardized approach to management of diamniotic twin deliveries," Dr. Krishna said. "Findings may not be generalizable to many U.S. practices as obstetrics and gynecology residents often lack training in breech extraction or internal podalic version of the second twin. This underscores the importance of a concerted effort by skilled senior physicians to train junior physicians in vaginal delivery of the second twin to improve overall outcomes amongst women with diamniotic twin gestations."

Michael F. Greene, MD, professor emeritus of obstetrics, gynecology, and reproductive biology at Massachusetts General Hospital, Boston, agreed that the findings are not generalizable to the national population. Approximately 10% of the patients in the study had prepregnancy obesity, whereas doctors practicing in other areas likely encounter higher rates, Dr. Greene said in an interview.

Monochorionic pregnancies entail a risk of twin-twin transfusion syndrome and other complications, including an increased likelihood of birth defects.

Dr. Greene is an associate editor with the New England Journal of Medicine, which in 2013 published results from the Twin Birth Study, an international trial where women with dichorionic or monochorionic twins were randomly assigned to planned vaginal delivery or planned cesarean delivery (2013 Oct 3. doi: 10.1056/NEJMoa1214939). Outcomes did not significantly differ between groups. In the trial, the rate of cesarean delivery in the group with planned vaginal delivery was 43.8%. Since then, the obstetrics and gynecology community "has been focusing in recent years on trying to avoid the first cesarean section" when it is safe to do so, Dr. Greene said.

And patients should know that it is an option, Dr. Krishna added.

A study coauthor disclosed serving on the speakers bureau for Natera and Hologic. Other authors, Dr. Krishna, and Dr. Greene disclosed no conflicts of interest.

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Continued from previous page

changing practice patterns over time, the researchers noted.

However, "this study demonstrates increased perioperative morbidity and mortality for patients who underwent hysterectomy by low-volume surgeons, in comparison with high-volume surgeons, at high-volume hospitals," and that Black patients were more likely to be treated by low-volume surgeons, they said. "Although centralization of complex surgical care to higher-volume hospitals may have benefit, there are additional surgeon-level factors that must be considered to address disparities in access to high-quality care for patients undergoing hysterectomy."

Explore range of issues to improve access

"It is always beneficial to review morbidity and mortality statistics," Constance J. Bohon, MD, a gynecologist in private practice in Washington, D.C., said in an interview. "With a heightened awareness of equity and equality, now is a good time to review the data with that focus in mind. Hospital committees review the data on a regular basis, but they may not have looked closely at demographics in the past.


Dr. Bohon

"It was always my understanding that for many procedures, including surgery, volume impacts outcome, so the finding that low-volume surgeons had worse outcomes than high-volume surgeons was not particularly surprising," said Dr. Bohon. However, the question of how hospitals might address disparities in access to high-volume surgeons "is a difficult question, because there are a variety of issues that may not be caused by disparities," she added. "It may be that the high-volume surgeons do not take Medicare. It may be that some of the emergent/urgent surgeries come from patients seen in the ED and the high-volume surgeons may not take call or see new patients in the ED. There may be a difference in the preop testing done that may be more extensive with the high-volume surgeons as compared with the low-volume surgeons. It may be that it is easier to get an appointment with a low-volume rather than a high-volume surgeon.

"Additional research is needed to determine whether there is an algorithm that can be created to determine risk for morbidity or mortality based on factors such as the number of years in practice, the number of hysterectomies per year, and the age of the physician," Dr. Bohon explained. "The patient data could include preexisting risk factors such as weight, preexisting medical conditions, prior surgeries, and current medications, along with demographics. It would be interesting to determine whether low-risk patients have similar outcomes with low- as compared with high-volume surgeons while high-risk patients do not. The demographics could then be evaluated to determine if disparities exist for both low- and high-risk patients."

The study received no outside funding. One coauthor disclosed serving as a consultant for Clovis Oncology, receiving research funding from Merck, and receiving royalties from UpToDate. Lead author Dr. Knisely had no financial conflicts to disclose. Dr. Bohon had no financial conflicts to disclose, but serves on the Ob.Gyn. News editorial advisory board.

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Toward a clearer risk model for postpartum psychosis

BY LEE S. COHEN, MD

Postpartum depression, in many respects, has become a household term. Over the last decade, there has been increasing awareness of the importance of screening for postpartum depression, with increased systematic screening across clinical settings where care is delivered to women during pregnancy and the postpartum period. There have also been greater efforts to identify women who are suffering postpartum depression and to support them with appropriate clinical interventions, whether through psychotherapy and/or pharmacologic therapy. Clinical interventions are supplemented by the increasing awareness of the value of community-based support groups for women who are suffering from postpartum mood and anxiety disorders.

Despite the growing, appropriate focus on recognition and acute treatment of postpartum depression as well as assessing clinical outcomes for those who suffer from postpartum mood and anxiety disorders, less attention has been given to postpartum psychosis, the most severe form of postpartum depression. It is indeed, the least common postpartum psychiatric syndrome (1 in 1,000 births) and comes to public attention when there has been a tragedy during the acute postpartum period such as maternal suicide or infanticide. In this sense, postpartum psychosis is ironically an underappreciated clinical entity across America given its severity, the effect it has on longer-term psychiatric morbidity, and its effect on children and families.

Our group at the Center for Women's Mental Health has been interested in postpartum psychosis for years and started the Postpartum Psychosis Project in an effort to better understand the phenomenology, course, treatment, outcome, and genomic underpinnings of postpartum psychosis. Risk factors that are well established for postpartum psychosis have been described and overwhelmingly include patients with bipolar disorder. The risk for recurrent postpartum psychosis in women who have had a previous episode is as great as 75%-90% in the absence of prophylactic intervention. With that said, we are extremely interested in understanding the etiology of postpartum psychosis. Various studies over the last 5 years have looked at a whole host of psychosocial as well as neurobiologic variables that may contribute to risk for postpartum psychosis, including dysregulation of the stress axis, heightened inflammation as well as a history of child adversity and heightened experience of stress during the perinatal period.

There have also been anecdotal reports during Virtual Rounds at the Center for Women's Mental Health of higher recent rates of postpartum psychosis manifesting during the postpartum period. This is a clinical observation and has not been systematically studied. However, one can wonder whether the experience of the pandemic has constituted a stressor for at-risk women, tipping the scales toward women becoming ill, or whether clinicians are seeing this finding more because of our ability to observe it more within the context of the pandemic.

Precise quantification of risk for postpartum psychosis is complicated; as noted, women with bipolar disorder have a predictably high risk for getting ill during the postpartum period and many go on to have clinical courses consistent with recurrent bipolar disorder. However, there are other women who have circumscribed episodes of psychotic illness in the postpartum period who recover and are totally well without any evidence of psychiatric disorder until they have another child, at which time the risk for recurrence of postpartum psychosis is very high. Interest in developing a model of risk that could reliably predict an illness as serious as postpartum psychosis is on the minds of researchers around the world.

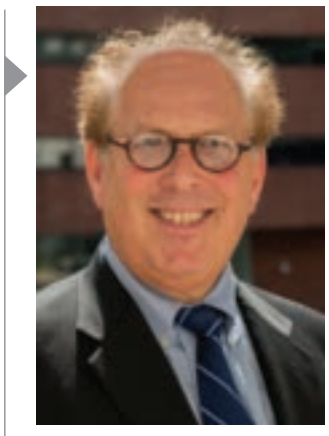
> "The data suggesting dysregulation of the stress axis as a predictor variable for risk in women vulnerable to postpartum psychosis **opens an array of opportunities that are nonpharmacologic**, such as mindfulness-based cognitive therapy or other interventions that help to modulate the stress axis."

One recent study that highlights the multiple factors involved in risk of postpartum psychosis involved a prospective longitudinal study of a group of women who were followed across the peripartum period from the third trimester until 4 weeks post partum. In this group, 51 women were at increased risk for postpartum psychosis based on their diagnosis of bipolar disorder, schizoaffective disorder, or a previous episode of postpartum psychosis. These women were matched with a control group with no past or current diagnosis of psychiatric disorder or family history of postpartum psychosis. The findings suggested that women at risk for postpartum psychosis who experienced a psychiatric relapse during the first 4 weeks post partum relative to women at risk who remained well had histories of severe childhood adversity as well as biomarkers consistent with a dysregulated stress axis (a statistically higher daily cortisol level). This is consistent with other data that have implicated the complex role between psychosocial variables as well as neurobiologic variables, such as a dysregulation in the hypothalamic-pituitary-adrenal axis and other studies that suggest that dysregulated inflammatory status may also drive risk for postpartum psychosis (Hazelgrove K et al. Psychoneuroendocrinology. 2021 Jun. doi: 10.1016/j.psyneuen.2021.105218).

At the end of the day, post partum psychosis is a psychiatric and obstetrical emergency. In our center, it is rare for women not to be hospitalized with this condition to ensure the safety of the mother as well as her newborn, and to also get her recompensated and functioning as quickly and as significantly as possible. However, an interesting extrapolation of the findings noted by Hazelgrove and colleagues is that it raises the question of what effective treatments might be used to mitigate risk for those at greatest risk for postpartum psychosis. For example, are there other treatments over and above the few effective ones that have been studied as prophylactic pharmacologic interventions that might mitigate risk for recurrence of an illness as serious as postpartum psychosis?

The data suggesting dysregulation of the stress axis as a predictor variable for risk in women vulnerable to postpartum psychosis opens an array of opportunities that are nonpharmacologic, such as mindfulness-based cognitive therapy or other interventions that help to modulate the stress axis. This is a terrific opportunity to have pharmacologic intervention meet nonpharmacologic intervention to potentially mitigate risk for postpartum psychosis with its attendant serious sequelae.

In our own work, where we are evaluating genomic data in an extremely well-characterized group of women with known histories of postpartum psychosis, we are interested to see if we can enhance understanding of the model of risk for postpartum psychosis by factoring in genomic underpinning, history of diagnosis, and psychosocial variables to optimally craft interventions for this population of at-risk women. This brings us one step closer to the future in women's mental health, to the practice of "precision reproductive psychiatry," matching interventions to specific presentations across perinatal populations. ■



Dr. Cohen is the director of the Ammon-Pinizzotto Center for Women's Mental Health at Massachusetts General Hospital in Boston, which provides information resources and conducts clinical care and research in reproductive mental health. He has been a consultant to manufacturers of psychiatric medications. Email Dr. Cohen at obnews@mdedge.com.

> "Interest in developing **a model of risk that could reliably predict an illness as serious as postpartum psychosis** is on the minds of researchers around the world."

PREGNANCY LOSS "Why should you be afraid of building your family?"

continued from page 1

use of IVF [in vitro fertilization], and the age at which we have children. These are not just anecdotal stories," she said.

For the study, a self-administered questionnaire was distributed electronically. Answers were collected from November 2020 to January 2021 through multiple U.S. surgical societies and social media among attending and resident surgeons with children. The control group for the study comprised 158 male surgeons who answered questions regarding their partners' pregnancies.

Female surgeons had fewer children compared with male surgeons and their female partners (mean [standard deviation],1.8 [0.8], versus 2.3 [1.1]; $P < .001$) and were more likely to delay having children because of surgical training: 450 of 692 (65.0%) versus 69 of 158 (43.7%) ($P < .001$).

In addition, Dr. Rangel and colleagues found that 57% of female surgeons worked more than 60 hours a week during pregnancy and that 37% took more than six overnight calls.

The data show that female surgeons who operated 12 or more hours per week during the last trimester of pregnancy were at higher risk compared with those who operated fewer hours (odds ratio, 1.57; 95% confidence interval, 1.08-2.26).

"Pregnant surgeons should not be operating more than 12 hours a week when they are in the third trimester," Dr. Rangel said.

"That is a modifiable risk factor," she told this news organization. "It's a very brief period of support – a couple of months of support for a woman who may do 25-30 more years of serving the public with surgical skills."

She said that training programs should be organized so as to have colleagues cover operating room shifts to reduce the operating hours for pregnant colleagues. In addition, advanced practice health care professionals should be paid to take up the paperwork and perform non-OR care to reduce the stigma associated with pregnant trainees overburdening other surgical trainees.

'It's too big' an ask

Obstetrician-gynecologist Maryam Siddiqui, MD, said in an interview that she was particularly struck by the number of female surgeons who experience involuntary childlessness.

"That's a big ask for people who want childbearing to be a part of the fulfillment of their life. It's too big," said Dr. Siddiqui, a gynecologic surgeon at UChicago Medicine.

She said the amount of detail in the article and the large number of participants were persuasive factors that can support establishing a more humane system than one in which one person at a time has to ask for change.

Pointing to the finding that three-fourths of the women in the study who had miscarriages didn't take time off, she said, "That's not really humane. But they're afraid to ask or they don't want to reveal they're trying [to get pregnant]. Why should you be afraid of building your family?"

The authors also found other adverse outcomes. Female surgeons were more likely to have musculoskeletal disorders compared with female nonsurgeon partners (36.9% versus 18.4%; $P < .001$), and they were more likely to undergo nonelective cesarean delivery (25.5% versus 15.3%; $P = .01$) and to experience postpartum depression (11.1% versus 5.7%; $P = .04$).

Dr. Siddiqui said the conditions that surgeons encounter on their return to work after childbirth are "a perfect storm" for postpartum depression among women who are not accustomed to being reliant on others.

Women often feel coerced into returning to work before they are physically or emotionally ready, then toggle back and forth from night shift to day shift, losing sleep, she said. "We can do better."

One of the solutions, she said, is to provide better work coverage for the surgeon while she is pregnant and when she returns to work. That includes properly compensating the person covering for the surgeon by giving that person extra pay or additional time off.

"You have to value both people," she said. "If both people are valued, there's still collegiality."

She acknowledged that that kind of compensation may be more readily available at large academic centers.

At UChicago, she said, they are creative with scheduling in training. For women at the height of pregnancy, rotations are less intensive, and trauma rotations are avoided.

Dr. Siddiqui said one of the most important aspects of the article is the authors' list of two dozen ways, both big and small, to improve conditions.

Adopting such changes will become increasingly important for hiring and retaining female surgeons. "You want to work someplace where you're respected as a whole person," she said.

fotostorm/Getty Images

> "Pregnant surgeons should not be operating **more than 12 hours a week** when they are in the third trimester."

Sarah Blair, MD, a surgical oncologist at University of California, San Diego, stated that the number of miscarriages in particular provides disturbing proof of a problem women in surgery frequently discuss.

For nearly a decade, she led a women-in-surgery committee at UCSD in which they discussed such issues regarding pregnancy and medicine.

She said she hopes these data can help push for change in flexibility in residency so that women can graduate on time and have the families they want.

"There's a movement away from time-based training to competency-based training, so maybe that will help women," she said.

'We will have to figure this out'

"We will have to figure this out, because more than half of the people in medical school are women, and there are a lot more women in surgery than when I trained more than 20 years ago. It's not a problem that's going away," she said.

One sign of improvement happened recently, Dr. Rangel said.

As previously reported, according to the American Board of Medical Specialties, as of July 1, 2021, residents and fellows are allowed a minimum 6 weeks away for medical leave or caregiving once during training, without having to use vacation time or sick leave and without having to extend their training.

"That's huge," she said. "But we still have a long way to go, because the residency programs still don't have to have policy that abides that. It merely says you can take 6 weeks off and take your boards. It doesn't say that the residency program has to allow you to take 6 weeks off."

The authors noted that the United States and Papua New Guinea are the only countries in the world without federally mandated paid parental leave.

"Most U.S. female surgeons rely on their employer for this benefit, but only half of top-ranked medical schools offer paid leave, and 33%-65% of U.S. surgical training programs lack clear maternity leave policies," she said.

Funding for the study was provided by the department of surgery at Brigham and Women's Hospital. The study authors, Dr. Blair, and Dr. Siddiqui have disclosed no relevant financial relationships.

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*Primary endpoint was defined as ≥50% bleeding volume reduction from baseline to Final Month and <80 mL bleeding volume at Final Month. Final Month is defined as the last 28 days before and including the last treatment visit date or the last dose date. This can occur anytime from Month 1 to 6 in the pivotal studies.[1]

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Thromboembolic Disorders and Vascular Events

- ORIAHNN is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events. Components of ORIAHNN increase the risk of thrombotic or thromboembolic disorders, including pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, especially in women at high risk for these events. In general, the risk is greatest among women over 35 years of age who smoke, and women with uncontrolled hypertension, dyslipidemia, vascular disease, or obesity.
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- ORIAHNN is contraindicated in women with current or a history of breast cancer and in women at increased risk for hormonally sensitive malignancies, such as those with mutations in BRCA genes.
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- Depression, depressed mood, and/or tearfulness were reported at a higher incidence in women taking ORIAHNN (3%) compared with placebo (1%) in the Phase 3 clinical trials. Suicidal ideation and behavior, including a completed suicide, occurred in women treated with lower doses of elagolix in clinical trials conducted for a different indication.
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- Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORIAHNN if such events occur.

Hepatic Impairment and Transaminase Elevations

- ORIAHNN is contraindicated in women with known hepatic impairment or disease.
- Transaminase elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred with ORIAHNN in Phase 3 clinical trials. No pattern in time to onset of these liver transaminase elevations was identified. Transaminase levels returned to baseline within 4 months after peak values in these patients.
- Instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice.

Elevated Blood Pressure

- ORIAHNN is contraindicated in women with uncontrolled hypertension. Maximum mean increases in systolic blood pressure occurred at Month 5, and a mean maximum increase in diastolic blood pressure occurred at Month 4 in ORIAHNN-treated women, as compared to placebo-treated women.
- For women with well-controlled hypertension, continue to monitor blood pressure and stop ORIAHNN if blood pressure rises significantly. Monitor blood pressure in normotensive women treated with ORIAHNN.

Gallbladder Disease or History of Cholestatic Jaundice

- Studies among estrogen users suggest a small increased relative risk of developing gallbladder disease. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, assess the risk-benefit of continuing therapy. Discontinue ORIAHNN if jaundice occurs.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

- ORIAHNN may delay the ability to recognize the occurrence of a pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding. Perform pregnancy testing if pregnancy is suspected and discontinue ORIAHNN if pregnancy is confirmed.
- The effect of hormonal contraceptives on the efficacy of ORIAHNN is unknown. Advise women to use non-hormonal contraception during treatment and for 1 week after discontinuing ORIAHNN.

Effects on Carbohydrate and Lipid Metabolism

- ORIAHNN may decrease glucose tolerance and result in increased glucose levels. More frequent monitoring in ORIAHNN-treated women with prediabetes and diabetes may be needed.
- In women with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Use of elagolix is associated with increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum triglycerides. Monitor lipid levels and consider discontinuing ORIAHNN if hypercholesterolemia or hypertriglyceridemia worsens.

Alopecia

- In Phase 3 clinical trials, more women experienced alopecia, hair loss, and hair thinning with ORIAHNN (3.5%) compared to placebo (1.0%). In almost one-third of affected ORIAHNN-treated women, alopecia was the reason for discontinuing treatment. No specific pattern was described. In the majority of these women, hair loss was continuing when ORIAHNN was stopped. Whether the hair loss is reversible is unknown. Consider discontinuing ORIAHNN if hair loss becomes a concern.

Effect on Other Laboratory Results

- The use of estrogen and progestin combinations may raise serum concentrations of binding proteins (e.g., thyroid-binding globulin, corticosteroid-binding globulin), which may reduce the free thyroid or corticosteroid hormone levels. Patients with hypothyroidism and hypoadrenalism may require higher doses of thyroid hormone or cortisol replacement therapy, respectively.
- The use of estrogen and progestin may also affect the levels of sex hormone-binding globulin, coagulation factors, lipids, and glucose.

RISK OF ALLERGIC REACTIONS DUE TO THE INACTIVE INGREDIENT (FD&C YELLOW NO. 5)

- ORIAHNN contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

- Most common adverse reactions occurring in ≥5% of women receiving ORIAHNN in clinical trials were hot flush, headache, fatigue, and metrorrhagia.

These are not all of the possible side effects of ORIAHNN.

Safety and effectiveness of ORIAHNN in pediatric patients have not been established.

Please see Brief Summary of full Prescribing Information on the following pages of this advertisement.

References: 1. ORIAHNN [package insert]. North Chicago, IL: AbbVie Inc. **2.** Data on file. ABVRRTI71860. **3.** Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med*. 2020;382(4):328-340.

ORIAHNN™ (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules) co-packaged for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: THROMBOEMBOLIC DISORDERS AND VASCULAR EVENTS

- **Estrogen and progestin combinations, including ORIAHNN, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in women at increased risk for these events *[see Warnings and Precautions]*.**
- **ORIAHNN is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke and women with uncontrolled hypertension *[see Contraindications]*.**

INDICATIONS AND USAGE

ORIAHNN is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

Limitation of Use:

Use of ORIAHNN should be limited to 24 months due to the risk of continued bone loss, which may not be reversible *[see Warnings and Precautions]*.

CONTRAINDICATIONS

ORIAHNN is contraindicated in women:

- With a high risk of arterial, venous thrombotic, or thromboembolic disorders *[see Boxed Warning and Warnings and Precautions]*. Examples include women over 35 years of age who smoke, and women who are known to have:
  - current or history of deep vein thrombosis or pulmonary embolism
  - vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral vascular disease)
  - thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
  - inherited or acquired hypercoagulopathies
  - uncontrolled hypertension
  - headaches with focal neurological symptoms or have migraine headaches with aura if over age 35
- Who are pregnant. Exposure to ORIAHNN early in pregnancy may increase the risk of early pregnancy loss *[see Use in Specific Populations]*.
- With known osteoporosis because of the risk of further bone loss *[see Warnings and Precautions]*.
- With current or history of breast cancer or other hormonally-sensitive malignancies, and with increased risk for hormonally-sensitive malignancies *[see Warnings and Precautions]*.
- With known hepatic impairment or disease *[see Warnings and Precautions]*.
- With undiagnosed abnormal uterine bleeding.
- With known anaphylactic reaction, angioedema, or hypersensitivity to ORIAHNN or any of its components.
- Taking inhibitors of organic anion transporting polypeptide (OATP)1B1 (a hepatic uptake transporter) that are known or expected to significantly increase elagolix plasma concentrations *[see Drug Interactions]*.

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders and Vascular Events

ORIAHNN is contraindicated in women with current or history of thrombotic or thromboembolic disorders and in women at increased risk for these events *[see Contraindications]*. In the Phase 3 clinical trials (Studies UF-1, UF-2, and UF-3), two thrombotic events occurred in 453 ORIAHNN-treated women (thrombosis in the calf and pulmonary embolism) *[see Adverse Reactions]*. Estrogen and progestin combinations, including the estradiol/norethindrone acetate component of ORIAHNN, increase the risk of thrombotic or thromboembolic disorders, including pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, especially in women at high risk for these events. In general, the risk is greatest among women over 35 years of age who smoke, and women with uncontrolled hypertension, dyslipidemia, vascular disease, or obesity.

Discontinue ORIAHNN if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs or is suspected. If feasible, discontinue ORIAHNN at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Stop ORIAHNN immediately if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis as these have been reported in patients receiving estrogens and progestins.

Bone Loss

ORIAHNN is contraindicated in women with known osteoporosis *[see Contraindications]*. ORIAHNN may cause a decrease in bone mineral density (BMD) in some patients. BMD loss is greater with increasing duration of use and may not be completely reversible after stopping treatment *[see Adverse Reactions]*.

In the Phase 3 clinical trials (Studies UF-1, UF-2, and UF-3), seven out of 453 (1.5%) ORIAHNN-treated women experienced fractures, including one (0.2%) with a fragility fracture, compared to one out of 196 (0.5%) placebo-treated women (patient had a non-fragility fracture). Five of the seven ORIAHNN-treated women reported these fractures in the post-treatment follow-up period. The impact of BMD decreases on long-term bone health and future fracture risk in premenopausal women is unknown.

Consider the benefits and risks of ORIAHNN treatment in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss, including taking medications that may decrease BMD (e.g., systemic or chronic inhaled corticosteroids, anticonvulsants, or proton pump inhibitors).

Assessment of BMD by dual-energy X-ray absorptiometry (DXA) is recommended at baseline and periodically thereafter. Consider discontinuing ORIAHNN if the risk associated with bone loss exceeds the potential benefit of treatment. Limit the duration of use to 24 months to reduce the extent of bone loss *[see Indications and Usage]*.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation for patients with inadequate dietary intake may be beneficial.

Hormonally-Sensitive Malignancies

ORIAHNN is contraindicated in women with current or history of breast cancer and in women at increased risk for hormonally-sensitive malignancies, such as those with mutations in BRCA genes *[see Contraindications]*.

In the Phase 3 clinical trials (Studies UF-1, UF-2, and UF-3), two (0.4%) cases of breast cancer in 453 ORIAHNN-treated women were observed. No breast cancer cases were seen in placebo-treated women *[see Adverse Reactions]*.

The use of estrogen alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. Surveillance measures, such as breast examinations and regular mammography, are recommended. Discontinue ORIAHNN if a hormonally-sensitive malignancy is diagnosed.

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

In Phase 3 placebo-controlled clinical trials (Studies UF-1 and UF-2), ORIAHNN-treated women had a higher incidence (3%) of depression, depressed mood, and/or tearfulness compared to placebo-treated women (1%) *[see Adverse Reactions]*. Suicidal ideation and behavior, including a completed suicide, occurred in women treated with lower doses of elagolix in clinical trials conducted for a different indication.

Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits. Patients with new or worsening depression, anxiety, or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORIAHNN if such events occur.

Hepatic Impairment and Transaminase Elevations

Contraindication in Patients with Hepatic Impairment

ORIAHNN is contraindicated in women with known hepatic impairment or disease *[see Contraindications and Use in Specific Populations]*.

Transaminase Elevations

In Phase 3 placebo-controlled clinical trials (Studies UF-1 and UF-2), elevations (> 3 times the upper limit of the reference range) in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred in 1.1% (4/379) and 1.3% (5/379) of ORIAHNN-treated patients, respectively, compared to no elevations in placebo. Transaminases peaked at 8 times the upper limit for ALT and 6 times the upper limit for AST. No pattern in time to onset of these liver transaminase elevations was identified. Transaminase levels returned to baseline within 4 months after peak values in these patients.

Instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice *[see Adverse Reactions]*.

Elevated Blood Pressure

ORIAHNN is contraindicated in women with uncontrolled hypertension *[see Contraindications]*. In Studies UF-1 and UF-2, a maximum mean increase in systolic blood pressure of 5.1 mmHg [95% confidence interval (CI) 2.68, 7.59] occurred at Month 5, and a maximum mean increase in diastolic blood pressure of 2.1 mmHg (95% CI 0.43, 3.84) occurred at Month 4 in ORIAHNN-treated women, as compared to placebo-treated women *[see Adverse Reactions]*.

For women with well-controlled hypertension, continue to monitor blood pressure and stop ORIAHNN if blood pressure rises significantly. Monitor blood pressure in normotensive women treated with ORIAHNN.

Gallbladder Disease or History of Cholestatic Jaundice

Studies among estrogen users suggest a small increased relative risk of developing gallbladder disease. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, assess the risk-benefit of continuing therapy. Discontinue ORIAHNN if jaundice occurs.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

ORIAHNN may delay the ability to recognize the occurrence of a pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding *[see Adverse Reactions]*. Perform pregnancy testing if pregnancy is suspected, and discontinue ORIAHNN if pregnancy is confirmed *[see Use in Specific Populations]*.

The effect of hormonal contraceptives on the efficacy of ORIAHNN is unknown. Advise women to use non-hormonal contraception during treatment and for one week after discontinuing ORIAHNN *[see Use in Specific Populations]*.

Effects on Carbohydrate and Lipid Metabolism

ORIAHNN may decrease glucose tolerance and result in increased glucose levels. More frequent monitoring in ORIAHNN-treated women with prediabetes and diabetes may be needed.

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Use of elagolix is associated with increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum triglycerides. Monitor lipid levels and consider discontinuing ORIAHNN if hypercholesterolemia or hypertriglyceridemia worsens *[see Adverse Reactions]*.

Alopecia

In Phase 3 clinical trials (Studies UF-1 and UF-2), more women experienced alopecia, hair loss, and hair thinning with ORIAHNN (3.5%) compared to placebo (1.0%). In almost one-third (4/14) of affected ORIAHNN-treated women, alopecia was a reason for discontinuing treatment. No specific pattern was described. In the majority of affected women, hair loss was continuing when ORIAHNN was stopped. Whether the hair loss is reversible is unknown. Consider discontinuing ORIAHNN if hair loss becomes a concern *[see Adverse Reactions]*.

Effect on Other Laboratory Results

The use of estrogen and progestin combinations may raise serum concentrations of binding proteins (e.g., thyroid-binding globulin, corticosteroid-binding globulin), which may reduce the free thyroid or corticosteroid hormone levels. Patients with hypothyroidism and hypoadrenalism may require higher doses of thyroid hormone or cortisol replacement therapy, respectively.

The use of estrogen and progestin may also affect the levels of sex hormone-binding globulin, coagulation factors, lipids, and glucose*]*.

Risk of Allergic Reactions Due to the Inactive Ingredient (FD&C Yellow No. 5)

ORIAHNN contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Thromboembolic Disorders and Vascular Events *[see Warnings and Precautions]*
- Bone Loss *[see Warnings and Precautions]*
- Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders *[see Warnings and Precautions]*
- Hepatic Transaminase Elevations *[see Warnings and Precautions]*
- Elevated Blood Pressure *[see Warnings and Precautions]*
- Effects on Carbohydrate and Lipid Metabolism *[see Warnings and Precautions]*
- Alopecia *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ORIAHNN was evaluated in two 6-month, randomized, double-blind, placebo-controlled trials (Studies UF-1 and UF-2), in which 790 premenopausal women received at least 1 dose of ORIAHNN (n=395), elagolix 300 mg twice daily (n=199), or placebo (n=196) *[see Clinical Studies (14)]*. Women who completed 6-month treatment in either Study UF-1 or Study UF-2 and met eligibility criteria (n=433) entered a 6-month extension study (Study UF-3), receiving either ORIAHNN (n=276) or elagolix 300 mg twice daily (n=157). Elagolix 300 mg twice daily is not an approved dosage but was included as a reference arm. A total of 341women received ORIAHNN for 6 months and 182 women received ORIAHNN for 12 months.

Serious Adverse Events

Serious adverse events were reported in three (0.8%) ORIAHNN-treated women in Studies UF-1 and UF-2. Two women had heavy menstrual bleeding and required blood transfusion due to anemia (0.5%) and one woman with history of bariatric surgery had a laparoscopic cholecystectomy due to cholelithiasis.

In Study UF-3, two women were diagnosed with breast cancer. One woman had completed 6 months of treatment with ORIAHNN in Study UF-1 and received 34 additional days of ORIAHNN in Study UF-3 when diagnosed. The second woman had received placebo in Study UF-2 and completed 6 months of ORIAHNN in Study UF-3 when diagnosed *[see Warnings and Precautions]*.

Adverse Reactions Leading to Study Discontinuation

In Studies UF-1 and UF-2, the discontinuation rate due to adverse reactions was 10% among ORIAHNN-treated women and 7% among placebo-treated women. The most common adverse reactions leading to study drug discontinuation in the ORIAHNN group were nausea (1%), headache (1%), alopecia (1%), metrorrhagia (1%), menorrhagia (1%), and hot flush (1%). One event each of the following adverse reactions led to study drug discontinuation: affect lability, angina pectoris, depression, hepatic enzyme increased, homicidal ideation, hypertension, irritability, thrombosis.

In women who received ORIAHNN in Studies UF-1 or UF-2 and then in Study UF-3, 4% discontinued treatment due to adverse reactions. Three women discontinued due to serious adverse events (one each for breast cancer, menorrhagia with pelvic pain, and hysterectomy).

Common Adverse Reactions

Adverse reactions reported in ≥5% of ORIAHNN-treated women in Studies UF-1 and UF-2 and at a greater frequency than placebo-treated women are presented in Table 1.

Table 1. Adverse Reactions that Occurred in at Least 5% of Women with Uterine Fibroids Who Received ORIAHNN in Studies UF-1 and UF-2 and at a Greater Incidence Than Placebo

Adverse Reaction	ORIAHNN N=395	Placebo N=196
Hot flush	22%	9%
Headache	9%	7%
Fatigue	6%	4%
Metrorrhagia	5%	1%

The most commonly reported adverse reactions in the blinded extension trial (Study UF-3) were consistent with those in the placebo-controlled trials.

Less Common Adverse Reactions

In Studies UF-1 and UF-2, adverse reactions reported in ≥3% and <5% in the ORIAHNN group and greater incidence than the placebo group included: libido decreased, arthralgia, hypertension, alopecia, mood swings, influenza, abdominal distension, upper respiratory tract infection, menorrhagia, vomiting, and weight increased.

Thromboembolic and Vascular Events

In the Studies UF-1, UF-2, and UF-3, two (0.4%) thrombotic events occurred in 453 ORIAHNN-treated patients (thrombosis in the calf and pulmonary embolism) *[see Warnings and Precautions]*. One obese woman developed thrombosis in the left calf after 30 days of treatment with ORIAHNN. Another woman developed a pulmonary embolism after taking ORIAHNN for approximately 8 months.

Bone Loss

The effect of ORIAHNN on BMD was assessed by dual-energy X-ray absorptiometry (DXA).

In Studies UF-1 and UF-2, there was a greater decrease in BMD in women treated with ORIAHNN for 6 months compared to women treated with placebo. In Study UF-3, continued bone loss was observed in some women who received ORIAHNN for 12 consecutive months. The mean percent change from baseline in lumbar spine BMD at Month 6 (Studies UF-1 and UF-2) and Month 12 (Study UF-3) is presented in Table 2.

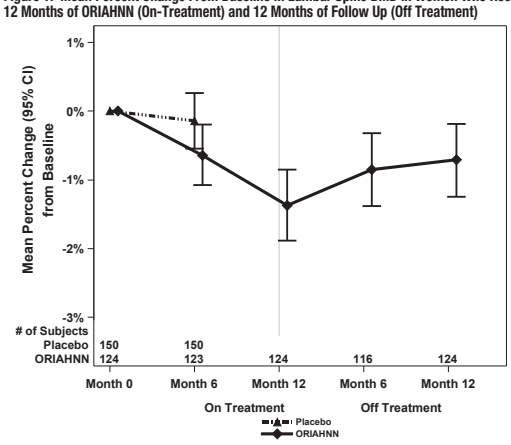
Table 2. Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD in Women with Fibroids at Month 6 in Studies UF-1 and UF-2 and Month 12 in Study UF-3

	Studies UF-1 and UF-2 Treatment Month 6		Study UF-3 Treatment Month 12
	Placebo	ORIAHNN	ORIAHNN
Number of Subjects	150	305	175
Percent Change from Baseline	-0.1	-0.7	-1.5
Treatment Difference, % (95% CI)		-0.6 (-1.0, -0.1)	
CI: Confidence interval			

Following 12 months of ORIAHNN treatment in Study UF-3, a decline in lumbar spine BMD of >3% was seen in 27% (48/175) of women and a decline of ≥8% was seen in 1.7% (3/175) of women.

To assess for recovery, the change in BMD over time was analyzed for women who received continuous ORIAHNN treatment for up to 12 months and were then followed after cessation of therapy for an additional 12 months in Study UF-3 (Figure 1). The LS mean percent change from baseline in BMD 12 months after cessation of therapy was -0.72 (95% CI -1.2, -0.2), -0.59 (-1.0, -0.2), and -0.95 (-1.6, -0.3) at the lumbar spine, total hip, and femoral neck, respectively. Twelve months after cessation of ORIAHNN, continued bone loss was observed at the lumbar spine, total hip, and femoral neck in 24%, 32%, and 40% of women, respectively. Partial recovery was observed in 46%, 33%, and 38% and full recovery was observed in 30%, 35%, and 22% of women at these same sites. The time to maximum recovery in women who partially recovered is unknown.

Figure 1. Mean Percent Change From Baseline in Lumbar Spine BMD in Women Who Received 12 Months of ORIAHNN (On-Treatment) and 12 Months of Follow Up (Off Treatment)



Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

In the placebo-controlled trials (Studies UF-1 and UF-2), ORIAHNN was associated with adverse mood changes. Depression, depressed mood, and/or tearfulness were reported in 3% of ORIAHNN-treated women compared to 1% of placebo-treated women. One woman treated with lower dose elagolix alone for another disease completed suicide 2 days after elagolix discontinuation.

Hepatic Transaminase Elevations

In Studies UF-1 and UF-2, elevations of serum ALT and AST with no concurrent elevations of bilirubin were reported.

- ALT elevations to at least 3 times the upper limit of normal (ULN) occurred in 1.1% (4/379) of ORIAHNN-treated women and no placebo-treated women. Peak elevation of ALT almost 8 times the ULN was reported in 1 ORIAHNN-treated woman.
- AST elevations to at least 3 times the ULN occurred in 5/379 (1.3%) in ORIAHNN-treated women and no placebo-treated women. Peak elevation of AST 6 times the ULN was reported in 1 ORIAHNN-treated woman.

Blood Pressure Elevations

There were more ORIAHNN-treated women with systolic blood pressure ≥ 160 mmHg (7.1%) and diastolic blood pressure ≥ 100 mmHg (11.3%) compared to placebo-treated women (3.7% and 6.3%, respectively). The incidence of hypertensive adverse reactions was 3.8% in ORIAHNN-treated women and 3.1% placebo-treated women. One ORIAHNN-treated woman in Study UF-1, with no prior history but with elevated cholesterol levels, had severe hypertension (BP 204/112) and chest pain. ECG was negative. Her hypertension was controlled with anti-hypertensives and she completed Study UF-3.

Changes in Lipid Parameters

Increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), serum triglycerides, and apolipoprotein B were noted during ORIAHNN treatment in Studies UF-1 and UF-2.

Of the women with Grade 0 LDL-C (<130 mg/dL) at baseline, 1/313 (0.3%) ORIAHNN-treated woman shifted to Grade 3 (≥ 190 mg/dL) compared to no placebo-treated woman. Of those with Grade 1 LDL-C (130 to <160 mg/dL) at baseline, 9/54 (16.7%) ORIAHNN-treated women shifted to Grade 3 compared to no placebo-treated woman. Of those with Grade 2 LDL-C (160 to <190 mg/dL) at baseline, 7/10 (70%) ORIAHNN-treated women shifted to Grade 3 compared to 1/5 (20%) placebo-treated woman.

Alopecia

In Phase 3 placebo-controlled clinical trials (Studies UF-1 and UF-2), 3.5% (14/395) of ORIAHNN-treated women experienced alopecia, hair loss, or hair thinning compared to 1.0% (2/196) of placebo-treated women. No specific pattern in hair loss was observed. In almost one-third (4/14) of affected ORIAHNN-treated women, alopecia was a reason for study drug discontinuation; no placebo-treated women discontinued because of alopecia. In ORIAHNN-treated women, 79% of the cases were mild and 21% were moderate in severity. Hair loss was ongoing at the end of the study for 4 out of 14 women (29%). Of these 4 women, one discontinued treatment due to hair loss, two had ongoing hair loss 12 months after discontinuing ORIAHNN, and one was lost to follow-up. In the remaining 10 women (71%), hair loss either resolved while on treatment or resolved within 24 days to approximately 9 months after discontinuing ORIAHNN.

Resumption of Menses after Discontinuation

After six months of ORIAHNN treatment, resumption of menses was reported by 39%, 68%, and 73% of women within 1, 2, and 6 months, respectively, in Study UF-1 and 39%, 85%, and 92% within 1, 2, and 6 months, respectively, in Study UF-2.

After 12 months of therapy with ORIAHNN (Study UF-1 or Study UF-2 then Study UF-3), resumption of menses was reported by 43%, 82%, and 90% of women within 1, 2, and 6 months after stopping treatment, respectively.

Whether those who did not resume having menses transitioned to a peri-postmenopausal status is unknown.

DRUG INTERACTIONS

Potential for ORIAHNN to Affect Other Drugs

Elagolix (a component of ORIAHNN) is:

- A weak to moderate inducer of cytochrome P450 (CYP3A). Co-administration with ORIAHNN may decrease plasma concentrations of drugs that are substrates of CYP3A.
- A weak inhibitor of CYP2C19. Co-administration with ORIAHNN may increase plasma concentrations of drugs that are substrates of CYP2C19 (see Table 3).
- An inhibitor of efflux transporter P-glycoprotein (P-gp). Co-administration with ORIAHNN may increase plasma concentrations of drugs that are substrates of P-gp (see Table 3).

The effects of co-administration of ORIAHNN on concentrations of concomitant drugs and the clinical recommendations for these drug interactions are summarized in Table 3.

Table 3. Drug Interactions: Effects of ORIAHNN on Other Drugs

Concomitant Drug Class: Drug Name	Effect on Plasma Exposure of Concomitant Drug	Clinical Recommendations
Cardiac glycosides: digoxin	↑ digoxin	Increase monitoring of digoxin concentrations and potential signs and symptoms of clinical toxicity when initiating ORIAHNN in patients who are taking digoxin. If ORIAHNN is discontinued, increase monitoring of digoxin concentrations.
Benzodiazepines: oral midazolam	↓ midazolam	Consider increasing the dose of midazolam by no more than 2-fold and individualize midazolam therapy based on the patient's response.
Statins: rosuvastatin	↓ rosuvastatin	Monitor lipid levels and adjust the dose of rosuvastatin, if necessary.
Proton pump inhibitors: omeprazole	↑ omeprazole	No dose adjustment needed for omeprazole 40 mg once daily when co-administered with ORIAHNN. When ORIAHNN is used concomitantly with higher doses of omeprazole, consider dosage reduction of omeprazole.
The direction of the arrow indicates the direction of the change in the area under the curve (AUC) (↑ = increase, ↓ = decrease).		

Potential for Other Drugs to Affect ORIAHNN

Elagolix (a component of ORIAHNN) is a substrate of CYP3A, P-gp, and OATP1B1; estradiol and norethindrone acetate are metabolized partially by CYP3A*]*. Concomitant use of ORIAHNN with:

- Strong CYP3A inducers may decrease elagolix, estradiol, and norethindrone plasma concentrations and may result in a decrease of the therapeutic effects of ORIAHNN.
- Rifampin is not recommended. The concomitant use of rifampin increased plasma concentrations of elagolix*]*.
- Strong CYP3A inhibitors are not recommended. Concomitant use of ORIAHNN with strong CYP3A inhibitors may increase elagolix, estradiol, and norethindrone plasma concentrations and increase the risk of adverse reactions.
- OATP1B1 inhibitors that are known or expected to significantly increase elagolix plasma concentrations is contraindicated due to increased risk of elagolix-associated adverse reactions *[see Contraindications]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors outcomes in women who become pregnant while treated with ORIAHNN. Pregnant patients should be encouraged to enroll by calling 1-833-782-7241.

Risk Summary

Use of ORIAHNN is contraindicated in pregnant women. Exposure to elagolix early in pregnancy may increase the risk of early pregnancy loss. Discontinue ORIAHNN if pregnancy occurs during treatment.

The limited human data with the use of elagolix in pregnant women are insufficient to determine whether there is a risk for major birth defects or miscarriage *[see Data]*.

When pregnant rats and rabbits were orally dosed with elagolix during the period of organogenesis, postimplantation loss was observed in pregnant rats at doses 12 times the maximum recommended human dose (MRHD). Spontaneous abortion and total litter loss were observed in rabbits at doses 4 and 7 times the MRHD. There were no structural abnormalities in the fetuses at exposures up to 25 and 7 times the MRHD for the rat and rabbit, respectively *[see Data]*.

Data

Human Data

There was one pregnancy reported in the 453 women who received ORIAHNN in the Phase 3 uterine fibroids clinical trials. The pregnancy resulted in a spontaneous abortion and the estimated fetal exposure to ORIAHNN occurred during the first 18 days of pregnancy.

Animal Data

Embryofetal development studies were conducted in the rat and rabbit. Elagolix was administered by oral gavage to pregnant rats (25 animals/dose) at doses of 0, 300, 600, and 1200 mg/kg/day and to rabbits (20 animals/dose) at doses of 0, 100, 150, and 200 mg/kg/day during the period of organogenesis (gestation day 6-17 in the rat and gestation day 7-20 in the rabbit).

In rats, maternal toxicity was present at all doses and included six deaths and decreases in body weight gain and food consumption. Increased postimplantation losses were present in the mid dose group, which was 12 times the MRHD based on AUC. In rabbits, three spontaneous abortions and a single total litter loss were observed at the highest maternally toxic dose, which was 7 times the MRHD based on AUC. A single total litter loss occurred at a lower non-maternally toxic dose of 150 mg/kg/day, which was 4 times the MRHD.

No fetal malformations were present at any dose level tested in either species even in the presence of maternal toxicity. At the highest doses tested, the exposure margins were 25 and 7 times the MRHD for the rat and rabbit, respectively. However, because elagolix binds poorly to the rat gonadotropin-releasing hormone (GnRH) receptor (~1000 fold less than to the human GnRH receptor), the rat study is unlikely to identify pharmacologically mediated effects of elagolix on embryofetal development. The rat study is still expected to provide information on potential
non-target-related effects of elagolix.

In a pre- and postnatal development study in rats, elagolix was given in the diet to achieve doses of 0, 100, and 300 mg/kg/day (25 per dose group) from gestation day 6 to lactation day 20. There was no evidence of maternal toxicity. At the highest dose, two dams had total litter loss, and one failed to deliver. Pup survival was decreased from birth to postnatal day 4. Pups had lower birth weights, and lower body weight gains were observed throughout the pre-weaning period at 300 mg/kg/day. Smaller body size and effect on startle response were associated with lower pup weights at
300 mg/kg/day. Post-weaning growth, development, and behavioral endpoints were unaffected.

Maternal plasma concentrations in rats on lactation day 21 at 100 and
300 mg/kg/day (47 and 125 ng/mL) were 0.04-fold and 0.1-fold the maximal elagolix concentration (C_{max}) in humans at the MRHD. Because the exposures achieved in rats were much lower than the human MRHD, this study is not predictive of potentially higher lactational exposure in humans.

Lactation

Risk Summary

There is no information on the presence of elagolix in human milk, the effects on the breastfed child, or the effects on milk production. When estrogen and progestins are administered to lactating women, these compounds and/or their metabolites are detected in human milk and can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. Advise the nursing female to use non-hormonal contraception until she discontinues breast-feeding. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for ORIAHNN and any potential adverse effects on the breast-fed child from ORIAHNN or from the underlying maternal condition *[see Data]*.

Data

There is no information on the presence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen and progestin combinations.

There are no adequate animal data on excretion of elagolix in milk.

Females and Males of Reproductive Potential

Based on the mechanism of action of elagolix, there is a risk of early pregnancy loss if ORIAHNN is administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

ORIAHNN may delay the ability to recognize the occurrence of a pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding *[see Adverse Reactions]*. Exclude pregnancy before initiating treatment with ORIAHNN. Perform pregnancy testing if pregnancy is suspected during treatment with ORIAHNN and discontinue treatment if pregnancy is confirmed *[see Contraindications and Warnings and Precautions]*.

Contraception

Advise women to use non-hormonal contraception during treatment with ORIAHNN and for one week after discontinuing ORIAHNN *[see Warnings and Precautions]*.

Pediatric Use

Safety and effectiveness of ORIAHNN in pediatric patients have not been established.

Renal Impairment

No dose adjustment of ORIAHNN is required in women with any degree of renal impairment or end-stage renal disease (including women on dialysis).

Hepatic Impairment

ORIAHNN is contraindicated in women with any hepatic impairment or disease *[see Contraindications]*. The use of estradiol (a component of ORIAHNN) in patients with hepatic impairment, compared to patients with normal hepatic function, is expected to increase the blood levels of estradiol and increase the risk of estradiol-associated adverse reactions. Additionally, the use of elagolix (a component of ORIAHNN) in patients with moderate and severe hepatic impairment, compared to patients with normal hepatic function, increased elagolix exposures 3-fold and 7-fold, respectively, and this increases the risk of elagolix-associated adverse reactions.

OVERDOSAGE

Overdosage of estrogen and progestin combination products may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness, fatigue, and withdrawal bleeding. In case of ORIAHNN overdose, monitor the patient for any signs or symptoms of adverse reactions and initiate appropriate symptomatic treatment, as needed.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Thromboembolic Disorders and Vascular Events

Advise patients that use of estrogen and progestin combinations may increase the risk of thromboembolic disorders and vascular events, especially in women at high risk for these events *[see Boxed Warning, Contraindications, Warnings and Precautions, and Adverse Reactions]*.

Bone Loss

Advise patients about the risk of bone loss. Advise patients that supplementary calcium and vitamin D may be beneficial if dietary intake of calcium and vitamin D is not adequate. Advise patients that oral iron supplement should not be taken at the same time as calcium and vitamin D *[see Warnings and Precautions and Adverse Reactions]*.

Suicidal Ideation and Exacerbation of Mood Disorders

Advise patients that suicidal ideation and exacerbation of mood disorders may occur with ORIAHNN use. Instruct patients with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention *[see Warnings and Precautions and Adverse Reactions]*.

Liver Injury

Advise patients to promptly seek medical attention in case of signs or symptoms that may reflect liver injury, such as jaundice *[see Warnings and Precautions and Adverse Reactions]*.

Change in Menstrual Bleeding Pattern

Advise patients that ORIAHNN may delay the recognition of pregnancy because it may reduce the duration and amount of menstrual bleeding. Advise patients to use effective non-hormonal contraception while taking ORIAHNN and to discontinue ORIAHNN if pregnancy is diagnosed. Advise pregnant patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to ORIAHNN during pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

Alopecia

Advise patients that alopecia, hair loss, and hair thinning in no specific pattern, may occur with ORIAHNN use. Advise patients that hair loss and hair thinning may not resolve completely after stopping ORIAHNN. Advise patients to contact their healthcare provider if they have concerns about changes to their hair *[see Warnings and Precautions* and *Adverse Reactions]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Advise patients to avoid grapefruit juice while taking ORIAHNN *[see Drug Interactions]*.

ORIAHNN Missed Dose Instructions

Instruct patients about what to do in the event a dose is missed. See "If you miss a dose of ORIAHNN" section in FDA-approved Medication Guide.

ORIAHNN Disposal Instructions

Instruct patients to dispose of unused medication via a take-back option if available or to otherwise follow FDA instructions for disposing of medication in the household trash, *www.fda.gov/drugdisposal*, and not to flush down the toilet.

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STI CARE "Prevention is a crucial first step"

continued from page 1

"For too long, STI prevention and treatment has been perceived as the sole responsibility of a narrow workforce of specialized STI and HIV service providers," Dr. Guilamo-Ramos and his coauthor, Marco Thimm-Kaiser, MPH, associate in research at Duke University and epidemiologist at CLAFH, wrote in an email.

> "For too long, STI prevention and treatment has been perceived **as the sole responsibility of a narrow workforce** of specialized STI and HIV service providers."

"However, the resources allocated to this STI specialty workforce have diminished over time, along with decreasing investments in the broader U.S. public health infrastructure," they continued. "At the same time – and in part due to this underinvestment – STI rates have soared, reaching a record high for the sixth year in a row in 2019."

Those factors led to the National Academies report (Sexually Transmitted Infections: Adopting a Sexual Health Paradigm. Washington: National Academies Press, 2021), which recommends moving "away from the traditional, disease-focused perspective on STIs in favor of a holistic perspective of sexual health as an integral component of overall health and well-being," Dr. Guilamo-Ramos and Mr. Thimm-Kaiser wrote to this news organization.

In their article, the authors review the limitations in the STI workforce, the implications of those limitations for the broader health care industry, and what it will take for STI and HIV specialists as well as regulators to ensure it's possible to achieve the paradigm shift recommended by the National Academies.

Currently, the biggest limitation is access to care, said Laura Mercer, MD, MBA, of the department of obstetrics and gynecology and the ob.gyn. clerkship director at the University of Arizona, Phoenix. Dr. Mercer, who was not involved with the National Academies report or the analysis of it, said in an interview that it's essential to emphasize "sexual health as a core element of routine primary and preventative care" to ensure it becomes more accessible to patients without the need to seek out specialty care.

Dr. Guilamo-Ramos and his colleagues drive home the importance of such a shift by noting that more than 200 million Americans live in counties with no practicing infectious disease physicians. The disparities are greatest in Southern states, which account for 40% of all reported STIs. The workforce shortage has continued to worsen alongside the deterioration of the clinical infrastructure supporting STI specialty services, the authors write.

Hence the need to expand accountability for care not only to primary care physicians but also to nurses, pharmacists, physician assistants, nurse practitioners, and behavioral health practitioners. Doing so also requires normalizing sexual health services across health care professions.

"Prevention is a crucial first step" to this, Dr. Mercer said. "This is particularly important as we recall that almost half of new sexually transmitted infections occur in teenagers. Destigmatizing sexual health and sexual health education will also help encourage patients of all ages to request and accept testing."

Further, with primary care practitioners managing most STI testing and treatment, subspecialists can focus primarily on complex or refractory cases, she added. Ways to help broaden care include developing point-of-care testing for STIs and improving the accuracy of existing testing, she said.

"The goal is to make routine sexual health services accessible in a wide range of settings, such as in primary care, at pharmacies, and in community-based settings, and to draw on a broader workforce for delivery of sexual health services," Dr. Guilamo-Ramos said in an interview.

Kevin Ault, MD, professor of obstetrics and gynecology and director of clinical and translational research at the University of Kansas Medical Center in Kansas City, said that many medical organizations, such as the American College of Obstetricians and Gynecologists, have long advocated incorporating sexual health into routine preventive care. He also noted that pharmacists have already become proactive in preventing STIs and could continue to do so.

"Vaccines for hepatitis and human papillomavirus are commonly available at pharmacies," Dr. Ault said. He was not involved in the article by Dr. Guilamo-Ramos and colleagues or the original report. "Pharmacists could also fill a gap by administering injectable medications such as penicillin. States would have to approve changes in policy, but many states have already done this for expedited partner therapy."

Dr. Guilamo-Ramos and Mr. Thimm-Kaiser noted similar barriers that must be removed to broaden delivery of STI services.

"Unfortunately, too many highly trained health care providers who are well-positioned for the delivery of sexual health services face regulatory or administrative barriers to practice to the full scope of their training," they wrote. "These barriers can have a particularly negative impact in medically underserved communities, where physician shortages are common and where novel, decentralized health care service delivery models that draw on nonphysician providers may hold the greatest promise."

> "**The goal is to make routine sexual health services accessible in a wide range of settings**, such as in primary care, at pharmacies, and in community-based settings, and to draw on a broader workforce for delivery of sexual health services."

As more diverse health care practitioners take on these roles, ID and HIV specialists can provide their expertise in developing training and technical assistance to support generalists, Dr. Guilamo-Ramos and Mr. Thimm-Kaiser wrote. They can also aid in aligning "clinical training curricula, licensing criteria, and practice guidelines with routine delivery of sexual health services."

Dr. Guilamo-Ramos and his coauthors offer specific recommendations for professional training, licensing, and practice guidelines to help overcome the "insufficient knowledge, inadequate training, and absence of explicit protocols" that currently impede delivery of STI services in general practice settings.

Although the paradigm shift recommended by the National Academies is ambitious, it's also necessary, and "none of the recommendations are out of reach," Dr. Guilamo-Ramos said in an interview. They pointed out how the COVID-19 pandemic has highlighted how underresourced the health care workforce and infrastructure are and how great health care disparities are.

"There is momentum toward rebuilding the nation's health and public health system in a more effective and efficient way," they said, and many of the STI report's recommendations "overlap with priorities for the broader health and public health system moving forward."

Dr. Mercer also believes the recommendations are realistic, "but only the beginning," she told this news organization. "Comprehensive sexual education to expand knowledge about STI prevention and public health campaigns to help destigmatize sexual health care in general will remain crucial," she said.

Sexual education, expanded access, and destigmatizing sexual care are particularly important for reaching the populations most in need of care, such as adolescents and young adults, as well as ethnic, racial, sexual, and gender-minority youth.

"It cannot be overstated how important of a priority population adolescents and young adults are," Dr. Guilamo-Ramos and Mr. Thimm-Kaiser wrote. They noted that those aged 15-24 account for half of all STIs each year but represent only a quarter of the sexually active population. "Targeted efforts for STI prevention and treatment among adolescents and young adults are therefore essential for an overall successful strategy to address STIs and sexual health in the United States."

The National Academies report was supported by the Centers for Disease Control and Prevention and the National Association of County and City Health Officials. Dr. Mercer, Dr. Ault, and Mr. Thimm-Kaiser have disclosed no relevant financial relationships. Dr. Guilamo-Ramos has received grants and personal fees from ViiV Healthcare.

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Gynecologic Oncology

Recommendations from a gynecologic oncologist

Part 2

BY EMMA C. ROSSI, MD

In this month's column we continue to discuss recommendations from the gynecologic oncologist to the general gynecologist.

Don't screen average-risk women for ovarian cancer

Ovarian cancer is most often diagnosed at an advanced stage, which limits the curability of the disease. Consequently, there is a strong focus on attempting to diagnose the disease at earlier, more curable stages. This leads to the impulse by some well-intentioned providers to implement screening tests for all women. Unfortunately, the screening of "average-risk" women for ovarian cancer is not recommended. Randomized controlled trials of tens of thousands of women have not observed a clinically significant decrease in ovarian cancer mortality with the addition of screening with tumor markers and ultrasound.[1] These studies did observe a false-positive rate of 5%. While that may seem like a low rate of false-positive testing, the definitive diagnostic test which follows is a major abdominal surgery (oophorectomy) and serious complications are encountered in 15% of patients undergoing surgery for false-positive ovarian cancer screening.[1] Therefore, quite simply, the harms are not balanced by benefits.

The key to offering patients appropriate and effective screening is case selection. It is important to identify which patients are at higher risk for ovarian cancer and offer those women testing for germline mutations and screening strategies. An important component of a well-woman visit is to take a thorough family history of cancer. Women are considered at high risk for having hereditary predisposition to ovarian cancer if they have a first- or second-degree relative with breast cancer younger than 45-50 years, or any age if Ashkenazi Jewish, triple-negative breast cancer younger than 60 years of age, two or more primary breast cancers with the first diagnosed at less than 50 years of age, male breast cancer, ovarian cancer, pancreatic cancer, a known BRCA 1/2 mutation, or a personal history of those same conditions. These women should be recommended to undergo genetic testing for BRCA 1/2

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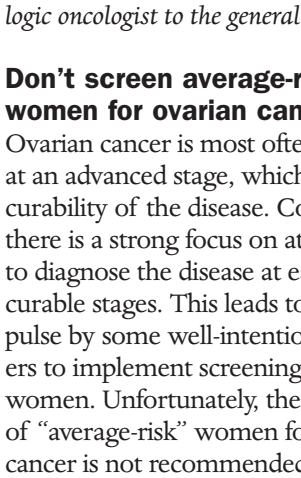

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Blood cancers carry marked risk of delivery complications

BY JALEESA BAULKMAN
FROM MAYO CLINIC PROCEEDINGS

The risk of in-hospital complications and poor birth outcomes were greater in pregnant women with current or historical cancer diagnoses, new research suggests.

The study, published in Mayo Clinic Proceedings (2021 Jul 13. doi: 10.1016/j.mayocp.2021.03.038), found that women with current and historical cancer diagnoses had an increased risk of death, kidney injury, and stroke during delivery hospitalizations, compared with those with no cancer. When it came to delivery outcomes, this group also had a higher risk for preterm birth and postpartum hemorrhage. Those with a current cancer diagnoses had a 1.7-fold increase in odds for a preterm birth, compared with women without cancer.

"Our study found that metastases increased the odds of mortality, cesarean delivery, preterm birth, and stillbirth," the researchers noted. "Coupled with previous research reporting that pregnant women are more likely to be diagnosed with advanced disease, this implies that pregnant women with newly diagnosed cancer have poor prognoses."

However, although women with prior cancer had increased odds of mortality, the researchers said it was not statistically significant.

"The study really did not show an increase of mortality [for women with prior cancer diagnosis]," said Justin Chura, MD, a specialist in gynecologic oncology who was not involved in the study. "And the reason might be because there is not or the reason might be because it's such a rare event. You would need 100 million births to assess that. So I would actually use caution in that interpretation."

Researchers analyzed more than 43 million delivery hospitalizations of women with or without current or historical cancer diagnoses between January 2004 and December 2014. They found that the most common cancer diagnoses were hematologic, thyroid, cervical, skin, and breast.

Of the five most common cancers, the prevalence of all maternal complications and negative delivery outcomes was the highest among women with hematologic cancers. They were more likely to experience peripartum cardiomyopathy, acute kidney injury, and arrhythmia, compared with other cancers. Postpartum hemorrhage, maternal mortality, and placental abruption was also more likely to occur in those with this type of cancer.

"I was surprised that it was the hematologic cancers that were worse when they did it by cancer type," said Dr. Chura, who is the chief of surgery and the director of gynecologic oncology and robotic surgery at the Cancer Treatment Centers of America's Eastern Regional Medical Center in Philadelphia. "I think this is a useful bit of information for counseling our patients and also to identify the cohort with the highest risk."

The findings also suggested that those with skin cancer had the highest odds for stroke, while women

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and Lynch syndrome. They should not automatically be offered ovarian cancer screening. If a patient has a more remote family history for ovarian cancer, their personal risk may be somewhat elevated above the baseline population risk, however, not substantially enough to justify implementing screening in the absence of a confirmed genetic mutation.

While screening tests may not be appropriate for all patients, all patients should be asked about the early symptoms of ovarian cancer because these are consistently present, and frequently overlooked, prior to the eventual diagnosis of advanced disease. Those symptoms include abdominal discomfort, abdominal swelling and bloating, and urinary urgency.[2] Consider offering all patients a dedicated ovarian cancer–specific review of systems that includes inquiries about these symptoms at their annual wellness visits.

Opt for vertical midline incisions when surgery is anticipated to be complex

What is the first thing gynecologic oncologists do when called in to assist in a difficult gynecologic procedure? Get better exposure. Exposure is the cornerstone of safe, effective surgery. Sometimes this simply means placing a more effective retractor. In other cases, it might mean extending the incision. However, if the incision is a low transverse incision (the go-to for many gynecologists because of its favorable cosmetic and pain-reducing profile) this proves to be difficult. Attempting to assist in a complicated case, such as a frozen pelvis, severed ureter, or rectal injury, through a pfannensteil incision can be extraordinarily difficult, and while these incisions can be extended by incising the rectus muscle bellies, upper abdominal visualization remains elusive in most patients. This is particularly problematic if the ureter or splenic flexure need to be mobilized, or if extensive lysis of adhesions is necessary to ensure there is no occult enterotomy. As my mentor John Soper, MD, once described to me: "It's like trying to scratch your armpit by reaching through your fly."

While pfannensteil incisions come naturally to most gynecologists, all gynecologists should be confident in the steps and anatomy for vertical midline, or paramedian incisions. This is beneficial not only for complex gynecologic cases, but also in the event of vascular emergency. In the hands of an experienced abdominal/pelvic surgeon, the vertical midline incision is the quickest way to safely enter the abdomen, and provides the kind of exposure that may be critical in safely repairing or controlling hemorrhage from a major vessel.

> "Randomized controlled trials of tens of thousands of women **have not observed a clinically significant decrease in ovarian cancer mortality** with the addition of screening with tumor markers and ultrasound."

Our first concern as surgeons should be mitigating complications. In situations where risks of complications are high, it is best to not handicap ourselves with the incision location. And always remember, wound complications are highest when a transverse incision needs to be converted to a vertical one with a "T."

It's not just about diagnosis of cancer, it's also prevention

Detection of cancer is an important role of the obstetrician gynecologist. However, equally important is being able to seize opportunities for cancer prevention. Cervical, vulvar, endometrial, and ovarian cancer are all known to have preventative strategies.

All patients up to the age of 45 should be offered vaccination against HPV. Initial indications for HPV vaccination were for women up to age 26; however, recent data support the safety and efficacy of the vaccine in older women.[3] HPV vaccination is most effective at preventing cancer when administered prior to exposure (ideally age 9-11), leaving this in the hands of our pediatrician colleagues. However, we must be vigilant to inquire about vaccination status for all our patients and encourage vaccines for those who were missed earlier in their life.

Patients should be counseled regarding the significant risk reduction for cancer that is gained from use of oral hormonal contraceptives and progestin-releasing IUDs (especially for endometrial and ovarian cancers). Providing them with knowledge of this information when considering options for contraception or menstrual cycle management is important in their decision-making process.

Endometrial cancer incidence is sadly on the rise in the United States, likely secondary to increasing rates of obesity. Pregnancy is a time when many women begin to gain and accumulate weight, and therefore obstetric providers have a unique opportunity to assist patients in strategies to normalize their weight after pregnancy. Many of my patients with endometrial cancer state that they have never heard that it is associated with obesity. This suggests that more can be done to educate patients on the carcinogenic effect of obesity (for both endometrial and breast cancer), which may aid in motivating change of modifiable behaviors.

The fallopian tubes are the source of many ovarian cancers and knowledge of this has led to the recommendation to perform opportunistic salpingectomy as a cancer risk–reducing strategy. Hysterectomy and sterilization procedures are most apropos for this modification. While prospective data to confirm a reduced risk of ovarian cancer with opportunistic salpingectomy are lacking, a reduced incidence of cancer has been observed when the tubes have been removed for indicated surgeries; there appear to be no significant deleterious sequelae.[4,5] A focus should be made on removal of the entire distal third of the tube, particularly the fimbriated ends, as this is the portion most implicated in malignancy. ■

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TRANSforming Gynecology

Gender-affirming mastectomy and breast cancer screening

BY K. ASHLEY BRANDT, DO

Since the reversal of the Medicare exclusion in 2014, the rates of gender-affirming surgery have increased markedly in the United States.[1] Gender-affirming mastectomy, otherwise known as "top surgery," is one of the more commonly performed procedures; with 97% of patients having either undergone or expressed desire for the surgery.[2]

The goals of this procedure are to remove all visible breast tissue and reconstruct the chest wall so it is more masculine in appearance. For transmasculine and nonbinary patients, this procedure is associated with significant improvements in mental health and quality of life.[3,4] While the mastectomy procedure is often performed by plastic surgeons, patients will see an ob.gyn. in the preoperative or postoperative period. Ob.gyns. should have a general understanding of the procedure, but most importantly know how to screen for breast cancer in patients who have undergone a gender-affirming mastectomy.

Providers will likely encounter transmasculine or nonbinary patients during annual screening examinations or for a preoperative exam. If a patient is seeking a preoperative risk assessment prior to undergoing a gender-affirming mastectomy, assessing a patient's risk status for breast cancer is paramount. While testosterone therapy is no longer a prerequisite for gender-affirming mastectomies, documenting hormone use, age at initiation, and dosage is important.[5] The overall effects of testosterone on breast tissue are inconsistent. However, studies have demonstrated that patients taking testosterone are not at an increased risk of breast cancer secondary to testosterone use.[5-7]

Patients should be asked about a personal of family history of breast cancer, breast surgery, history of prior breast biopsies, parity, age at menarche, smoking status, and breastfeeding history if applicable. Patients with high-risk mutations or a strong family history of breast cancer should be referred to genetic counselors, surgical oncologists, and possibly undergo genetic testing.[8] Before an examination, providers should counsel patients about the nature of the examination and use gender-neutral language such as "chest" to avoid exacerbating gender dysphoria.

It is important to educate transmasculine patients about their risk for the development of breast cancer after mastectomy. Larger-scale, population-based studies of breast cancer in the transgender population have reported an incidence of 5.9 per 100,000 patients-years and an overall incidence comparable to cisgender men in age-standardized national samples.[5-7] Unfortunately, data on the rates of breast cancer in transmasculine patients after gender-affirming mastectomy are limited, which makes defining postoperative guidelines challenging. Additionally, the amount of residual breast tissue remaining varies based on the surgeon and technique.

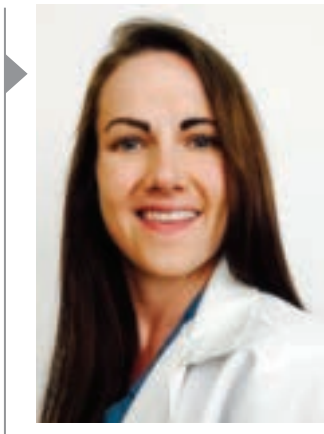
> "It is important to educate transmasculine patients about their **risk for the development of breast cancer after mastectomy.**"

Several techniques are described for mastectomy procedures with differences that can affect the amount of residual breast tissue. The most common type of gender-affirming mastectomy is the double incision. With this procedure, the nipple-areolar complex is reduced in size, removed, and thinned to improve graft take. Dissection is then carried to the level of the breast capsule and the breast tissue and axillary tail are removed en bloc.[5] During the dissection, the subcutaneous fat is left on the skin flap to provide appropriate contour and to avoid creating a concave-appearing chest wall. Prior to closure, the superior and inferior flaps are inspected for any visible residual breast tissue, which is removed if needed.

In a circumareolar mastectomy, the nipple-areolar complex is also reduced but is preserved on a 1- to 1.5-cm-thick pedicle to maintain perfusion.[5] The mastectomy is performed through an inferior periareolar incision and all visible breast tissue and the axillary tail are removed. Breast tissue specimens are sent for pathologic evaluation at the end of the procedure.

Following gender-affirming mastectomy, there is limited evidence to guide screening. During the patient visit, the provider should obtain a thorough history regarding mastectomy type, and if unknown, attempt to acquire the operative report detailing the procedure. For low-risk patients who undergo a subcutaneous mastectomy such as the double-incision or circumareolar technique, screening mammography is not indicated nor is it technically feasible.[9] For patients with a high-risk genetic mutation or a strong family history of breast cancer, monitoring with alternative modalities such as breast ultrasound or breast MRI may be beneficial, although there is no evidence to currently support this suggestion. Given the variety of surgical techniques of breast tissue removal, it is difficult to develop strong evidence-based guidelines.

Annual chest wall examinations have been suggested as a screening modality; however, the clinical utility of clinical breast and chest exams has been debated and is no longer recommended as a screening method in cisgender patients.[9] Clinicians can promote chest self-awareness and discuss the possibility of breast cancer in postmastectomy patients at annual examination visits. As research continues to resolve some of these unknowns, it is important that patients are informed of these areas of ambiguity and updated regarding any changes in screening recommendations.[10] ■



Dr. Brandt is an ob.gyn. and fellowship-trained gender affirming surgeon in West Reading, Pa.

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with cervical and breast cancers were more likely to experience acute kidney injury and preterm birth.

Dr. Chura said cancer treatments can have an impact on a woman's health when she's giving birth. For example, if a woman is diagnosed with cervical cancer, doctors may perform a cone biopsy on her where they remove a large portion of the cervix and still leave them with the ability to conceive and become pregnant. However, those patients are left with a higher risk of a preterm delivery.

For women with a hematologic cancer like non-Hodgkin's lymphoma, chest radiation may cause some subsequent damage to their heart muscles "and now the stress of pregnancy puts more demand on the heart that can lead to cardiac complications for that patient," Dr. Chura said.

Previous studies have shown that chemotherapy may affect pregnancy and delivery. A 2019 study published in the Journal of Cancer (doi: 10.7150/jca.33746) also found that 59 pregnant women with cancer had increased mortality compared with those without the long-term illness. Meanwhile, another 2018 study published in Cancer (doi: 10.1002/cncr.31732) found that women who conceived less than a year after starting chemotherapy had higher risks of preterm birth in comparison with those who conceived more than a year after starting chemotherapy. The study also found that cancer survivors who conceived more than a year after finishing chemotherapy with or without radiation had no higher risk of a preterm birth than those without cancer.

Dr. Chura said the new study could force doctors to think about the long-term effects of their cancer therapies and make them more likely to think about how to make cancer therapy less toxic with less long-term health consequences, while still curing patients.

"Most oncologists, when dealing with younger patients, are very focused on curing the cancer at hand, but not necessarily thinking 5 or 10 years down the road," Dr. Chura said. "[This study] could help inform or at least make us aware of the long-term consequences of our cancer therapies."

Dr. Chura had no relevant financial disclosures.

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Risk score applicability falters in those of African descent

BY NANCY A. MELVILLE
FROM JAMA NETWORK OPEN

THE POTENTIAL of polygenic risk scores (PRSs) to become key components in the assessment of individual risk for disease in the clinical setting is inching closer to fruition; however, the technology is plagued by one glaring omission of most existing PRSs – the lack of applicability to those of non-European ancestry.

PRSs predict an individual's risk of disease based on common genetic variants identified in large genome-wide association studies (GWASs). They have gained ground in research, as well as in the unregulated realm of the direct-to-consumer market where they are sold as add-ons to DNA ancestry kits such as 23andMe and MyHeritage.com.

While the risk scores show strong validation in estimating risk among people of European descent, their striking caveat is the lack of applicability to other ancestries, particularly African, and their use in practice outside of clinical trials is discouraged in National Comprehensive Cancer Network guidelines.

Study underscores need for ethnically diverse datasets

In a recent study published in JAMA Network Open (2021 Aug 4. doi: 10.1001/jamanetworkopen.2021.19084), researchers evaluated the use of PRSs models in a clinical setting. Researchers tested seven PRSs models for breast cancer risk against the medical records data of 39,591 women of European, African, and Latinx ancestry.

The PRSs models – all used only for research purposes – included three models involving European ancestry cohorts, two from Latinx cohorts, and two from women of African descent.

After adjustment for factors including age, breast cancer family history, and ancestry, the PRSs from women with European ancestry highly corresponded to breast cancer risk, with a mean odds ratio of 1.46 per standard-deviation increase in the score.

PRSs were also generalized relatively well among women of Latinx ancestry with a mean OR of 1.31. The authors noted that association is likely caused by Latinx individuals in the United States having a greater proportion of European ancestry than individuals with African ancestry. Importantly, however, the effect size was lower for women of African ancestry with a highest OR of 1.19 per standard deviation.

In the highest percentiles of breast cancer risk, women of European descent had odds ratio as high as 2.19-2.48, suggesting a statistically significant association with overall breast cancer risk. No statistically significant associations were found among women of Latinx and African ancestry.

The PRSs models were smaller for women of non-European ancestry and included fewer genetic variants for women of non-European ancestry and were notably smaller and hence reflected fewer genetic variants. Of

the two risk scores involving African ancestry, the Women's Health Initiative for Women with African ancestry risk score had just 75 variants, while the African diaspora study (ROOT) had 34 variants, compared with 3,820 and 5,218 in the two largest European ancestry PRSs, the Breast Cancer Association Consortium and the UK Biobank, respectively.

"These results highlight the need to improve representation of diverse population groups, particularly women with African ancestry, in genomic research cohorts," the authors wrote.

First author, Cong Liu, PhD, of Columbia University Irving Medical Center, New York, said that efforts are underway to improve the inclusivity in the Electronic Medical Records and Genomics network data set used in this study.

"Until well-developed and validated PRSs for women with non-European ancestry become available, the current PRSs based on cohorts with European ancestry could be adapted for Latinx women, but not women with African ancestry until additional data sets become available in this important and high-risk group," Dr. Liu and colleagues wrote.

In a commentary published with the study (JAMA Netw Open. 2021;4[8]:e2119333), Payal D. Shah, MD, of the Basser Center for BRCA at the University of Pennsylvania, Philadelphia, said that PRSs are "disproportionately applicable to patients with European ancestry and are insufficiently vetted and developed in other populations. If an instrument exists that has clinical utility in informing effective cancer risk mitigation strategies, then we must strive to ensure that it is available and applicable to all."

Higher mortality among African American women

While American Cancer Society data show women with African ancestry generally have incidence rates of breast cancer similar to White women, they have significantly higher mortality from the disease in part because of later-stage diagnosis and health care barriers.

Anne Marie McCarthy, PhD, of the University of Pennsylvania, Philadelphia, and Katrina Armstrong, MD, of Harvard Medical School, Boston, wrote in the Journal of the National Cancer Institute (2020 Dec;112[12]:1179-80) that African American women "have 42% higher breast cancer mortality than white women, despite having lower disease incidence, and are more likely to be diagnosed with triple-negative breast cancer, which has poorer prognosis than other molecular subtypes."

Dr. McCarthy and Dr. Armstrong wrote that African American women are chronically underrepresented in breast cancer studies. And as such, it is impossible to know the extent of the prevalence of mutations and risk.

Failing to address the lack of diversity in genomic studies may worsen health disparities for women with African ancestry, Dr. Liu and colleagues wrote. The higher mortality "underscores the urgent need to increase diversity in genomic studies so that future clinical applications of the PRS do not exacerbate existing health disparities. These results highlight the need to improve representation of diverse population groups, particularly women with African ancestry, in genomic research cohorts."

Dr. Pederson

> **"It is important for Black women to know that data is limited in the African American population,** particularly given the vast genomic diversity of the African continent."

Potential PRS benefits underscore need to eliminate bias

The potentially important benefits of PRSs as risk prediction tools used in combination with family history, reproductive history and other factors, should provide strong incentive to push for improvement, Dr. Shah wrote.

For instance, if an individual is estrogen receptor positive and shows elevations in breast cancer risk on a reliable PRS, "this may inform antiestrogen chemoprevention strategies," she wrote.

A risk score could furthermore influence the age at which breast cancer screening should begin or factor into whether a patient should also receive surveillance breast MRI.

Importantly, PRSs could also add to other risk factors to provide more precise risk estimates and inform management of women with a pathogenic variant in a breast cancer risk predisposition gene, Dr. Shah wrote.

Confluence project

Among the most promising developments in research is the National Cancer Institute's Confluence Project, a large research resource aiming to include approximately 300,000 breast cancer cases and 300,000 controls of different races/ethnicities, utilizing the confluence of existing GWAS and new genomewide genotyping data.

Having started enrollment in 2018, the project is approaching implementation, said Montserrat García-Closas, MD, MPH, DrPH, deputy director of cancer epidemiology and genetics with the National Cancer Institute.

"We expect genotyping to be completed by the end of 2022 and for the data to be made available to the research community soon after that," she said. Among the project's key objectives are the development of PRSs to be integrated with known risk factors to provide a personalized risk assessment for breast cancer, overall and by ancestral subtype. "We plan to apply novel methods to derive multiancestry PRS that will account for differences and similarities in genetic architecture across ethnic/racial groups to develop breast cancer PRSs that can be applied in multiethnic/racial populations," she said.

Dr. García-Closas

NCI is working with investigators in Africa, Central and South America, and Asia, and reaching out to non-European organizations such as AORTIC for studies of African populations.

Direct-to-consumer global PRS

In the commercial PRS market, efforts to address diversity shortcomings are also gaining momentum, with Myriad Genetics touting a first-of-its kind "global PRS."

The PRS, a recalibrated version the company's riskScore PRS, sold as part of its Myriad myRisk Hereditary Cancer test, will reportedly apply to all ethnicities in estimating an individual's 5-year and lifetime risk of breast cancer.

A study presented in June at the American Society of Clinical Oncology meeting describes the development of the model with the use of three large ancestry-specific PRSs based on African American, Asian, and European cohorts, with the system including a total of 149 single-nucleotide polymorphisms, including 93 well established for breast cancer and 56 that are ancestry specific.

In validation of the data in an independent cohort of 62,707 individuals, the global PRS was strongly associated with breast cancer in the full combined validation cohort as well as in all three of the ancestry subcohorts.

However, the effect size among women with African ancestry was still the lowest of all of the groups, with a mean OR of 1.24 per standard deviation, versus the highest rate of mixed ancestry (OR, 1.59).

According to senior author Holly Pederson, MD, director of medical breast services at the Cleveland Clinic, the applicability of the PRS to women with African ancestry is expected to further improve as additional data become available.

"The discriminatory power in women of African descent was significantly improved but still suboptimal," she said. "The need for more data, particularly in Black women, is challenging not only because there is likely more diversity in the genomic landscape of women of African descent, but also because the barriers created by historical, cultural, institutional, and interpersonal dynamics result in the paucity of this data."

Dr. Pederson noted that the global PRS is nevertheless "still clinically useful in Black women," and recommended that clinicians be up front with patients on the status of the research challenges.

"As with any clinical shared decision-making conversation between a patient and her provider, it is important for Black women to know that data is limited in the African American population, particularly given the vast genomic diversity of the African continent," she said.

Commercial PRSs may benefit research

While the commercial marketing of PRSs direct to consumer have raised some concerns, such as how individuals respond to their risk scores, there could be important benefits as well, commented Megan C. Roberts, PhD.

"There may be an opportunity to learn from these companies about how to engage diverse communities in genomic testing," said Dr. Roberts, an assistant professor and director of implementation science in precision health and society at the University of North Carolina at Chapel Hill. "Moreover, the data they collect from their customers often can be used for research purposes as well."

In a recent perspective (Ethn Dis. 2019 Summer;29[3]:513-6), Dr. Roberts and colleagues addressed the role of health disparities in PRSs.

Dr. Pederson disclosed that she is a consultant for Myriad Genetics.

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Reproductive Rounds

COVID-19 and fertility: Unmasking the truth

BY MARK P. TROLICE, MD

In 1839, English author Edward Bulwer-Lytton is credited with originating the metonymic adage "The pen is mightier than the sword," implying the written word is a more effective tool for communication than is violence. More than 180 years later, this statement defines the current impact of social media, specifically regarding COVID-19. Sadly, in addition to misinforming, the written word can also beget violence.

Irrespective of an individual's degree, expertise, or the lack of scientific evidence, the written word, once posted, is emboldened in many a mind and is often more indelible than reliable information that is substantiated. While one can ponder reasons many are drawn toward negativity (evolutionary survival instincts) or why conspiracy theories are immensely popular (fear of a tyrannical leadership), one fact remains – once a seed of social medial influence is planted, the roots exponentially grow in a malignant manner.

> "Hesitancy and skepticism prevail for many unvaccinated, **and women wanting to conceive are no exception.**"

Since its inception, the pandemic has wreaked havoc on the infertility population. First by causing temporary but devastating discontinuation of treatments since infertility procedures are deemed "nonurgent." Next, by women facing a self-imposed delay in pursuing pregnancy because of the dangers of COVID-19 in pregnancy and the unknown effects of the virus on a fetus. Lastly, and the focus of this article, by the fears in preconception and pregnant women of the vaccine causing infertility or, even, sterility.

As of this writing, we are amid the SARS-CoV-2 Delta variant surge of infections, reversing the course of prior improvements and optimism. Hospitalizations have spiked, with more than 95% of patients being unvaccinated; expectedly, deaths have also increased. Despite the vaccine for COVID-19 being available for over 7 months, only approximately 50% of the U.S. population is fully vaccinated – the highest category is for those aged 65 and older of whom 80% have completed their vaccination. Hesitancy and skepticism prevail for many unvaccinated, and women wanting to conceive are no exception.

Background of vaccine

In December 2020, the Food and Drug Administration granted emergency use authorization (EUA) to the Pfizer-BioNTech and Moderna vaccines, both of which are mRNA based so they do not contain live viral particles. This technology has been studied for over a decade and is novel by using the cell's transcription process to produce the particles that generate an immune response. The mRNA enters cells to create the "spike proteins" (the same used by the SARS-CoV-2 virus) that create the response for immunity.

Baseless claims

The same month of EUA for the vaccine, German physician Wolfgang Wodarg, who is a pulmonary specialist, and British pharmacologist Michael Yeadon, a former Pfizer chief science officer and respiratory research head, petitioned Europe's health regulator, the European Medicines Agency, to suspend clinical trials and approval of the Pfizer/BioNTech vaccine. The two cited baseless claims of female sterilization in an online blog that has since been removed. Their contention was the vaccine would induce the formation of antibodies against a protein called syncytin-1, which is involved in the development of the placenta in humans, and lead to infertility.

Although syncytin-1 is important for placenta formation, it bears no resemblance to the SARS-CoV-2 spike protein except for a very small amino acid sequence. Experts agree this similarity is not enough to trigger an immune response leading to female infertility. For additional reassurance, the vaccine does not contain syncytin-1, or the mRNA sequence for the protein, or code for the same protein to which the vaccine causes antibodies.

Reproductive risks

While occurrence of severe infections in pregnancy is, fortunately, low, pregnant women who experience a severe infection are at greater risk of ICU admission, mechanical ventilation, and death than are nonpregnant women. The pregnancy is at increased risk of preeclampsia, preterm birth, and still birth (Fertility and Sterility Dialogue, 2021 Jan 19 [https://tinyurl.com/kt9wndw7], and Fertil Steril. 2021 Jul;116[1]:16-24). There is limited evidence for impaired male reproductive health and fertility from COVID-19 infection. Of note, the SARS-CoV-2 virus is about 1 year old so the impact, if any, on reproductive potential following infection is still unknown.

Racial differences in reactions to vaccination

One in three women surveyed reported changing their fertility preferences because of the COVID-19 pandemic. Black or African American women were 5.45 times more likely than were White women to alter fertility timing and nonheterosexual women reported a 2.76 times higher likelihood of change compared with heterosexual women (Fertil Steril. 2021 Jul 26. doi: 10.1016/j.fertnstert.2021.05.092).

Women's health society responses

The COVID-19 vaccine is endorsed by ASRM, ACOG, and SMFM in a joint statement (ASRM Bulletin, Feb. 5, 2021). Further, the Centers for Disease Control and Prevention and Advisory Committee for Immunization Practices also support the vaccine for those planning to conceive or who are pregnant.

The ASRM Task Force qualifies its endorsement of the vaccine to be received without delay in women at the time they are undergoing fertility treatment, given the vaccine is not live. It is advised for women undergoing elective surgery or fertility-related procedures to defer the vaccine from 3 days before through 3 days after to avoid confusing a potential vaccine reaction (e.g., fever) to a procedural complication.

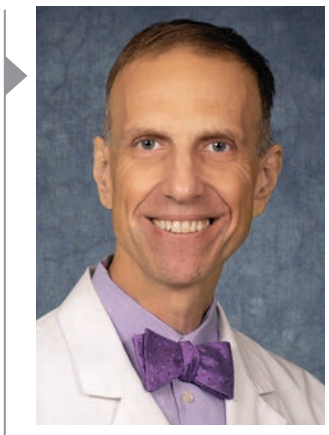
Conclusion

In summary, there is no evidence linking the SARS-CoV-2 vaccine to female infertility, risk of miscarriage (Am J Obstet Gynecol. 2020 Oct 7. doi: 10.1016/j.ajog.2020.10.005), or a significant decrease in any sperm parameter (JAMA. 2021;326[3]:273-4). Evidence also supports that protective antibodies to COVID-19 cross the placenta and provide protection to the baby after delivery (J Clin Invest. 2021 Jul 1. doi: 10.1172/JCI150319).

Those couples wanting to conceive, as well as pregnant women, should receive the COVID-19 vaccine to prevent general health morbidity and mortality, pregnancy risks to mother and fetus, and the potential risks to male reproductive health from actual COVID-19 disease.

Pregnant women were excluded from the initial vaccination studies but now are being enrolled in trials. Safety data accumulating from the FDA and the CDC through the Vaccine Adverse Event Reporting System (VAERS) have not shown adverse pregnancy outcomes from the vaccine.

The allure of sensationalism may continue to supersede integrity. Public opinion will presumably continue to have an ambivalent relationship with those who are in a position of authority or expertise. Those who can influence the choice of COVID-19 vaccinations should not be the most charismatic but be the most trusted. It is our mission to gain and maintain that trust, now more than ever. ■



Dr. Trolice is director of Fertility CARE: The IVF Center in Winter Park, Fla., and professor of obstetrics and gynecology at the University of Central Florida, Orlando.

"Safety data accumulating from the FDA and the CDC through the Vaccine Adverse Event Reporting System **have not shown adverse pregnancy outcomes from the vaccine.**"

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Pandemic demand soars for NPs, softens for primary care

BY MEGAN BROOKS

The COVID-19 pandemic has fueled a growing demand for nurse practitioners (NPs), while demand for primary care physicians has cooled, according to Merritt Hawkins' annual review of physician and advanced practitioner recruiting trends.

This marks the first time in the review's 28-year history that NPs have topped the list of the most recruited practitioners, according to the medical search firm. In the 27 prior years, physicians held the top spot. For the previous 14 years, the No. 1 position was held by family physicians.

"COVID-19 and other market forces are changing the dynamics of physician and advanced practitioner recruiting. NPs are coming into their own in a market that puts a premium on easy access to care and cost containment," Tom Florence, president of Merritt Hawkins, said in a statement.

Primary care 'recruiting frenzy' over

Mr. Florence said primary care physicians remain a "vital part of team-based care and will be increasingly responsible for coordinating the care of older patients with multiple chronic conditions. But the recruiting frenzy in primary care is over."

Merritt Hawkins says that overall COVID-19 has had a "severely inhibiting" effect on demand for physicians. The number of searches the company conducted dropped 25%, compared with 2020, and many hospitals and medical groups shut down or lost money during the pandemic.

But the drop-off in demand for physicians is likely to be temporary because the underlying dynamics driving physician supply and demand remain in place, according to the report. These include a growing and aging population, a limited supply of newly trained physicians, and an aging physician workforce.

Mr. Florence

> "COVID-19 and other market forces are changing the dynamics of physician and advanced practitioner recruiting. **NPs are coming into their own** in a market that puts a premium on easy access to care and cost containment."

COVID-19 will not permanently change these market conditions, and demand for physicians already is rebounding, the company said.

The 2021 review of physician and advanced practitioner recruiting is based on a representative sample of 2,458 permanent search engagements that Merritt Hawkins/AMN Healthcare's physician staffing companies conducted or were in the process of conducting during the 12-month period from April 1, 2020, to March 31, 2021.

Among the key findings:

- 18% of Merritt Hawkins' recruiting searches were for advanced practitioners, including NPs, physician assistants (PAs), and certified registered nurse anesthetists, up from 13% in the 2020 review. This represents the highest percentage in the 28 years the review has been conducted.
- About two-thirds (64%) of Merritt Hawkins' search engagements were for physician specialists, including radiologists, psychiatrists, gastroenterologists, and others, "highlighting the robust demand for specialty physicians."
- In 2021, 18% of Merritt Hawkins' search engagements were for primary care physicians, down from 20% in 2020 and 22% in 2019, "signaling a relative decline in demand for primary care doctors."
- Psychiatrists placed fourth on the list of most requested search engagements, a sign of continued strong demand for mental health professionals that is likely to accelerate because of COVID-19.

Starting salaries take a pandemic hit

Because of the reduced demand for practitioners, starting salaries decreased for many types of health care professions, with the exception of NPs and PAs.

Average starting salaries for NPs showed strong growth, increasing 12% year over year, from $125,000 to $140,000. The average starting salaries for PAs also showed strong growth, increasing by 14% year over year, from $112,000 to $128,000.

Among physicians, interventional cardiologists were offered the highest average starting salaries, at $611,000, followed by orthopedic surgeons, at $546,000. Pediatricians were offered the lowest average starting salaries, at $236,000.

Merritt Hawkins said only 3% of their search engagements were for solo practice or partnership settings, "underscoring the decline of physician private practice."

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Physicians wearing white coats rated more experienced

BY DIEDTRA HENDERSON
FROM JAMA NETWORK OPEN

PHYSICIANS WEARING white coats were rated as significantly more experienced and professional than peers wearing casual attire. Regardless of their attire, however, female physicians were more likely to be judged as appearing less professional and were more likely to be misidentified as medical technicians, physician assistants, or nurses, found research published in JAMA Network Open (2021 Jul 30. doi: 10.1001/jamanetworkopen.2021.17779).

"A white coat with scrubs attire was most preferred for surgeons (mean preference index, 1.3), whereas a white coat with business attire was preferred for family physicians and dermatologists (mean preference indexes, 1.6 and 1.2, respectively; $P < .001$)," Helen Xun, MD, Johns Hopkins University, Baltimore, and colleagues wrote. "A male model wearing business inner wear with a white coat, fleece jacket, or softshell jacket was perceived as significantly more professional than a female model wearing the same attire (mean professionalism score: male, 65.8; female, 56.2; mean difference in professionalism score: white coat, 12.06; fleece, 7.89; softshell, 8.82; $P < .001$). ... A male model wearing hospital scrubs or fashion scrubs alone was also perceived as more professional than a female model in the same attire."

While casual attire, such as fleece or softshell jackets emblazoned with the names of the institution and wearer, has become more popular attire for physicians in recent years, the researchers noted theirs is the first published research to identify associations between gender, attire, and how people distinguish between various health care roles.

The study authors launched their web-based survey from May to June 2020 and asked people aged 18 years and older to rate a series of photographs of deidentified models wearing health care attire. Inner wear choices were business attire versus scrubs with and without outer wear options of a long white coat, gray fleece jacket, or black softshell jackets. Survey respondents ranked the images on a 6-point Likert scale with 1 being the least experienced, professional, and friendly and 6 being the most experienced, professional, and friendly. Survey respondents also viewed individual images of male or female models and were asked to rate their professionalism on a scale of 0-100 – with 100 as the "most professional" as well as to identify their profession as either physician, surgeon, nurse, medical technician, or physician assistant.

The study team included 487 (93.3%) of 522 completed surveys in their analyses. Respondents' mean age was 36.2 years; 260 (53.4%) were female; 372 (76.4%) were White; 33 (6.8%) were Black or African American. Younger respondents and those living in the Western United States who had more exposure to physician casual attire appeared more accepting of it, the authors wrote.

"I remember attending my white-coat ceremony as a medical student, and the symbolism of it all representing me entering the profession. It felt very emotional and heavy and I felt very proud to be there. I also remember taking a 'selfie' in my long white coat as a doctor for the first time before my first shift as a resident. But, I've also been wearing that same white coat, and a large badge with a 'DOCTOR' label on it, and been mistaken by a patient or parent for something other than the physician," Alexandra M. Sims, a pediatrician and health equity researcher in Cincinnati, said in an interview. "So, I'd really hope that the take-home here is not simply that we must wear our white coats to be considered more professional. ... Women, people of color, and other marginalized groups were certainly not a part of the defining, but we must be a part of the reimagining of an equitable health care profession in this new era."

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