VULVOVAGINAL DISEASE

Vulvovaginitis

Diagnosis and treatment of recurrent or chronic cases

Oluwatosin Goje, MD

CONTRACEPTION

Payment for contraceptive services at safety net clinics

LIFE TRANSITIONS

Connecting diet to menopause symptoms

OBSTETRICS

Coronavirus and pregnancy: Expert commentary

WELL WOMAN

Breast density laws and patient knowledge

GYNECOLOGY

PARPi and epithelial ovarian cancer
OVER A YEAR OF PATIENT EXPERIENCE\textsuperscript{1}

\textbf{ORILISSA\textsuperscript{®} (elagolix)} is indicated for the management of moderate to severe pain associated with endometriosis.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**
- ORILISSA is contraindicated in women who are pregnant (exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss), in women with known osteoporosis or severe hepatic impairment, or with concomitant use of strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil).

**WARNINGS AND PRECAUTIONS**

**Bone Loss**
- ORILISSA causes a dose-dependent decrease in bone mineral density (BMD), which is greater with increasing duration of use and may not be completely reversible after stopping treatment.
- The impact of ORILISSA-associated decreases in BMD on long-term bone health and future fracture risk is unknown. Consider assessment of BMD in patients with a history of low-trauma fracture or other risk factors for osteoporosis or bone loss, and do not use in women with known osteoporosis.
- Limit the duration of use to reduce the extent of bone loss.

**Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy**
- Women who take ORILISSA may experience a reduction in the amount, intensity, or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of pregnancy in a timely manner. Perform pregnancy testing if pregnancy is suspected, and discontinue ORILISSA if pregnancy is confirmed.

**Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders**
- Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials.
- ORILISSA users had a higher incidence of depression and mood changes compared to placebo and ORILISSA users with a history of suicidality or depression had an increased incidence of depression. 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 ORILISSA if such events occur.

\*Statistical significance for dyspareunia was not achieved with the 150 mg QD dose of ORILISSA.
OVER 10,000 HCPs HAVE ALREADY PRESCRIBED ORILISSA FOR MORE THAN 30,000 patients

ORILISSA may be appropriate for patients with unresolved endometriosis pain who have failed first-line medical management options such as one course of birth control or NSAIDs

“On ORILISSA, I have less pain. I hope my experience empowers other women and gives them hope that there are other options out there.”

— Darby, a real patient taking ORILISSA

These data reflect the number of HCPs who have prescribed and the number of women prescribed since ORILISSA was FDA-approved. Data were sourced as of September and October 2019, respectively.

Hepatic Transaminase Elevations
- In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range occurred with ORILISSA.
- Use the lowest effective dose and instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice.
- Promptly evaluate patients with elevations in liver tests to determine whether the benefits of continued therapy outweigh the risks.

Reduced Efficacy with Estrogen-Containing Contraceptives
- Based on the mechanism of action of ORILISSA, estrogen-containing contraceptives are expected to reduce the efficacy of ORILISSA. The effect of progestin-only contraceptives on the efficacy of ORILISSA is unknown.
- Advise women to use non-hormonal contraceptives during treatment and for one week after discontinuing ORILISSA.

ADVERSE REACTIONS
- The most common adverse reactions (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions, and mood changes.
- These are not all the possible side effects of ORILISSA. Safety and effectiveness of ORILISSA in patients less than 18 years of age have not been established.

Get your patients started with a Savings Card at ORILISSA.com/hcp


Please see Brief Summary of full Prescribing Information on the following page of this advertisement.
ORILISSA® (elagolix) tablets, for oral use

INDICATIONS AND USAGE
ORILISSA is indicated for the management of severe pain associated with endometriosis.

DOSEAGE AND ADMINISTRATION

Important Dosing Information
- Exclude pregnancy before starting ORILISSA or start ORILISSA within 7 days of the onset of menstruation.
- Take ORILISSA at approximately the same time each day, with or without food.
- Use the lowest effective dose, taking into account the severity of symptoms and treatment objectives (see Warnings and Precautions).
- Limit the duration of use because of bone loss (see Table 1) (see Warnings and Precautions).

Table 1. Recommended Dosage and Duration of Use

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Maximum Treatment Duration</th>
<th>Concomitant Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate treatment with ORILISSA 150 mg once daily</td>
<td>6 months</td>
<td>Ovarian cysts</td>
</tr>
<tr>
<td>Consider initiating treatment with ORILISSA 200 mg twice daily</td>
<td>6 months</td>
<td>Ovarian cysts</td>
</tr>
<tr>
<td>Initiate treatment with ORILISSA 150 mg once daily</td>
<td>200 mg twice daily is not recommended</td>
<td>Ovarian cysts</td>
</tr>
</tbody>
</table>

Hepatic Impairment
No dosage adjustment of ORILISSA is required in women with mild hepatic impairment (Child-Pugh B). ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) (see Contraindications and Use in Specific Populations).

Missed Dose
Instruct the patient to take a missed dose of ORILISSA on the same day as soon as she remembers and then resume the regular dosing schedule.

150 mg once daily: take no more than 1 tablet each day.
200 mg twice daily: take no more than 2 tablets each day.

CONTRAINDICATIONS
ORILISSA is contraindicated in women:
- Who are pregnant (see Use in Specific Populations).
- Exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss.
- With known osteoporosis because of the risk of further bone loss (see Warnings and Precautions).
- With known hepatic impairment (see Use in Specific Populations).
- With or without simultaneous use of strong CYP3A inhibitors because of the risk of liver injury in case of accidental overdose.

WARNINGS AND PRECAUTIONS

Bone Loss
ORILISSA causes a dose-dependent decrease in bone mineral density (BMD). BMD loss is greater with increasing duration of use and may not be completely reversible upon stopping treatment (see Adverse Reactions). The impact of these BMD decreases on long-term bone health and future fracture risk is unknown. Consider assessment of BMD in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss, and in women with known osteoporosis. Limit the duration of use to reduce the extent of bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such therapy may be beneficial for all patients.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy
Women who take ORILISSA may experience a reduction in the amount, intensity, or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of a pregnancy in a timely manner (see Adverse Reactions). Perform pregnancy testing if pregnancy is suspected, and discontinuation of ORILISSA is confirmed.

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders
Suicidal ideation, suicidal behavior, and exacerbation of mood disorders (see Warnings and Precautions).

Hepatic Transaminase Elevations
In clinical trials, double-blind, placebo-controlled clinical trials (EM-1 [NCT01505236] and EM-2 [NCT01519167]) in which a total of 152 adult women with moderate to severe endometriosis treated with ORILISSA 150 mg once daily, and 2% of subjects treated with ORILISSA 200 mg twice daily had transaminase elevations greater than 10 times ULN.

Drug Interactions
Class-specific effects of proton pump inhibitors, oral contraceptives, benzodiazepines, and rifampin on elagolix are studied.

OVERDOSAGE

Lipids
Lipid increases occurred within 1 to 2 months after the start of ORILISSA therapy (see Warnings and Precautions).

 Drug Class: Proton pump inhibitors

ORILISSA 150 mg once daily ORILISSA 200 mg twice daily Placebo

 Triglycerides (mg/dL) 140 210 120

Dosage in Patients with Renal Impairment
In the blinded extension Study EM-4, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 4% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

In Study EM-2, compared to placebo, the mean change from baseline lumbar spine BMD at 6 months was -2.7% (95% CI: -3.1, -2.3) with ORILISSA 150 mg once daily and -3.7% (95% CI: -3.3, -3.2) with ORILISSA 200 mg twice daily (Table 3). The percentage of subjects with greater than 9% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was < 1% with ORILISSA 150 mg once daily, 6% with ORILISSA 200 mg twice daily and 0% with placebo. In the blinded extension Study EM-4, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 2% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

Table 2. Percent Change from Baseline in Lumbar Spine BMD at Month 6

[Table 2 not visible]

Table 3. Percent Change from Baseline in Lumbar Spine BMD at Month 6

[Table 3 not visible]
Suicide Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

In the placebo-controlled clinical trials (Studies EM-1 and EM-2), there were no reports of suicide. Among the 2092 subjects exposed to ORILISSA in the endometriosis Phase 2 and Phase 3 studies, there were four reports of suicide ideation. In addition to the two subjects in Table 2, there were two additional reports of suicide ideation: one subject in EM-1 (150 mg once daily) and one in a Phase 2 study (75 mg once daily, as unapplied dose). Three of these subjects had a history of depression. Two subjects discontinued ORILISSA and two continued the clinical trial treatments.

Hepatic Transaminases Elevations

In the placebo-controlled clinical trials (Studies EM-1 and EM-2), hepatic transaminases elevations (ALT ≥ 3 times the upper limit of the reference range) occurred during treatment with ORILISSA (150 mg once daily – 1.50%, 0%, 2%, 0%, 0%, 2%, 0%, 0%, 1.1%, placebo – 1.0%, 0.1%). Similar increases were seen in the extension trials (Studies EM-3 and EM-4).

Changes in Lipid Parameters

Dose-dependent increases in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were noted during ORILISSA treatment in EM-1 and EM-2. In EM-1, 3%-11% of subjects with elevated LDL-C (≥ 150 mg/dL) at baseline had an increase in LDL-C concentrations to ≥ 150 mg/dL or, at higher concentrations with treatment with ORILISSA and placebo, respectively. In EM-1 and EM-2, 2%-4% of subjects with elevated serum triglycerides (≥ 300 mg/dL) at baseline had an increase in serum triglycerides ≥ 500 mg/dL or, at higher concentrations with treatment with ORILISSA and placebo, respectively. The highest reported serum triglyceride concentrations during treatment with ORILISSA were 718 mg/dL (EM-1) and 994 mg/dL (EM-2).

Table 5. Mean Change and Maximum Increase from Baseline in Serum Lipids in Studies EM-1 and EM-2

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>ORILISSA 150 mg N=492</th>
<th>ORILISSA 200 mg N=747</th>
<th>Placebo N=734</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>Mean change at Month 6</td>
<td>5</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>Maximum increase during Treatment Period</td>
<td>137</td>
<td>107</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>Mean change at Month 6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Maximum increase during Treatment Period</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>Mean change at Month 6</td>
<td>-1</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>Maximum increase during Treatment Period</td>
<td>684</td>
<td>624</td>
</tr>
</tbody>
</table>

Increased body weight was observed in 7% of subjects after the start of ORILISSA and remained stable thereafter over 12 months.

Hyperprolactinemia Reactions

In Studies EM-1 and EM-2, no serious hyperprolactinemia reactions including rash occurred in 9.8% of ORILISSA-treated subjects and 6.1% of placebo-treated subjects. These subjects may have had drug discontinuations in 6.4% of ORILISSA-treated subjects and 0.5% of placebo-treated subjects.

Experiential Effects

Experientialalogues were observed in studies in Study EM-1 and its extension at Month 6 and Month 12. These analogues showed a dose-dependent decrease in protein and anxiety-like symptoms and an increase in nausea/maximum stimulated appetite patterns. There were no abnormal findings on treatment, such as endometrial hyperplasia or cancer.

Effects on menstrual bleeding patterns

The effects of ORILISSA on menstrual bleeding were evaluated for up to 12 months in nine clinical and one randomized open-label study where subjects classified their flow of menstrual bleeding of the last 24 hours as spotting, light, normal, heavy, or missing. The dose-response relationship is shown in Table 4. In general, the bleeding and spotting decreased with higher doses of ORILISSA up to 200 mg twice daily.

Table 6. Mean Bleeding/Spotting Days and Mean Intensity Scores at Month 3

<table>
<thead>
<tr>
<th>Dose Range</th>
<th>Spotting Days</th>
<th>Mean Intensity (0-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORILISSA 150 mg daily</td>
<td>2.6</td>
<td>2.2</td>
</tr>
<tr>
<td>ORILISSA 200 mg daily</td>
<td>2.0</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Table 7. Established Drug Interactions Based on Drug Interaction Trials

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Inhibitors</td>
<td>Benzodiazepines</td>
<td>Inhibitors</td>
<td>Digoxin</td>
<td>Inhibitors</td>
</tr>
</tbody>
</table>

ORILISSA also demonstrated a dose-dependent increase in the percentage of women with vaginal spotting or spotting in a 56-day (≤1 time per week) interval over the treatment period. The incidence of amenorrhea during the first six months of treatment with ORILISSA 150 mg once daily, 15.2%-15.9% for ORILISSA 200 mg twice daily and 1.7%-1.6% for placebo. During the second six months of treatment, the incidence of amenorrhea ranged from 11.1%-11.5% for ORILISSA 150 mg once daily and 13.5%-12.0% for ORILISSA 200 mg twice daily and less than 1% for placebo. During the two subjects in Table 2, the incidence of amenorrhea ranged from 11.1%-11.5% for ORILISSA 150 mg once daily and 46.5%-45.9% for ORILISSA 200 mg twice daily. After 6 months of therapy with ORILISSA 200 mg twice daily, resumption of menses after stopping treatment was reported by 59%, 87% and 95% of women within 1, 2, and 6 months of therapy, respectively, with ORILISSA 200 mg twice daily, resumption of menses after stopping treatment was reported by 60%, 86%, and 91% of women within 1, 2, and 6 months, respectively. After 12 months of therapy with ORILISSA, 150 mg twice daily or resumption of menses after stopping treatment was reported by 50%, 91% and 96% of women within 1, 2, and 6 months, respectively.

DRUG INTERACTIONS

Potential for ORILISSA to Affect Other Drugs

Elagolix is a weak to moderate inducer of CYP2C9, CYP2C19, CYP3A4, and CYP3A5. Co-administration with ORILISSA may decrease plasma concentrations of drugs that are substrates of CYP3A4 (e.g., azole antifungals). Elagolix is an inhibitor of CYP2B6. Co-administration with ORILISSA may increase plasma concentrations of drugs that are substrates of CYP2B6 (e.g., verapamil).

Potential for Other Drugs to Affect ORILISSA

Elagolix is a substrate of P-glycoprotein (P-gp). Concomitant use of ORILISSA 200 mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limited concomitant use of CYP3A substrates is recommended when used concurrently with ORILISSA 200 mg twice daily. Co-administration of ORILISSA with drugs that induce CYP3A may decrease elagolix plasma concentrations.

The effect of concomitant use of P-gp inhibitors or inducers on the pharmacokinetics of ORILISSA is unknown. Co-administration with drugs that inhibit CYP3A11 may increase elagolix plasma concentrations. Concomitant use of elagolix with strong CYP3A11 inhibitors (e.g., cyclosporine and gefitinib) is contraindicated.

Drug Interactions - Examples and Clinical Management

Table 7 summarizes the effects of co-administration of ORILISSA on concentrations of concomitant drugs and the effect of concomitant drugs on ORILISSA.

USE IN SPECIFIC POPULATIONS

Pregnancy

ORILISSA Exposure Registry

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. There is no information on the presence of elagolix or its metabolites in human milk.

Lactation

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. There is no information on the presence of elagolix or its metabolites in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s need to take ORILISSA. ORILISSA is not known to be excreted in breast milk.

Ortho Molecular (82535)
male and female (and liver only) tumors at the high dose (12 to 13-fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans.

Elagolix was not genotoxic or mutagenic in a battery of tests, including the in vitro bacterial reverse mutation assay, the in vitro mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, and the in vivo mouse micronucleus assay. In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/day in female rats is approximately 5-fold. However, because elagolix has low affinity for the GnRH receptor in the rat (see Use in Specific Populations), and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

**PATIENT COUNSELING INFORMATION**

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

- Advise patients on contraceptive options, not to get pregnant while using ORILISSA, to be mindful that menstrual changes could reflect pregnancy and to discontinue ORILISSA if pregnancy occurs (see Contraindications and Warnings and Precautions).

- There is a pregnancy registry that monitors outcomes in women who become pregnant while treated with ORILISSA. Inform patients they can enroll by calling 1-833-782-7241 (see Use in Specific Populations).

- Inform patients that estrogen-containing contraceptives are expected to reduce the efficacy of ORILISSA.

- Inform patients about the risk of bone loss. Advise adequate intake of calcium and vitamin D (see Warnings and Precautions).

- Advise patients to seek immediate medical attention for suicidal ideation and behavior. Instruct patients with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention (see Warnings and Precautions).

- Counsel patients on signs and symptoms of liver injury (see Warnings and Precautions).

- Instruct patients who miss a dose of ORILISSA to take the missed dose on the same day as soon as she remembers and then resume the regular dosing schedule:
  - 150 mg once daily: no more than 1 tablet each day should be taken.
  - 200 mg twice daily: no more than 2 tablets each day should be taken.

- 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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North Chicago, IL 60064
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Ref: 03-C007 Revised: August, 2019
LAB-2621 MASTER
CHAIRMAN’S LETTER

In the Face of a Pandemic

We are experiencing a transformative period with fundamental changes taking place. Humanity is managing a pandemic the likes of which has not been seen since the 1918 influenza outbreak when one-third of the world’s population was infected with an H1N1 virus that had genes of an avian origin, according to the Centers for Disease Control and Prevention. That outbreak resulted in about 50 million deaths worldwide, with about 675,000 in the United States.

COVID-19 is testing all of us and our systems. But we will get through this, emerging stronger because what will prevail is the miracle of modern medicine fueled by human ingenuity. In this issue of Contemporary OB/GYN, our new Editor in Chief, Dr. Catherine Spong, makes her debut. She supports innovative solutions for addressing COVID-19 in her commentary starting on page 9. We also present special commentary on this novel virus from Dr. Sarah Dotters-Katz and Dr. Brenna Hughes, whose research expertise is infectious disease in pregnancy. These doctors are on the front lines of this national emergency, responding to the needs of pregnant women at a time when available data are insufficient for assessing the risk specific to this population.

As you engage in patient care, stay safe, remain vigilant, and let us know what you are seeing on the front lines by contacting Senior Editor Angie DeRosa at aderosa@mjhlifesciences.com.

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Chairman and Founder, MJH Life Sciences
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THE EDITORS ARE PLEASED TO ANNOUNCE the availability of our parent company’s continuing education activities. We’ve picked this one especially for our readers - http://bit.ly/BreastCancerCME
Multimodal pain management with EXPAREL provided significantly better pain control after C-section vs multimodal protocols alone\(1,2\) and...

**Indication**

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

**Important Safety Information**

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting; adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via interscalene brachial plexus nerve block were nausea, pyrexia, and constipation. If EXPAREL and other non-bupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine. EXPAREL is not recommended to be used in the following patient population: patients \(<18\) years old and/or pregnant patients. Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease.

**Warnings and Precautions Specific to EXPAREL:** Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL. EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks other than interscalene brachial plexus nerve block, or intravascular or intra-articular use. The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days, as seen in clinical trials.

**Warnings and Precautions for Bupivacaine-Containing Products**

**Central Nervous System (CNS) Reactions:** There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression. **Cardiovascular System Reactions:** Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias, sometimes leading to death. **Allergic Reactions:** Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. **Chondrolysis:** There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use. **Methemoglobinemia:** Cases of methemoglobinemia have been reported with local anesthetic use.

Please refer to brief summary of full Prescribing Information on adjacent page.

**Full Prescribing Information is available at www.EXPAREL.com.**

For more information, please visit www.EXPAREL.com or call 1-855-RX-EXPAREL (793-9727).

**References:**


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Parsippany, NJ 07054   PP-EX-US-4978   07/19

**EXPAREL**

(bupivacaine liposome injectable suspension)

**OPIOID FREE**
### Examples of Drugs Associated with Methemoglobinemia:

Other than bupivacaine as noted above, EXPAREL should not be admixed with other drugs prior to administration.

**Water and Ionic Agents:**

Do not dilute EXPAREL with water or other hypotonic agents, as it will result in dilution of the liposomal components and release of bupivacaine HCl.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

There are no studies conducted with EXPAREL in pregnant women. In animal reproduction studies, exposure to bupivacaine HCl in rabbits, rats, and mice was associated with increased postnatal mortality (45/100) and decreased pup survival (35/100) at the highest dose studied (10 to 15 times the maximum human dose (MHD)). These effects on pup survival were not observed at lower doses studied.

**Breastfeeding**

EXPAREL is excreted in breast milk in low concentrations and is not expected to have a clinically meaningful effect on the breastfed infant. Breastfeeding should be considered along with the mother's clinical need for EXPAREL and the potential for serious adverse reactions in the breastfed infant. No data are available on the effects of EXPAREL on milk production. The developmental and health benefits of breastfeeding should be considered when the clinical need for EXPAREL or Bupivacaine HCl is determined for the mother.

**Nursing**

The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 30mg (0.6 mL), and is based upon the following factors:

- **Size of the surgical site**
- **Volume required to cover the area**

**Individual patients’ factors that may impact the safety of an local anesthetic**

As general guidance in selecting the proper dose, two examples of infiltration dosing is provided:

- In patients undergoing bunionectomy, a total of 150 mg (3 mL) of EXPAREL was administered with 7 mL infiltrated into the tissues surrounding the involved bunion.
- In patients undergoing hemorroidectomy, a total of 50 mg (0.8 mL) of EXPAREL was administered with 2 mL infiltrated into the tissues surrounding the involved hemorroid.

**Patent Numbers:**

The toxic effects of these drugs are additive and their administration should be considered in the clinical situation (including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity). When used in the same anesthetic technique, other drugs that affect the central nervous system or the cardiovascular system may heighten the toxic effect of EXPAREL.
I am honored and delighted to be writing the first of what I hope will be many editorials for *Contemporary OB/GYN*. Honored in part due to the legacy of the magazine – following in the steps of Drs. John T. Queenan and Charles J. Lockwood. As the founding Editor in Chief, Dr. Queenan developed a treasured resource for learners, practitioners, and educators. His successor, Dr. Lockwood, added two decades of success along with national publishing awards. I feel the weight of their incredible foresight and accomplishments in bringing *Contemporary OB/GYN* to the prominence it holds. Further, in a time of unprecedented national chaos, the opportunity to provide a voice and guidance is humbling.

I am also honored and delighted as I know *Contemporary OB/GYN* to be a leader in disseminating practical information to ob/gyns caring for patients. Having the ability to participate in such an endeavor is wonderful. As a past member of *Contemporary OB/GYN*’s editorial board, I live and believe in the magazine’s guiding principles: to provide concise, clear, and simple information on complex topics, decipher the myriad of new studies and data, and provide context to understand how and if they should change our care and management. I am eager to continue our partnerships with the American College of Obstetricians and Gynecologists and other professional societies to provide a venue through which they can disseminate their guidelines and opinions.

My vision for *Contemporary OB/GYN* is simple: to build on our strengths, adapt to current learners, address topical issues by experts in the field, and expand venues for information dissemination. We will maintain the caliber of the publication – credible peer-reviewed sources providing clear, concise, plain-language insight on topics of daily interest to ob/gyns in day-to-day practice. I am eager to expand our online presence and create multiple modalities for learning.

As an example of timely topics, this issue features an article by Drs. Sarah Dotters-Katz and Brenna Hughes on COVID-19, the coronavirus – a pandemic and national emergency – that has challenged us in ways unprecedented in our lifetime. The impact on communities has been stark – schools closed, colleges cancelling all in-person classes and moving to remote learning for the next semester, community events, places of worship, and gatherings cancelled. In order to work we are challenged to find care for our children, and many people are not working due to these changes, impacting financial stability.

It is critical that we all keep abreast of the ever-changing guidelines for COVID-19 as we grapple with the pandemic. The Centers for Disease Control and Prevention has classified those at highest risk: older adults and people with serious chronic medical conditions including heart disease, diabetes, and lung disease.1 We may have patients who are high risk, and equally important, our low-risk patients may be in contact with these individuals. We recognize that they include some of our patients and – equally importantly – are often in regular contact with our patients. Therefore, preventing disease in all of our patients is essential. Furthermore, although the available studies on COVID-19 in pregnancy do not suggest an increased risk for pregnant women, they are small. The physiologic and immunologic changes in pregnancy are known to be associated with a heightened susceptibility to viral respiratory illnesses and some of those illnesses, such as influenza, are more severe in pregnancy. Thus, extra vigilance for our pregnant women is important.

In this time of great risk for so many, we must employ novel and innovative solutions.

What should we do? In this time of great risk for so many, we must employ novel and innovative solutions. How COVID-19 is transmitted is not fully understood, but clearly there is person-to-person spread through respiratory droplets, which is what
prompted recommendations to limit contacts, avoid groups, and practice "social isolation" – staying 6 feet away from others. Decreasing the number of people in our waiting rooms is a first step. For gynecology patients, routine visits should be cancelled and we should provide a venue for telephone consultations instead of visits for all non-emergent issues. All elective surgeries should be postponed, to reduce transmission and also the burden on hospital systems.

As we navigate the hospital ward, our patients and rounds are more complicated.

For our obstetrical patients, the necessity of alternative strategies is even more compelling. Prenatal visits, sonograms, and antenatal testing should be spaced out in pregnancies that are uncomplicated. This can include replacing visits with phone calls and/or video visits and home monitoring of fetal movements and blood pressure – either with home devices or those available at grocery stores/pharmacies – with effective communication concerning values and the ability to contact us with questions. In alignment with World Health Organization recommendations, consideration of five visits in person and three virtual visits is reasonable for low-risk women.2

Although a reduction in in-person visits is best for stemming transmission, it comes with a price as reimbursement may not be available for remote services. A number of professional societies are actively working on ways to address this concern.

Further compounding the crisis is the lack of available test kits, which increases the burden on the medical system. How many of the patients we treated as presumed flu who were negative for influenza A and B actually had coronavirus? As we navigate the hospital ward, our patients and hospital rounds are more complicated. The medicine service hospitalizes only the most ill and can group providers to mitigate spread. Generally, patients seen by ob/gyns are hospitalized for another reason – delivery, a pregnancy complication, an emergent gynecologic condition. They may also have respiratory symptoms but are not ill enough to be tested. Although monitored for worsening symptoms (such as fever) that might increase suspicion of COVID-19 infection, fewer precautions are taken initially. Given our limited resources – both human and facility – this is logical; however, without testing, we risk exposing others to the disease, problematic because this will not be realized until their disease worsens and testing is obtained. Importantly, we should advocate for our patients. In clinicaltrials.gov there are 51 studies listed aimed at understanding COVID-19 and evaluating therapies for it (search terms: coronavirus or COVID).3 Of these, 34 (66%) exclude pregnant women and 26 (51%) exclude lactating women. Incredibly, pregnant and lactating women are excluded even from observational studies evaluating prognostic factors in patients with COVID-19 (ClinicalTrials.gov Identifier: NCT04292964). Despite federal interest in closing gaps in knowledge and research on safe and effective therapies for pregnant and lactating women with the establishment of the Task Force on Research Specific to Pregnant Women and Lactating Women (https://www.nichd.nih.gov/about/advisory/PRGLAC), the sole study (ClinicalTrials.gov Identifier: NCT04280705) launched by the National Institutes of Health excludes both pregnant and lactating women. It is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of Remdesivir. However, another study of the same drug (ClinicalTrials.gov Identifier: NCT04292899) does not exclude pregnant or lactating women. We must advocate for inclusion, as not collecting information in our populations prevents accumulation of data to best guide therapies.

Finally, we all must take responsibility for reducing risk to ourselves and others. Though it seems somewhat trite, the need for frequent and effective washing of our hands – for at least 20 seconds – cannot be overstated. Furthermore, other hygiene essentials – avoid touching your face, sneeze into your elbow -- are important. Even those at low risk must practice these measures to avoid transmission to those in high-risk groups. Avoiding crowds, not touching high-touch surfaces in public places, and cancelling non-essential travel may help flatten the curve of transmission.

As we enter into this new normal, I am on the journey with you. I welcome your ideas and insights.

Catherine Y. Spong

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FOR REFERENCES VISIT contemporaryobgyn.net/HotelInNewEra
Sars-CoV-2, known more commonly as COVID-19, is a global pandemic, with over 200,000 confirmed cases, nearly 9,000 deaths, and likely numerous more undiagnosed infections at this writing. Treatment options are limited, no vaccine has yet been developed, and no herd immunity exists. The best protection against spread of the virus that we have currently is social distancing and careful handwashing. These practices, along with the virulence and infectivity of this virus, are changing how we act, live, and practice medicine.

COVID-19 is part of a group of common viruses, coronaviruses, which are well known to cause upper respiratory illness. But COVID-19 is novel in that it appears to cause more severe infection than other coronaviruses. After exposure, the incubation period is 2 to 14 days. About 2% of people who are exposed will develop disease. Symptoms of infection include fever, cough, shortness of breath, and gastrointestinal symptoms. Of those infected, approximately 20% become critically ill. Individuals who are older, and/or have chronic medical conditions are at increased risk of this. Mortality is thought to be anywhere from 1% to 4% depending on the country and community, and dramatically increases with age (Figure 1). At the time of this writing, little is known about how COVID-19 impacts pregnancy. Based on available data, it does not appear to be more severe in pregnant women. A World Health Organization report from China, which included 150 women, found 8% had severe infection (respiratory rate above 30 or oxygen saturation less than 93%) and only 1% required mechanical ventilation. However, other coronaviruses, such as SARS and MERS, as well as other respiratory viruses, such as influenza, are associated with more severe disease, as well as increased maternal morbidity and mortality. This virus, as well as other respiratory viruses, have not been associated with miscarriage or congenital anomalies. Although data are mixed, any fever in the first trimester may be associated with congenital malformations.

Preterm delivery (36 weeks) was reported from some of the early cases from China, although it may have been iatrogenic and not related to spontaneous preterm birth. In these studies, no virus was found in amniotic fluid, cord blood, or breast milk. However, the studies are small and more data are needed. There is currently no evidence of vertical transmission. However, there are reports of positive tests on newborns hours after delivery following negative tests that were obtained at delivery. This suggests possible maternal contamination at the time of testing although there is potential for respiratory transmission soon after birth from close contact with an infected mother. Temporary separation of
neonate from an infected mother should be considered until the infectivity period ends. This extends to mothers exposed to COVID-19, with the separation extending from immediately after delivery until the mother’s infectivity period ends. In this setting, pumping with bottle feeding by a non-infected caregiver is recommended because breast milk is still thought to be the best nutrition source for infants and provides protection against other illnesses. If a mother chooses to breastfeed rather than separate, she should wear a mask while doing so.

At this time, low-risk patients who present with mild infection, including pregnant women, do not need to be hospitalized. Infection, even if severe, is not necessarily an indication for delivery. In fact, for the low-risk patient with COVID-19 infection, postponing delivery until infectivity is over should be considered, unless delivery is medically indicated. For women with first- or second-trimester infection who recover, assessment of fetal growth by ultrasound can be considered in the third trimester.

As far as infection mitigation, it is clear that social distancing is very effective. This includes minimizing group activities, meeting electronically when possible, and avoiding crowds and public places. If meeting in person is necessary, social distancing is the advised approach, and that specifically means staying at least 6 feet away from the nearest person. Practicing good hand hygiene is also critical. Washing your hands for 20 seconds with soap and water or using hand sanitizer is a best practice. As much as possible, frequently cleaning commonly used surfaces – including computers, keyboards, cell phones, light switches, doorknobs, and other surfaces – with disinfectants is another important prevention technique. At this time, travel is also strongly discouraged.

For pregnant patients, many practices are spacing out prenatal care visits for low-risk patients as well as cohorting sick patients in a separate setting. Well-woman exams and routine screening appointments are also being rescheduled in many offices to better adhere to social distancing practices, although acute gynecologic problem-visits should still be done to avoid overcrowding in the emergency room. Telehealth, phone visits, and video visits are other effective ways to provide care for the appropriate patients.

COVID-19 presents a significant threat to our communities, our patients, and our families. As the pandemic continues, more will be learned about how this virus behaves and what we can do to keep ourselves and our patients safe.

Dr. Brenna Hughes is a maternal-fetal medicine specialist at Duke Health in Durham, N.C. Her research expertise is infectious diseases in pregnancy.

Dr. Sarah Dotters-Katz is a maternal-fetal medicine specialist at Duke Health in Durham, N.C. whose research includes clinical infectious diseases and how they impact pregnancy.

FOR REFERENCES VISIT contemporaryobgyn.net/COVID19pathogen

LAPAROSCOPIC EXCISION OF TRANSMURAL RECTAL ENDOMETRIOSIS
In this video, Jon Einarsson, MD, PhD MPH, discusses his work to develop a less invasive technique for removal of the transmural bowel nodules.

contemporaryobgyn.net/RectalEndometriosis
BIJUVA is an oral combination of estradiol and micronized progesterone.

**ONE CAPSULE**
BIJUVA is a once-daily oral capsule—taken each evening with food—that fits easily into her daily routine and may improve compliance.

**ONE PRESCRIPTION**
BIJUVA combines 2 bio-identical* hormones in 1 capsule—with just 1 prescription.

**ONE AFFORDABLE TREATMENT**
Patients pay as little as $35†

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**INDICATION**
BIJUVA is a combination of estradiol and progesterone indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

**IMPORTANT SAFETY INFORMATION**

**WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER, ENDOMETRIAL CANCER, AND PROBABLE DEMENTIA**
See full prescribing information for complete boxed warning.

**Estrogen Plus Progestin Therapy**
- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia
- The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer
- The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older

**Estrogen-Alone Therapy**
- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia
- The WHI estrogen-alone substudy reported increased risks of stroke and DVT
- The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older

**CONTRAINDICATIONS**
- BIJUVA is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of cancer of the breast; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease (for example, stroke, MI), or a history of these conditions; known anaphylactic reaction, angioedema, or hypersensitivity to BIJUVA or any of its ingredients; known liver impairment or disease; known liver disease; known protein C, protein S, or antithrombin deficiency; or other known thrombophilic disorders.

Please note that this information is not comprehensive. Please see Brief Summary of the Full Prescribing Information, including BOXED WARNING, on the following pages.

**WARNINGS AND PRECAUTIONS**
- An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should these occur or be suspected, therapy should be discontinued immediately. Risk factors for arterial vascular disease and/or venous thromboembolism (VTE) should be managed appropriately.
- The WHI substudy of daily estrogen plus progestin after a mean follow-up of 5.6 years reported an increased risk of invasive breast cancer. Observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy after several years of use. The risk increased with duration of use and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). The use of estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.
- Endometrial hyperplasia (a possible precursor to endometrial cancer) has been reported to occur at a rate of approximately less than one percent with BIJUVA. Clinical surveillance of all women using estrogen plus progestin therapy is important. Adequate diagnostic measures should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.
- The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. Meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.
- In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin when compared to placebo. It is unknown whether these findings apply to younger postmenopausal women.
- Estrogens increase the risk of gallbladder disease.
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridermia, or cholestatic jaundice occurs.
- Monitor thyroid function in women on thyroid replacement hormone therapy.

**ADVERSE REACTIONS**
The most common adverse reactions (≥3%) for BIJUVA are breast tenderness (10.4%), headache (3.4%), vaginal bleeding (3.4%), vaginal discharge (3.4%) and pelvic pain (3.1%).

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*Bio-identical hormones are structurally identical to the hormones produced within a woman’s body. The relevance of risks associated with the use of synthetic hormones compared to bio-identical hormones is not known but cannot be excluded.
†Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state healthcare programs (including any state pharmaceutical assistance programs). Please see Program Terms, Conditions, and Eligibility Criteria at savings.bijuva.com.

References:
In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in years 1 through 5 (see Clinical Studies (14.4) in full prescribing information). Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggested no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (13 versus 21 per 10,000 women-years).

Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 (see Clinical Studies (14.4) in full prescribing information).

In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo (see Clinical Studies (14.4) in full prescribing information). Subgroup analysis of women 50 to 59 years of age suggested a statistically non-significant reduction in CHD events (CE (0.625 mg)-alone compared to placebo) in women in less than 10 years since menopause (see Clinical Studies (14.4) in full prescribing information).

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study (HERS)), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary artery disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not in the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II has been an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater risk of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 6 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted (see Clinical Studies (14.4) in full prescribing information). Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years (see Clinical Studies (14.4) in full prescribing information). Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

If feasible, estrogen should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy report an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be in situ, and were associated with a less favorable clinical stage in the estrogen plus progestin group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups (see Clinical Studies (14.4) in full prescribing information).

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer (relative risk (RR) 0.80) (see Clinical Studies (14.4) in full prescribing information).

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping).

Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, in users of estrogen plus progestin therapy compared to users of estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation. In a one-year trial, among 1,604 women who received a combination of estradiol plus progestin (1 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 50 mg progesterone or 0.25 mg estradiol plus 50 mg progesterone) or placebo (n=151), six new cases of breast cancer were diagnosed, two of which occurred among the group of 41 women who continued with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg. No new cases of breast cancer were diagnosed in the group of 51 women treated with placebo.
Endometrial Cancer

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with BUJIVA (estradiol and progesterone) capsules, 1 mg/100 mg.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year.

The greatest increased risk associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 6 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestogen therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestogen to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95% confidence interval [CI], 0.77 to 3.34). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,101 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% CI, 1.32 to 1.52); there was no difference in the risk estimates by duration of the exposure (<5 years [median of 3 years] vs. greater than 5 years [median of 10 years]) of use before the cancer diagnosis (the relative risk associated with combined current and recent use [discontinued use within 5 years before cancer diagnosis] was 1.37 [95% CI, 1.27 to 1.48], and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products). The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

Probable Dementia

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg plus MPA 2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.35 (95% CI, 1.21 to 4.38). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg) or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 1.49 (95% CI, 0.83 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the overall relative risk for probable dementia was 1.76 (95% CI, 1.19 to 2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papillitis or retinal vascular lesions, estrogens should be permanently discontinued.

Addition of a Progestogen When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestogen for 10 or more days of a cycle of estrogen administration, or daily with estrogens in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestogen with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progesteron should be considered.

Hereditary Angiokeratoma

Exogenous estrogens may exacerbate symptoms of angiokeratoma in women with hereditary angiokeratoma.

Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms.

Drug Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet agglutination time, increased platelet counts, increased factors II, VII, IX, X, 8, 9, 10, and V, decreased fibrinogen and/or factor XIII, decreased factor VII activity, increased levels of fibrinogen and fibrin degradation activity, increased plasma antithrombin III activity, and increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated T3. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and steroid metabolites, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen, ceruloplasmin).

ADVERSE REACTIONS

In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reactions with BUJIVA (incidence ≥ 3% of women and greater than placebo) were breast tenderness (10.4%), headache (3.4%), vaginal bleeding (3.4%), vaginal discharge (3.4%) and pelvic pain (3.1%).

Drug INTERACTIONS

Inducers and inhibitors of CYP3A4 may affect estrogens at drug metabolism and decrease or increase the effect of estrogens, respectively.

USE IN SPECIFIC POPULATIONS

Pregnancy

BUJIVA is not indicated for use in pregnancy. There are no data with the use of BUJIVA in pregnant women, however, 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 combined hormonal contraceptives (estrogen and progesterone) before conception or during early pregnancy.

Lactation

BUJIVA is not indicated for use in females of reproductive potential. Estrogens are present 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.

Pediatric Use

BUJIVA is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use

There have been sufficient numbers of geriatric women involved in clinical studies utilizing BUJIVA to determine whether those over 65 years of age differ from younger women in their response to BUJIVA.

An increased risk of probable dementia in women over 65 years of age was reported in the Women’s Health Initiative Memory ancillary studies of the Women’s Health Initiative OVERDOSAGE

Overdosage of estrogen plus progestogens may cause nausea, vomiting, breast tenderness, abdominal pain, diarrhea, and blood in the stool. In cases of overdose, treatment consists of discontinuation of BIJUVA therapy with institution of appropriate symptomatic care.

PRESSURE COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Manufactured by TherapeuticsMD, Inc. Boca Raton, FL 33431

Based on BUJIVA-LAB-20003.4 Revised: 11/2019

BUJIVA-20564.1 12/2019
Bacterial Vaginosis and the Risk for Sexually Transmitted Infections

Steven E. Chavers, MD, FACOG, GCPP

AIDS, syphilis, gonorrhea, and chlamydia are transmitted through unprotected sexual intercourse. When these infections are not treated, they can increase the risk of other sexually transmitted infections (STIs), including HIV, and can cause pelvic inflammatory disease,盆腔炎 (PID), and other complications. Bacterial vaginosis (BV) is considered to be a polymicrobial infection. It is characterized by a decrease in Lactobacillus spp, an increase in Gardnerella vaginalis, and other clue cells. The diagnosis is based on the Amsel criteria, which include an abnormal vaginal discharge and three of the following: a homogeneous, malodorous discharge, a clue cell test positive, a discharge that changes color when treated with 10% potassium hydroxide, and a pH of 4.5 or higher.

The treatment of BV is important because it can reduce the risk of acquiring other STIs. A 2018 systematic review found that BV treatment was associated with a reduction in the risk of acquiring HIV, chlamydia, and gonorrhea. The Centers for Disease Control and Prevention (CDC) recommends that all women be screened for BV at least once during their reproductive years and that those who test positive be treated with metronidazole or clindamycin.

In conclusion, vaginal dysbiosis, as represented by bacterial vaginosis, is associated with an increased risk of HIV acquisition. This highlights the importance of routine screening and treatment of BV, as well as the need for ongoing research to better understand the mechanisms underlying this association.
HUMAN IMMUNODEFICIENCY VIRUS
Human immunodeficiency virus (HIV) is a retrovirus that is both a public health and a personal health concern, with an annual incidence among US women estimated at 8000 new infections per year. However, an estimated 2.6 million women in the United States are living with HIV and are at risk of acquiring additional infections, such as from sexual intercourse with an infected partner. The risk of HIV acquisition through sexual contact is estimated at 1 in 2000 for each sexual act, with a lifetime risk of infection of about 1 in 2000 for women in the United States. Therefore, HIV is a significant public health concern for women, particularly those who are at risk of acquiring the virus through sexual contact.

HUMAN PAPILLOMAVIRUS
Human papillomavirus (HPV) is a group of related viruses that can cause a range of conditions, including warts, genital warts, and cervical cancer. In women, HPV infection can lead to cervical dysplasia and cervical cancer, which are the most common refractory cancers in women. HPV infection is also associated with an increased risk of ovarian cancer and other cancers of the anogenital tract.

HUMANKIND'S EVOLUTIONARY INVESTMENT
It has long been proposed that sexual selection has been an important force in the evolution of the human species, with many features of the human body and behavior thought to have evolved in part to enhance reproductive success. However, the role of sexual selection in human evolution is still a subject of debate, with some researchers arguing for a significant role and others suggesting that it has played a more limited role.

HERPES SIMPLEX VIRUS TYPE 2
Varicella-zoster virus (VZV) is the virus that causes chickenpox and shingles. VZV is a member of the herpesvirus family and is highly contagious, with an estimated 1000 new infections occurring every day in the United States. Herpes simplex virus type 2 (HSV-2) is a herpesvirus that causes genital herpes, which is a common sexually transmitted infection. HSV-2 is highly contagious, with an estimated 9000 new infections occurring every day in the United States. HSV-2 is most common in women and men of reproductive age, with an estimated 400,000 new infections occurring every year in the United States.

STUDY BACKGROUND
The study described in this section was a retrospective cohort study that included 20,518 women from the United States who were enrolled in the Study of Women's Health Across the Nation (SWAN) from 2004 to 2018. The study was designed to assess the relationship between BV and incident HIV, with a focus on the role of BV in the risk of HIV acquisition.

METHODS
The study used a nested case-control design, in which cases of incident HIV were matched to control subjects who were not infected with HIV. The cases were selected from participants who were enrolled in the study between 2005 and 2016 and who had at least one visit with incident HIV detected through the follow-up visit before the visit when incident HIV was diagnosed (N = 727). The control subjects were selected from participants who were enrolled in the study between 2005 and 2016 and who did not have incident HIV detected through the follow-up visit before the visit when incident HIV was diagnosed (N = 727). The cases and control subjects were matched on age, race, and study site.

RESULTS
The study found that baseline BV (diagnosed by Nugent score 7–10) was a risk factor for incident HIV, with an overall adjusted effect of 1.53 (95% CI, 1.36–1.90). Baseline interlabial vaginal flora (Gardnerella vaginalis or Lactobacillus species) was also a risk factor, with an overall adjusted effect of 1.41 (95% CI, 1.26–1.58). Other BV diagnoses did not show a statistically significant association with incident HIV.

CONCLUSIONS
The study found that BV is a risk factor for incident HIV, with a baseline Nugent score of 7–10 increasing the risk of HIV by 53%. This finding highlights the importance of BV in the risk of HIV acquisition and underscores the need for further research to understand the mechanisms underlying this relationship.

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**Discussion**

**Bacterial Vaginosis and the Risk for Sexually Transmitted Infections**

Steven E. Chansky, MD, FACOG, GCCP; Alma Sofia Morinello, MS; Michael Henn, PhD

Vector/Steering Committee

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Michael Henn, PhD is a research assistant at the Mayo Clinic.

**References**

Practical path for an onerous condition

Recurrent or chronic vulvovaginitis is frustrating to patients and a burden to the health care system. Here is a guide to addressing it.

by OLUWATOSIN GOJE, MD, MSCR

Vulvovaginitis may be infectious or non-infectious in etiology, and it is often under-diagnosed or misdiagnosed. Chronic or recurrent vulvovaginitis is frustrating to patients and a burden to the health care system. The three types of infectious vulvovaginitis most commonly seen in reproductive-age women are bacterial vaginosis (BV), vulvovaginal candidiasis (VVC) and trichomoniasis. Other differential diagnoses to consider include herpes simplex infection, allergic reaction to irritants and non-infectious vaginitis such as lichen planus, genitourinary syndrome of menopause (GSM), and desquamative inflammatory vaginitis (DIV). Infection and/or inflammation of the vulva and vagina are associated with itching, burning, irritation, dyspareunia, and abnormal and/or malodorous vaginal discharge.\(^1\)\(^4\) This article focuses on the diagnosis and treatment of recurrent and chronic cases.

Initial evaluation

All patients who present with complaints suggestive of vulvovaginitis should have a complete history; physical examination of the vulva, vagina and perianal area; saline microscopy (including pH, 10% potassium hydroxide (KOH) whiff test) if available; point-of-care testing if available; and culture and molecular diagnosis testing as needed.\(^5\) History should include relationship of symptoms to sexual intercourse, menstrual cycle, use of feminine products and practices, over-the-counter medications, and medical and medication history.

On examination, patients with BV may have a malodorous grey, creamy or thin homogeneous discharge whereas patients with VVC may present with evidence of inflammation such as erythema, edema, fissures, or excoriations in moderate to severe cases, while patients with trichomoniasis may exhibit signs of inflammation like erythema.\(^4\) Patients with GSM may show signs of vulvovaginal atrophy while patients with DIV may show signs of inflammation (Figures 1 to 4). Vaginal samples should be obtained from the posterior fornix in BV and lateral vaginal wall in VVC and microscopy performed. (Table 1).

Clinical testing

Office based testing of the vaginal discharge using pH test, 10% KOH and saline microscopy is preferred if available. This approach may provide immediate diagnosis, and treatment can be initiated. The United States Food and Drug Administration (FDA)-approved commercially available tests

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Recurrent infectious vulvovaginitis

**BACTERIAL VAGINOSIS**

BV, the most common cause of abnormal vaginal discharge in reproductive-age women is characterized by abnormal vaginal flora, decreased or absent lactobacilli, and an increased number of anaerobes and facultative anaerobes. It is a dysbiosis, and some of the associated bacteria include *Gardnerella vaginalis*, *Prevotella* species, *Atopobium vaginae*, *Megasphaera* type 1, and *Sneathia sanguinegens*. BV is associated with increased risk of pelvic inflammatory disease; increased risk of acquisition and transmission of sexually transmitted infections (STIs); adverse obstetric and gynecologic outcomes such as preterm labor, preterm birth, and chorioamnionitis; and vaginal cuff cellulitis post-hysterectomy. Patients may describe the malodorous discharge as “rotten egg or fishy” and worse after sexual intercourse or a menstrual period. The diagnosis is usually clinical (Table 1).

### Table 1. Vaginal secretion test results and diagnosis of vulvovaginitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vaginal discharge</th>
<th>Examination findings</th>
<th>Saline microscopy +/- 10% KOH</th>
<th>pH level</th>
<th>Diagnostic test</th>
<th>Gold standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>White, creamy, clear</td>
<td>Normal anatomy, discharge adherent to vaginal wall and posterior fornix</td>
<td>Normal vaginal epithelial cells, normal flora, lactobacillus present, few WBCs</td>
<td>3.5-4.5</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>Creamy, grey, fishy, rotten egg odor</td>
<td>Creamy-gray, malodorous homogenous discharge</td>
<td>Clue cells, lactobacillus may be absent or reduced, coccobacillary flora, positive whiff</td>
<td>&gt; 4.5</td>
<td>Amsel criteria, FDA-approved commercial test</td>
<td>Gram stain with Nugent score</td>
</tr>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>Thick creamy-yellow, curdlike discharge</td>
<td>Curd-like or cottage cheese like discharge adherent to vaginal side wall. Vulvar erythema, edema, fissure, excoriations maybe seen in severe cases</td>
<td>Fungal elements may be seen, WBCs may be present</td>
<td>3.5-4.5</td>
<td>Microscopy, FDA-approved commercial test</td>
<td>Fungal culture</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>Yellow-green discharge</td>
<td>Grey, yellow, frothy discharge, vaginal and cervical erythema, occasional vulvar erythema</td>
<td>Motile trichomonads may be seen, WBCs maybe abundant</td>
<td>Variable</td>
<td>Microscopy, FDA approved commercial test</td>
<td>NAAT</td>
</tr>
<tr>
<td>Atrophic vaginitis (GSM)</td>
<td>Scanty or white</td>
<td>Normal, or atrophy (pale, loss of rugae and elasticity) of vulva, vagina</td>
<td>Normal flora, vaginal epithelial cells may be decreased or absent. WBCs may be present or increased, parabasal cells maybe present</td>
<td>&gt; 4.5</td>
<td>Microscopy, Vaginal maturation index</td>
<td>Vaginal maturation index</td>
</tr>
<tr>
<td>Desquamative inflammatory vaginitis</td>
<td>Yellow-green copious discharge</td>
<td>Yellow-green discharge, erythema, excoration of vulva and vestibule in severe cases</td>
<td>Sheets of WBCs (leukorrhoea) parabasal cells maybe present, mixed flora</td>
<td>&gt; 4.5</td>
<td>Clinical diagnosis PLUS microscopy</td>
<td>Clinical Diagnosis PLUS microscopy</td>
</tr>
</tbody>
</table>

A = US Food and Drug Administration; NAAT = nucleic acid amplification test; WBC = white blood cell
Presence of three of four Amsel criteria is needed to make the diagnosis:
- Homogenous discharge
- Clue cells
- pH > 4.5
- Positive whiff test

Gram stain with Nugent score is the gold/reference standard used in research settings, while Amsel criteria are used in clinical setting. Although microscopy is preferred and cost effective, it may not be available in all clinical settings and data evaluating US Food and Drug Administration (FDA)-approved commercially available tests have acceptable performance against the reference standards. FDA-approved commercially available tests can be used to diagnose BV but should be interpreted alongside patient history and examination.

**RECURRENT BV**
Recurrent bacterial vaginosis (RBV) is defined as three or more episodes in 12 months. Recurrence rate is high, and often involves frequent telephone calls and visits to the clinic; multiple treatments are prescribed in the absence of curative therapy. Bradshaw et al. reported recurrence rates of 58% over a 12-month period in women treated with oral metronidazole for 7 days. In their study, recurrence was associated with prior history of BV, lack of hormonal contraceptive use, having the same sex partner throughout the study duration, and having female sex partners. Other factors that have been associated with recurrence include douching, frequent sexual intercourse without condoms, and failure to reestablish a *lactobacillus*-predominant vaginal flora. It has also been suggested that formation of a vaginal biofilm in BV could be one of the factors in RBV.

Women with RBV should be appropriately treated based on the Centers for Disease Control and Prevention (CDC) recommended conventional therapy of nitroimidazole or clindamycin administered orally or vaginal and offered additional suppressive therapy with 0.75% metronidazole intravaginal gel twice weekly for 4 months. In a multicenter study, Sobel et al randomized patients with RBV to twice-weekly intravaginal metronidazole gel or placebo for 16 weeks after initial treatment. He documented that during 28-week follow-up, recurrence was less in the suppressive therapy group. Recurrence occurred in 51% of treated women compared with 75% of women receiving placebo. Patients should be educated about the risk of possible yeast infection during the suppressive therapy phase.

Another option for RBV is a combination of oral nitroimidazole with intravaginal boric acid as the induction phase, followed by suppression therapy. Reichman et al treated women who met criteria with either tinidazole or metronidazole 500 mg orally twice daily for 7 days followed by intravaginal boric acid 600 mg at bedtime for 21 days as the induction phase. Asymptomatic patients then proceeded to the maintenance phase of intravaginal metronidazole gel twice weekly. In this study, the cure rate was 92% at 7 weeks, 88% at 12 weeks, and 50% at 36 weeks. We have modified the suppression therapy in our clinical practice, and documented success with 0.75% metronidazole intravaginal gel once a week for 4 months.

**VULVOVAGINAL CANDIDIASIS**
VVC is the second most common cause of vulvovaginitis. Although *Candida albicans* is the most common cause of VVC (85%-90%), other non-*albicans* candida (NAC) (*C. glabrata, C. krusei, C. parapsilosis*) could be colonizers or pathogenic.

Diagnosis should not be based on clinical findings alone due to lack of specificity; symptoms of external dysuria, itching,
and burning are not always sufficient to make a diagnosis.6,18 Clinical features may include curd-like vaginal discharge (Figure 1). On examination, patients may have erythema, edema, fissures, or excoriations (Figure 2). Microscopy with or without addition of 10% KOH may reveal fungal elements. Fungal culture is helpful in patients with clinical features suggestive of VVC but who have a negative saline microscopy. It is also helpful in patients who have failed therapy or those with suspected resistance to commonly used anti-fungals.18 FDA-approved molecular testing is commercially available for providers who do not have access to microscopy. Some molecular testing has rapid turnover, but may not give speciation and sensitivities. Although fungal culture results may take a week to be returned, they may be needed to plan treatment.

**RECURRENT VULVOVAGINAL CANDIDIASIS**

RVVC is defined as at least three symptomatic episodes in 12 months.19 Risk of recurrence is increased in patients who frequently take antibiotics, are chronic users of corticosteroids, on prolonged immunosuppressant (e.g. transplant patients) or immunosuppressed patients (uncontrolled HIV/AIDS), have uncontrolled or poorly controlled diabetes, or have azole-resistant or non- *C. albicans* VVC.

Patients with RVVC would benefit from maintenance therapy after the induction treatment phase has been successfully completed.20 Those with azole-resistant *C. albicans* should have sensitivity testing performed and be treated based on the results. Sobel et al and Marchaim et al have documented success with compounded medications in patients with azole resistance and those who have failed multiple doses of first-line medications.21,22 In patients with azole-resistant VVC, treatment options include intravaginal boric acid 600 mg daily for 14-21 days, intravaginal 15.5% fluclotysine vaginal cream (5 g) daily for 14 days, and intravaginal amphotericin B 50-mg vaginal suppository daily for 14 days. It is important to consider other differential diagnosis of vulvovaginal itch. All that itches is not yeast and patients with persistent itching despite treatment should be referred to a specialist.

**Examples of vaginal specialist-recommended regimens for RVVC include.**

1. Fluconazole 150 mg orally every 72 hours x 3 doses; followed by fluconazole orally 150 mg weekly x 6 months or miconazole 1200 mg vaginally weekly x 6 months (for patients who prefer vaginal route for maintenance therapy).
2. Itraconazole 200 mg orally twice daily x 3 days followed by itraconazole orally, 100-200 mg daily for 6 months.

**RECURRENT TRICHOMONIASIS**

Trichomoniasis is the most common non-viral STI in women worldwide.2 It is associated with reproductive morbidity and increased risk of HIV acquisition and transmission. Patients may be asymptomatic or present with abnormal yellow-green vaginal discharge, inflammatory symptoms such as itching, burning, and dyspareunia. On examination, there may be erythema of the vulva, vagina and "strawberry cervix." Microscopy, if available, may reveal motile trichomonads; other diagnostic modalities include point-of-care testing or FDA-approved commercially available molecular testing. Nucleic acid amplification testing (NAAT) is recommended for diagnosis of trichomoniasis.2

Treatment of the patient and her sex partner(s) is recommended.5,23 Nitroimidazole is the drug of choice. Treatment is usually a single 2-g dose of metronidazole or tinidazole.5 Kissing et al, in a randomized trial of single-dose 2-g metronidazole versus 7 days of metronidazole, showed that the 7-day oral-dose metronidazole is the preferred treatment for trichomoniasis treatment in non-HIV-infected women.24 Relapse is more common than treatment failure, but patients suspected to have failed treatment or who have nitroimidazole resistance should be referred to an infectious disease specialist. Patients with nitroimidazole allergy should be referred for desensitization. CDC offers resistance testing by request. Health providers can access the CDC website and contact the office in charge for this service.

In women who fail 2 g metronidazole without evidence of reinfection, metronidazole 500 mg orally twice daily x 7 days is recommended. If
treatment fails, tinidazole or metronidazole 2 g orally for 5 days is then recommended.

If persistent infection is documented despite the previous therapy without evidence of reinfection, there are case series and reports documenting success using high-dose tinidazole and compounded paromomycin in management of refractory trichomoniasis, as follows: 25,26

1. Tinidazole 500 mg orally 4 times daily for 1 week OR
2. Tinidazole 500 mg orally 4 times daily PLUS Tinidazole 500 mg vaginally twice daily x 14 days OR
3. Tinidazole 1 g orally 3 times daily plus 5 g of compounded 5% intravaginal paromomycin nightly X 14 days.

We have had success in our clinical practice with use of 5 g of 5% compounded paromomycin alone x 14 days in three patients who were allergic to nitroimidazole. (Unpublished data). Of significance, the compounded creams could be irritants to the skin and should be inserted inside the upper and mid third of the vagina at bedtime. Patients should apply an emollient as barrier to the vulva, and refrain from all sexual intercourse while using compounded vaginal medications. Compounded medications are also expensive.

Non-infectious vulvovaginitis

A review of chronic/recurrent vulvovaginitis would not be comprehensive without a discussion of the two commonly encountered non-infectious causes: GSM and DIV.

DIV, a diagnosis of exclusion, is a chronic vulvovaginitis that is poorly understood. It occurs mostly in perimenopausal and postmenopausal women, and may be associated with low estrogen levels. Diagnosis is usually clinical with patients complaining of copious yellow-green discharge. They may describe the discharge as thick, “sticky,” mucoid staining of their underwear. Patients sometimes wear panty liners or sanitary pads due to the volume or discoloration of their undergarments. They may complain of itching, pain, burning, and sometimes dyspareunia. On examination, the vulva may be erythematous, friable and may bleed on contact. The vagina may be erythematous and purulent yellow-green discharge noted (Figure 3). Microscopy shows sheets of white blood cells and parabasal cells may be present if the patient is hypoestrogenic (Figure 4).

**Diagnosis is based on specific criteria:**
- At least one symptom (vaginal discharge, dyspareunia, pruritus, pain, irritation or burning)
- Evidence of vulvovaginal inflammation
- Vaginal pH > 6
- Leukorrhea +/- parabasal cells on microscopy

Management involves counseling and education about this poorly understood condition. Initial treatment is 2% intravaginal clindamycin for 4 to 6 weeks. Patient who fail to respond to vaginal clindamycin may repeat treatment with 10% intravaginal compounded hydrocortisone for the same duration. Patient education should include the possibility of failed therapy and relapse. Presence of parabasal cells indicates a hypoestrogenic state and vaginal estrogen twice a week should be included in the regimen. Patients who relapse should be referred to a vaginal specialist.

GSM is often seen in postmenopausal patients or hypoestrogenic women such as those who are breastfeeding or who have undergone menopause due to surgery or exposure to chemotherapy or radiation. Patients may present with vaginal dryness, pain, itching, thin watery discharge, and dyspareunia. 27,28 On examination, the vagina may be pale, with loss of elasticity. Vaginal pH is elevated in symptomatic patients. Microscopy may show some parabasal cells, paucity of normal vaginal epithelial cells, and lack of lactobacilli.
1. First-line management is with vaginal lubricants and moisturizers. Patients who remain symptomatic and have no contraindications to use of hormones may benefit from systemic or vaginal hormones. In our practice, we usually start with vaginal estrogen in various formulations or vaginal dehydroepiandrosterone before considering systemic formulations.1,27,28

FOR REFERENCES VISIT contemporaryobgyn.net/vulvovaginitis

Dyspareunia and infertility concerns with endometriosis

BY BOB KRONEMYER

In women with endometriosis, there is a modest association between superficial dyspareunia and concerns about infertility, whereas this connection is not present between deep dyspareunia and infertility concerns, according to a cross-sectional study. Published by Canadian researchers in Sexual Medicine, the report also found that the association between superficial dyspareunia and infertility concerns persisted, even after adjusting for potential confounders.

Said principal investigator Paul Yong, MD, PhD, an assistant professor of ob/gyn at the University of British Columbia in Vancouver, Canada, “The goal is to have a more personalized understanding of endometriosis dyspareunia, rather than simply grouping all patients together.”

The authors noted that deep dyspareunia is a major symptom of endometriosis, but that up to 40% of women with endometriosis may be afflicted by comorbid superficial dyspareunia.

The study consisted of consenting patients who were newly referred or re-referred to the BC Women’s Center for Pelvic Pain and Endometriosis, in Vancouver, between 2013 and 2017. Data on the 300 reproductive-aged participants were obtained from the Endometriosis Pelvic Pain Interdisciplinary Cohort (EPPIC) prospective data registry.

Odds of infertility concerns did not increase with severity of deep dyspareunia: odds ratio (OR) = 1.02; 95% confidence interval (CI): 0.95 to 1.09 (P = 0.58). However, they increased slightly with severity of superficial dyspareunia: OR = 1.09; 95% CI: 1.02 to 1.16 (P = 0.011).

Furthermore, the relationship between superficial dyspareunia and infertility concerns persisted after adjusting for endometriosis-specific factors, infertility risk factors, reproductive history and demographic characteristics: adjusted odds ratio (AOR) = 1.14; 95% CI: 1.06 to 1.24 (P < 0.001).

Four other factors in the model that were independently associated with increased infertility concerns were previous difficulty conceiving (AOR = 2.09; 95% CI: 1.04 to 4.19; P = 0.038), currently trying to conceive (AOR = 5.23; 95% CI: 2.77 to 9.98; P < 0.001), nulliparity (AOR = 3.21; 95% CI: 1.63 to 6.41; P < 0.001), and a younger age (AOR = 0.94; 95% CI: 0.89 to 0.98, P = 0.005).

What was unexpected was that superficial dyspareunia was more important to patients than deep dyspareunia, “given that endometriosis is traditionally seen as a cause of deep dyspareunia,” Dr. Yong said. “This points to the fact that superficial dyspareunia can occur in women with endometriosis, and can be clinically very significant in some cases.”

It is crucial that clinicians assess for both deep and superficial dyspareunia in patients with endometriosis, according to Dr. Yong. “In those with superficial dyspareunia, it may be worth screening for concerns about fertility and proactively addressing those concerns,” he said, adding that women experiencing introital dyspareunia may have difficulty achieving penetrative intercourse.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

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- Females over 35 years old who smoke should not use ANNOVERA.
- Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive use.

CONTRAINDICATIONS

ANNOVERA is contraindicated and should not be used in women with a high risk of arterial or venous thrombotic diseases; current or history of breast cancer or other estrogen- or progestin-sensitive cancer; liver tumors, acute hepatitis, or severe (decompensated) cirrhosis; undiagnosed abnormal uterine bleeding; hypersensitivity to any of the components of ANNOVERA, and use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir.

WARNINGS AND PRECAUTIONS

- Stop ANNOVERA if a thrombotic or thromboembolic event occurs, and at least 4 weeks before and through 2 weeks after major surgery. Start ANNOVERA no earlier than 4 weeks after delivery, in females who are not breastfeeding. Consider cardiovascular risk factors before initiating in all females, particularly those over 35 years.
- Discontinue if jaundice occurs.
- Stop ANNOVERA prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir. ANNOVERA can be restarted 2 weeks following completion of this regimen.
- Do not prescribe ANNOVERA for females with uncontrolled hypertension or hypertension with vascular disease. Monitor blood pressure and stop use if blood pressure rises significantly in females with well-controlled hypertension.
- Monitor glucose in pre-diabetic or diabetic females taking ANNOVERA. Consider an alternate contraceptive method for females with uncontrolled dyslipidemias.
- Patients using ANNOVERA who have a significant change in headaches or irregular bleeding or amenorrhea should be evaluated. ANNOVERA should be discontinued if indicated.
CONTRAINDICATIONS

ANNOVERA is contraindicated and should not be used in pregnancy. ANNOVERA is also contraindicated in females with any of the following conditions:

- Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive use. Females over 35 years old who smoke should not use ANNOVERA.
- Other warnings include: gallbladder disease; depression; cervical cancer; increased serum concentrations of binding globulins; hereditary angioedema; chloasma (females who tend to develop chloasma should avoid exposure to the sun or UV radiation while using ANNOVERA); toxic shock syndrome (TSS) (if a patient exhibits symptoms of TSS, remove ANNOVERA, and initiate appropriate medical treatment); vaginal use (ANNOVERA may not be suitable for females with conditions that make the vagina more susceptible to vaginal irritation or ulceration).

ADVERSE REACTIONS

The most common adverse reactions reported in at least 5% of women who received ANNOVERA were: headache/migraine, nausea/vomiting, vulvovaginal mycotic infection/candidiasis, lower/upper abdominal pain, dysmenorrhea, vaginal discharge, urinary tract infection, breast pain/tenderness/discomfort, bleeding irregularities including metrorrhagia, diarrhea, and genital pruritus.

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of ANNOVERA or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with ANNOVERA.

INDICATION

ANNOVERA is a progestin/estrogen combination hormonal contraceptive indicated for use by females of reproductive potential to prevent pregnancy.

Limitation of Use: ANNOVERA has not been adequately studied in females with a body mass index of >29 kg/m².

Please note this information is not comprehensive. Please see Brief Summary of the Full Prescribing Information on the next page, including BOXED WARNING, or visit www.Annovera.com/pi.pdf.


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ANNOVERA-20142 02/2020
ANNOVERA® (segesterone acetate and ethinyl estradiol vaginal system)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ANNOVERA safely and effectively. Please visit ANNOVERA.com/pfd for Full Prescribing Information (Pf).

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs should not be used by females who are over 35 years of age and smokers.

INDICATIONS AND USAGE

ANNOVERA is indicated for use by females of reproductive potential to prevent pregnancy. Limitations of Use: ANNOVERA has not been adequately studied to determine its potential to prevent pregnancy.

ANNOVERA is indicated for use by females of reproductive potential to use ANNOVERA safely and effectively. Please visit ANNOVERA.com/pfd for Full Prescribing Information (Pf).

Dosage and Administration

One ANNOVERA is inserted in the vagina. The vaginal system must remain in place continuously for 3 weeks (21 days) followed by a 1-week (7-day) vaginal system-free interval. One vaginal system provides contraception for thirteen 28-day cycles (26 weeks of use) for females who are starting ANNOVERA, including switching from other contraceptive methods, and use after abortion, miscarriage, or childbirth (see How to Start ANNOVERA in the Package Insert).

Contraceptive efficacy of ANNOVERA may be reduced if a woman deviates from the recommended use. If ANNOVERA is out of the vagina for more than 2 hours or less than 2 cumulative hours during the 21 days of continuous use, then back up protection, such as male condoms or spermicides, should be used until the vaginal system has been in the vagina for 7 consecutive days.

CONTRAINDICATIONS

ANNOVERA is contraindicated in females who are known to have the following conditions: • A high risk of arterial or venous thrombotic diseases. Examples include females who are known to have had a current or history of deep vein thrombosis or pulmonary embolism; have cerebrovascular disease; have coronary artery disease; have thrombogenic vascular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation); have inherited or acquired hypercoagulopathies; have uncontrolled hypertension or hypertension with vascular disease; have diabetes mellitus and are over age 35, diabetes mellitus with hypertension or vascular disease or other organ damage; or diabetes mellitus of >20 years duration; have headaches with focal neurological symptoms, migraine headaches with aura, or are over age 35 with any aura headache. • Current or history of breast cancer or other estrogen- or progesterin-sensitive cancer. • Liver tumor, including colorectal tumor, severe (decompensated) cirrhosis. • Undiagnosed abnormal uterine bleeding. • Hypersensitivity to any of the components of ANNOVERA. Hypersensitivity reactions reported include facial edema, throat constriction, facial edema, urticaria, hives, and wheezing. • Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations.

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders and Other Vascular Conditions

Females are at increased risk for a venous thrombotic event (VTE) when using ANNOVERA. Stop ANNOVERA if a thrombotic or thromboembolic event occurs or unexplained loss of vision, proposis, diplopia, paresthesia, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately. Stop ANNOVERA at least 4 weeks before and followed by 2 weeks after major surgery. Start ANNOVERA no earlier than 4 weeks after delivery in females who are not breastfeeding. Before starting ANNOVERA, consider history and risk factors of thrombotic or thromboembolic disorders. ANNOVERA is contraindicated in females with a high risk of arterial or venous thromboembolic disorders.

Arterial Events

Consider cardiovascular risk factors before initiating in all females of reproductive potential over 35 years. CHCs increase the risk of cardiovascular events and cerebrovascular events, such as stroke and myocardial infarction. The risk is greater among older females (>35 years of age), smokers, and females with hypertension, dyslipidemia, diabetes, or obesity.

Venous Events

The use of CHCs increases the risk of VTE, such as deep vein thrombosis and pulmonary embolism. Risk factors for VTE include CHC use, obesity, and family history of VTE, in addition to other factors that contraindicate use of CHCs. The rates of VTE are even greater during pregnancy, and especially during the postpartum period. The risk of VTE is highest during the first year of CHC use and when restarting hormonal contraception following a break of 4 weeks or longer. The risk of VTE due to CHCs gradually decreases after discontinuation.

Lipid Disorders

Cholesterol

Cholestan, a minor estrogen in ANNOVERA, may increase serum total cholesterol in females with a history of cholesterol or hypercholesterolemia. Advise females who tend to develop cholestan to avoid exposure to the sun or ultraviolet radiation while using ANNOVERA.

Pediatric Use

Clinical Trials Experience

No studies were conducted in subjects with renal impairment. ANNOVERA is not recommended in patients with renal impairment.

Body Mass Index (BMI)/Body Weight

The safety and efficacy of ANNOVERA in females with a BMI >29 kg/m2 have not been adequately evaluated because this subset population was excluded from the clinical trials after 2 VTE occurred in females with a BMI >29 kg/m2. Higher body weight is associated with lower systemic exposure of SA and EE.

Healthy Ancestry

In females with healthy ancestry, estrogenic exogenous may decrease or exacerbate symptoms of angiodema. Cholestan

Cholestan may cause an increased risk of developing angiodema in females with a history of angiodema. Advise females who tend to develop cholestan to avoid exposure to the sun or ultraviolet radiation while using ANNOVERA.

HIV/HEP C Virus Combinations

If a patient exhibits signs/symptoms of TSS, consider the possibility of this diagnosis, remove ANNOVERA, and initiate appropriate medical evaluation and treatment.

Vaginal Use

Some females are aware of the vaginal system on occasion during the 21 days of use or during coitus, and partners may feel the vaginal system during coitus. ANNOVERA may not be suitable for females with conditions that make the vagina more susceptible to vaginal irritation or ulceration. Vaginal cervical erosion and/or ulceration has been reported in females using other contraceptive vaginal devices. In some cases, the ring adhered to vaginal tissue, which necessitated removal by a healthcare provider.

ADVERSE REACTIONS

Clinical Trial Experience

Most Common Adverse Reactions

In clinical trials, adverse reactions reported in >5% of ANNOVERA- and placebo- treated subjects include: headache, including migraine (38.8%); nausea/vomiting (25.0%); vulvovaginal mycotic infection/vaginal candidiasis (14.5%); abdominal pain/ lower back pain (13.3%); dysmenorrhea (11.8%); UTI/cystitis/peyroniephritis/genitourinary tract infection (10.0%); breast pain/tenderness/discomfort (9.5%); metrorrhagia/menstrual disorder (8.7%); diarrhea (7.2%); and genital pruritus (5.5%).

Adverse Reactions Leading to Discontinuation

Among ANNOVERA users, severe VTE, with or without cause for contraception, 1% discontinued from the clinical trials due to an adverse reaction. Adverse reactions leading to discontinuation by >1% of ANNOVERA-treated subjects, include: metrorrhagia/menorrhagia (7.1%); headache, including migraine (1.3%); vaginal discharge/vulvovaginal mycotic infections (1.3%); nausea/vomiting (1.2%). In addition, 1.4% of subjects discontinued ANNOVERA use due to vaginal system expulsions. Serious Adverse Reactions

Serious adverse reactions occurring in >2 subjects were: VTE (deep venous thrombosis, cerebral vein thrombosis, pulmonary embolism), myocardial infarction, psychiatric drug hypersensitivity reactions, and spontaneous abortions.

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of ANNOVERA or increase breakthrough bleeding. Counsel patients to use a backup or alternative method of contraception when enzyme inducers are used with ANNOVERA. Do not co-administer ANNOVERA with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations.

USE IN SPECIFIC POPULATIONS

Pregnancy

Discontinue ANNOVERA if pregnancy occurs.

Lactation

Not recommended for nursing mothers; can decrease milk production.

Pediatric Use

Safety and efficacy of ANNOVERA have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 15 as for users 18 years and older. Use of ANNOVERA before menarche is not indicated.

Geriatric Use

ANNOVERA has not been studied in females who have reached menopause and is not indicated in this population.

Hepatic Impairment

No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of ANNOVERA. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal and CHC causation has been excluded.

Renal Impairment

No studies were conducted in subjects with renal impairment. ANNOVERA is not recommended in patients with renal impairment.

Manufactured for: TherapeuticMD, Inc.

Brick, New Jersey 08509

Based on AWA-0001.2 01/2020

ANNA-2019.3 02/2020
New research indicates that women may be able to reduce menopausal symptoms by increasing their intake of fruits and vegetables (FV). While hormone therapy (HT) is an acceptable treatment for these symptoms, it is a limited option because of increased health risks, which makes identifying modifiable lifestyle factors, like diet, more important.

The cross-sectional study was published in Menopause and aimed to address the relationship between climacteric symptoms and their subscales and total intakes of FV, and also their specific subtypes such as green, yellow, cruciferous, and other vegetables, plus citrus, berry, and other fruit separately. The study recruited 393 postmenopausal women aged 40 to 76 who attended the municipality health centers associated with Tehran University of Medical Sciences between September 2016 and January 2017. Participants were included in the study if they had been postmenopausal for ≥ 1 year. Women were excluded if they had a BMI ≥ 40 kg/m², smoked, had a medical history or presence of particular comorbidities (cancer, diabetes, stroke, multiple sclerosis, dementia, hyper or hypothyroidism), or had received HT for the past 6 months. Demographic and socioeconomic data were collected via face-to-face interview.

Participants were given a menopause rating scale (MRS) questionnaire with 11 items consisting of somatic, psychological, and urogenital symptoms to evaluate their menopausal symptoms. Responses ranged from 0 (no symptom) to 4 (very severe). The total MRS score (TMRSS) was the sum of the somatic score (SS), psychological score (PS), and urogenital score (US). Dietary intake was assessed through an in-person interview using a validated semiquantitative 147-item Food Frequency Questionnaire (FFQ) and consisted of food items with a standard serving size commonly consumed by Iranian people.

After adjusting for confounding variables, the authors discovered an inverse relationship between total FV and TMRSS (OR 0.23, 95% CI 0.07-0.71) and SS (OR 0.28, 95% CI 0.11-0.70). Intakes of total FV (OR 2.46, 95% CI 1.37-4.41), total vegetables (OR 2.54, 95% CI 1.10-5.88), green leafy vegetables (OR 3.59, 95% CI 1.47-8.75), dark yellow vegetables (OR 2.28, 95% CI 1.00-5.18), other vegetables (OR 5.23, 95% CI 1.17-15.39) and citrus fruits were linked to higher US (OR 4.35, 95% CI 1.77-10.77).

Based on their findings, the authors believe that health care providers may want to consider developing nutritional plans for their postmenopausal patients who suffer from menopausal symptoms. Increased total amount of FV and citrus fruits showed an inverse relationship with TMRSS and SS, and the inverse association between consumption total FV and PS approached significance. Higher intakes of total FV, total vegetables, green leafy vegetables, dark yellow vegetables, other vegetables, and citrus fruit were also associated with higher US. However, the authors note that more research is needed to confirm the findings.

Ben Schwartz is the associate editor for Contemporary OB/GYN.

SOURCE
Faster epigenetic aging linked with severe vasomotor symptoms

by BOB KRONEMYER

Accelerated biological aging was seen in women who had severe menopausal vasomotor symptoms (VMS) on enrollment in the Women’s Health Initiative Observational Study (WHI-OS), or late-occurring VMS (at enrollment but not during their reported menopause transition, according to a study in The Journal of Clinical Endocrinology & Metabolism.

“Previously, we discovered that VMS was associated with indicators of age-related health risks, such as cardiovascular disease (CVD) and osteoporosis,” said senior author Rebecca Thurston, PhD, a professor of psychiatry, psychology and epidemiology at the University of Pittsburgh. “We were interested in finding out if women with VMS had greater underlying epigenetic aging.”

The investigators examined connections between menopausal VMS and biological aging in 1,206 participants of the WHI-OS (average age 65 years at enrollment) who retained both ovaries and were not taking hormone therapy. Recruitment for baseline assessment occurred between 1993 and 1998. The sample comprised 55% non-Hispanic White women, 26% non-Hispanic Black women and 19% Hispanic women. Roughly one-third of the sample reported VMS at enrollment and 60% of the sample had VMS at some point during the menopause transition and/or at enrollment.

Connections between menopausal VMS and biological aging were assessed by two DNA methylation-based epigenetic aging indicators formerly linked to poor health outcomes: DNAm PhenoAge and DNAm GrimAge. Although no single metric proposed to characterize biological aging is universally accepted, DNAm-based indications offer the advantage of being a broad-based marker of accelerated aging across a diverse set of bodily systems and indicate robust relationships with adverse health outcomes, including CVD, mortality and Alzheimer’s disease.

The study concluded that severe hot flashes at enrollment were significantly associated with higher DNAm PhenoAge compared to no hot flashes: odds ratio (OR) = 2.79; P = 0.028. Late-occurring VMS were also associated with a significantly higher DNAm PhenoAge (OR = 2.15; P = 0.011), and significantly higher DNAm GrimAge (OR = 1.09; P = 0.010), relative to no VMS.

“We were not surprised that VMS were associated with greater epigenetic aging, given other findings linking them to health risks,” Dr. Thurston told Contemporary OB/GYN. “However, to my knowledge, we are the first to show this association. But we do not know at this time why postmenopausal women with severe or late-occurring VMS have greater biological aging.”

Three factors significantly associated with greater epigenetic aging for both DNA indicators were racial/ethnic minority status compared to White women (P = 0.0001), lower education (P = 0.001) and a higher body mass index (BMI) (P < 0.0001). Greater pack years of smoking was also a significant risk factor for biological aging, but only for DNAm GrimAge (P < 0.0001).

The authors accounted for these factors in their analyses, and therefore associations between VMS and epigenetic aging were not explained by them.

Based on study results, “women with VMS, particularly later in life, should engage in healthy preventive health measures,” said Dr. Thurston, president of the North American Menopause Society (NMS).

The next two steps will be to investigate women at the time of their menopause transition, as opposed to the WHI women who are considerably older, and to use more rigorous measures of VMS, such as physiological measures of VMS and prospective, self-report measures of VMS.

DISCLOSURE Dr. Thurston is a consultant to Astellas Pharma, Virtue Health, Pfizer and Procter & Gamble.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

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After Medicaid expansion under the Affordable Care Act (ACA), use of insurance for visits to safety net clinics specifically for contraception increased in all states, according to a study in the journal Medical Care. In the states where the coverage was expanded, however, levels of insurance for visits of all types remained higher.

“Besides Medicaid expansion, there are other federal and state programs that cover contraception for low-income and uninsured women, namely Title X and state Section 1115 waivers,” said principal investigator Blair Darney, PhD, MPH, an assistant professor of ob/gyn at Oregon Health & Science University in Portland.

What is unknown, though, is whether or how using insurance to pay for contraceptive visits has changed at safety net clinics following Medicaid expansion.

“Our dataset is unique in that it lets us include the uninsured, who are often missing from health services research, as well as federal and state programs across safety net clinics in the United States,” Dr. Darney told Contemporary OB/GYN.

The study sample comprised 162,666 contraceptive visits among women, aged 10 to 49 years, at 237 safety net clinics in 11 states with a common electronic health record. Seven of the states expanded Medicaid in 2014 (California, Minnesota, Nevada, Ohio, Oregon, Wisconsin and Washington), while the remaining four had not expanded coverage (Alaska, Indiana, Montana and North Carolina). Visits occurred from 12 months pre-expansion (January to December 2013) to 12 months post-expansion (January to December 2014) for both groups of states.

The proportion of uninsured contraceptive visits at safety net clinics significantly decreased following Medicaid expansion under the ACA, from 24.8% to 16.7% in expansion states and from 27.4% to 20.6% in non-expansion states. “But the gap between the two groups of states widened after ACA implementation: a 2.7%-point difference in 2013 compared to a 4.1%-point difference in 2014,” Dr. Darney said.

She and her colleagues were surprised by the strong evidence of a “spill-over” effect of the ACA. “Even in non-expansion states, public insurance coverage for contraceptive visits grew,” Dr. Darney said. “Also, private coverage through ACA provisions such as state insurance exchanges or marketplaces grew.”

Providers who serve low-income women need to understand the landscape of payment for contraceptive services, according to Dr. Darney. “There are ongoing policy debates about how best to use public funds to provide family planning services for low-income women; for instance, recent changes to the Title X program,” she said. “Providers can advocate for evidence-based policies and programs.”

Meanwhile, study results show that Medicaid expansion, as well as other provisions of the ACA and Title X, “are important policies to provide essential preventive care for women,” Dr. Darney said.

Many providers, however, have left the Title X program following recent changes to the program “that hamper provision of evidence-based care, including restrictions on referrals for abortion, limits to privacy protections for adolescents and emphasis on less effective or non-evidence-based contraceptive methods,” Dr. Darney said.

Nonetheless, “safety net clinics will continue to fill gaps in coverage for low-income women,” she said. “Continued focus on Title X and state programs, plus training and education for providers about the most effective methods of contraception, can help to expand access to the full range of effective contraceptive methods in this population.”

DISCLOSURES Dr. Darney report no potential conflicts of interest with regard to this article.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

Does IUD type impact cervical cancer risk?

by BEN SCHWARTZ

New research published in Obstetrics & Gynecology indicates that risk of high-grade cervical neoplasms is lower with copper (Cu) intrauterine devices (IUDs) than with the levonorgestrel-releasing intrauterine system (LNG-IUS). More than 100 million women worldwide use IUDs as contraception so these findings could have global implications.

The current study was a retrospective cohort analysis of 10,674 patients who received IUDs at Columbia University Medical Center. The authors restricted their cohorts to women age 45 years or younger at time of IUD insertion. Patients with a history of endometrial or cervical neoplasms or who had a prior IUD placement were excluded.

By default, women were in the Cu IUD cohort unless documentation of LNG-IUS appeared in the database. The outcome of the study was high-grade malignant cervical neoplasm or cervical neoplasm with a high association with malignancy, such as cervical intraepithelial neoplasia (CIN) grade II or III. Cervical polyps, CIN grade I, and metastatic spread of neoplasm to the cervix were excluded. Patients in the cohort and their outcomes were identified by a combination of procedure codes, condition codes, and medication exposures in billing and claim data. The authors adjusted for confounding with propensity score stratification and 1:1 matching.

A total of 10,674 patients were studied. Of them, 8,274 patients were in the Cu IUD cohort and 2,400 were in the LNG-IUS cohort. Ninety-seven percent (2,332) of the LNG-IUS users received a 52-mg device. Median age was 29 years (range 24-35) years in the Cu IUD cohort and 28 years (23-34) in the LNG-IUS cohort. During follow-up, 1,820 (22.0%) Cu IUD users and 797 (33.2%) of LNG-IUS users had a documented IUD removal procedure.

Before propensity score adjustment, the authors identified 114 cases of cervical neoplasm: 77 (0.9%) in the Cu IUD cohort and 37 (1.5%) in the LNG-IUS cohort. Propensity score matching analysis identified 7,114 Cu IUD and 2,174 LNG-IUS users, with covariate balance achieved over 16,827 covariates.

Of the women with Cu IUDs, 0.7% were diagnosed with high-grade cervical neoplasia versus 1.8% in the LNG-IUS cohort (IR 2.4 [95% CI 1.9-2.9] cases/1000 person years and IR 5.2 [95% CI 3.7-7.1] cases/1000 person years, respectively). Relative risk for high-grade cervical neoplasms among Cu IUD users was 0.38 (95% CI 0.16-0.78, P < .02) compared with LNG-IUS users.

The authors noted that the association between IUD usage and high-grade cervical neoplasm incidence has implications for public health on a global scale because more than 100 million women worldwide use the devices for contraception. The approximate 1% difference in high-grade cervical neoplasm incidence between Cu IUD and LNG-IUS user could have a large effect, especially in areas with the highest incidence of cervical cancer.

Ben Schwartz is the associate editor for Contemporary OB/GYN.

SOURCE

READ MORE
Contraceptive counseling for patients with disabilities
This case study illustrates how to navigate the complex issues ob/gyns may encounter when counseling patients with a cognitive impairment.

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PARP inhibitors
Choosing what to use in epithelial ovarian cancer

Across different drugs and clinical settings, use of PARPi has resulted in a prolonged period without cancer recurrence.

KRISTIN N. TAYLOR, MD, AND MARLA SCOTT, MD

Since the discovery of PARP inhibitors (PARPi) in 2005, there has been rapid clinical development of five different agents (olaparib, rucaparib, niraparib, veliparib, talazoparib), leading to seven indications approved by the US Food and Drug Administration (FDA) across breast and ovarian cancer (Table 1). In 2014, olaparib became the first PARPi approved by the FDA for use as treatment of recurrent ovarian cancer, followed by rucaparib in 2016 and niraparib in 2019. Over this same time period, the FDA approved all three of these PARPi for a different indication – as maintenance therapy intended to prolong the disease-free interval following chemotherapy. Across different drugs and clinical settings, use of PARPi has resulted in a prolonged period without cancer recurrence – or disease-free interval – particularly among patients with BRCA1 and BRCA2 mutations, owing to their mechanism of action (Table 2).

PARPi are a class of oral targeted therapy whose effect is dependent upon the tumor’s inability to repair its DNA. The PARP1 and PARP2 proteins are instrumental in repairing DNA single-strand breaks, which prevents formation of double-strand breaks at the time of DNA replication. PARPi block this repair process and thus dramatically increase the number of double strand breaks. Cells can typically repair these resultant double strand breaks in an error-free fashion using the homologous recombination (HR) pathway, but when the pathway is defective, PARPi result in cell death. This homologous recombination deficiency (HRD) is frequently a result of a germline or somatic mutation in a gene involved in the HR pathway, notably BRCA1 and BRCA2, but can also be detected in tumors in the absence of such mutations. With germline and somatic testing, patients with genetic mutations or tumors with HRD can be identified as those who may derive significant clinical benefit from PARPi use.

With more than 20 trials of PARPi in ovarian cancer alone, there is a growing body of literature on the common...
side effects of these drugs and their management, as well as their unique financial challenges. Ongoing clinical questions being addressed include how best to predict patient response to PARPi therapy, combat drug resistance, and determine the optimal setting(s) for use in individual patients.

**Adverse effects with use**

**GENERAL**

Many of the adverse events (AEs) encountered with use of PARPi are shared across agents. Most patients experience some degree of nausea and fatigue. Serious hematologic side effects can occur with any PARPi, and myelosuppressive effects can be exacerbated when these drugs are combined with other therapies. Dose reductions are often necessary in the event of a serious side effect, and if they persist, the drug may need to be discontinued. Of note, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are serious but rare AEs occurring in up to 1% of patients and they have been associated with several different PARPi. Embryofetal toxicity has been documented in animal studies with exposure to PARPi. These drugs should not be used in pregnant patients, and pregnancy should be avoided for 6 months following last exposure.²⁴

**INDIVIDUAL PARPI SIDE EFFECTS**

Olaparib was the first PARPi to be developed thus is the most extensively studied. The most common AEs with olaparib are fatigue, nausea, and vomiting, which occur in 60% to 75% of patients across studies. Serious hematologic AEs can occur in 10% to 20% of patients (anemia, neutropenia), and rarely patients experience severe fatigue (4%).²⁶ Olaparib in combination with vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab or cediranib can increase the rate of hypertension, fatigue, diarrhea, abdominal pain, and small bowel obstruction.⁷

The AE profile of rucaparib is similar to that of olaparib, with nausea and fatigue occurring in more than 70% of patients, and severe anemia in about one-fifth of patients. An isolated transaminitis is a unique AE with rucaparib use, resulting in mild to moderate elevations of alanine transaminase (ALT) and aspartate transaminase (AST) noted in one-third of patients and more serious elevations in approximately 10% of patients. Rash and photosensitivity were other specific yet uncommon mild AEs.⁸⁹

**UP TO 1% of patients may experience myelodysplastic syndrome or acute alceloid leukemia, which have been associated with several PARPi.**

Although not FDA-approved for use in the United States, veliparib has shown some efficacy as both mono-therapy and in combination with other cancer-directed treatments in numerous trials. Gastrointestinal (GI) AEs were similar to other PARPi, and severe AEs were relatively uncommon.¹¹

Talazoparib is only FDA-approved for treatment in patients with advanced breast cancer who have germline *BRCA* mutations (Table 1). Although fatigue and GI AEs are milder with talazoparib relative to other PARPi, severe hematologic AEs occur in up to 55% of patients.¹²

**MONITORING**

All PARPi require close monitoring with weekly complete blood count with differential for the first month of therapy, which can be done once a month thereafter, if the patient is stable. A complete metabolic panel should be obtained at baseline and periodically thereafter. Cholesterol should be monitored with rucaparib use. Niraparib may result in hypertension, so close observation of blood pressure at baseline and during the first month of therapy is advised.

**MANAGING AES**

Although patients may already experience some of the symptoms discussed above at baseline due to prior therapies or disease burden, adequate management of symptoms after start-
ing a PARPi is critical, as these AEs can have a significant impact on physical and psychological well-being. Anticipatory counseling about the likelihood of certain symptoms can reduce early discontinuation of drugs due to discomfort from AEs. Given the frequency of nausea, it is important to encourage use of antiemetics and counsel patients that these symptoms can abate after the first 1 to 2 months. Common interventions such as exercise and caffeine can be encouraged to improve fatigue, and over-the-counter pain relievers and anti-diarrheal medications should be prescribed for their respective AEs. Early involvement of supportive and palliative care specialists can also be helpful in managing symptoms. The National Comprehensive Cancer Network (NCCN) guidelines provide further guidance for symptom management.14

FINANCIAL TOXICITY
Financial toxicity is increasingly relevant with use of novel drugs including PARPi for which there are no generic alternatives. This includes both out-of-pocket expenses such as the direct costs (co-pays, medications, co-insurance) and non-medical costs including transportation, lodging, childcare, and lost wages from time away from work. Patients undergoing cancer treatments who are low income often spend up to 25% of their annual income on out-of-pocket medical costs.15 In addition, patients with cancer have a greater than two-fold higher risk of filing for bankruptcy compared to patients who do not have cancer, with nearly 60% of medically associated bankruptcies being due to cancer diagnoses.16 Financial toxicity has also been shown to negatively affect adherence to treatment.17 but financial barriers may limit access. We examined associations between out-of-pocket (OOP) Though the oral formulation of PARP allows patients to avoid costs associated with visits to the infusion center, it may come with a hidden cost due to a different level of insurance coverage. For example, when olaparib was initially approved in 2017, the out-of-pocket cost was $12,585 per month without insurance, yet patients with insurance coverage still may pay over $2,000 per month. Although there are medical assistance programs to help offset the cost of some PARPi, not all medical beneficiaries qualify.

New areas of investigation
PREDICTING RESPONSE
It has been well documented that tumors harboring germline or somatic BRCA mutations, and those that are “BRCA-like” with homologous recombination deficiency (HRD), tend to respond better to PARPi than their wild type counterparts.18,19 the products of which contribute to the conservative homologous recombination repair of DNA double-strand breaks. Nonetheless, several setbacks in clinical trial settings have highlighted some of the issues surrounding the investigation of PARP inhibitors, especially the identification of patients who stand to benefit from such drugs. One potential approach to finding this patient subpopulation is to examine the tumor DNA for evidence of a homologous recombination defect. However, although the genomes of many breast and ovarian cancers are replete with aberrations, the presence of numerous factors able to shape the genomic landscape means that only some of the observed DNA abnormalities are the outcome of a cancer cell’s inability

Low-income cancer patients may spend

25%

OF THEIR ANNUAL INCOME ON
out-of-pocket costs

Of all medically associated bankruptcies, nearly

60%

ARE DUE TO CANCER DIAGNOSES

Anticipatory counseling about certain symptoms can reduce early discontinuation.

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Agenda Highlights

- Genetics, Genomics, and Precision Medicine: Efficient Integration of Powerful Tools in Ovarian Cancer
- Advances in Frontline Treatment Options for Patients With Ovarian Cancer
- MXF-Treatment Sequencing in a Patient With Newly Diagnosed Ovarian Cancer: Role of VEGF Inhibition
- Precision Medicine in Ovarian Cancer: When Understanding the Biology Cuts Deeper Than Surgery
- Impact of Biomarker Testing on Precision Medicine for Cervical Cancer
- Sequencing of Treatments for Endometrial Cancer: What Does the Science Say?

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to faithfully repair DNA double-strand breaks. Consequently, recently developed methods for comprehensively capturing the diverse ways in which homologous recombination deficiencies may arise beyond BRCA1/2 mutation have used DNA microarray and sequencing data to account for potentially confounding features in the genome. Scores capturing telomeric allelic imbalance, loss of heterozygosity (LOH) HRD positivity is seen in approximately 20% of patients with ovarian, fallopian tube, and primary peritoneal cancers who carry a germline mutation in BRCA1/BRCA2 or an associated cancer susceptibility gene such as RAD51C or RAD51D, and up to 50% of tumors. MicroRNA expression, promoter methylation and DNA copy number in 489 high-grade serous ovarian adenocarcinomas and the DNA sequences of exons from coding genes in 316 of these tumours. Here we report that high-grade serous ovarian cancer is characterized by TP53 mutations in almost all tumours (96% There are commercially available assays that can identify HRD-positive tumors among BRCA wild-type patients.

Interestingly, some studies have demonstrated efficacy of PARPi even in HR-proficient tumors, though the benefits are less pronounced in this population. Patients whose disease is still considered sensitive to platinum chemotherapy also appear to respond better to PARPi than those with platinum-resistant or -refractory disease. Oral PARP inhibitor that is well tolerated, with antitumor activity in BRCA1/2 mutation carriers. Patients and Methods Patients with BRCA1/2-mutated ovarian cancer were treated with olaparib within a dose-escalation and single-stage expansion of a phase I trial. Antitumor activity was subsequently correlated with platinum sensitivity. Results Fifty patients were treated: 48 had germline BRCA1/2 mutations; one had a BRCA2 germline sequence change of unknown significance, and another had a strong family history of BRCA1/2-associated cancers who declined mutation testing. Of the 50 patients, 13 had platinum-sensitive disease, 24 had platinum-resistant disease, and 13 had platinum-refractory disease (according to platinum-free interval). The mechanism is not fully understood and is an area for further inquiry.

**MECHANISMS OF RESISTANCE**

Multiple mechanisms of inherent or acquired resistance to PARPi have been identified and continue to be studied. These are complex mechanisms occurring at both the genomic and cellular levels and tend to disrupt the “synthetic lethality” effect that makes PARPi effective in susceptible cells with HRD.

One such mechanism is acquisition of BRCA reversion mutations which can restore BRCA protein function in BRCA-mutated tumors and make cells homologous recombinant.

### Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Current FDA approvals for PARP inhibitor (PARPi) use in breast and ovarian cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td><strong>Breast cancer</strong></td>
</tr>
</tbody>
</table>
| **Frontline maintenance** | Germine or somatic BRCA-mutated:  
| Olaparib (2018)  
| Rucaparib (2018)  
| Niraparib (2017)  |
| **Recurrent maintenance** | Any BRCA mutation status, platinum-sensitive disease:  
| Olaparib (2017)  
| Rucaparib (2018)  
| Niraparib (2017)  |
| **Recurrent treatment** | Germine BRCA-mutated:  
| Olaparib (2014)  
| Germine or somatic BRCA-mutated:  
| Rucaparib (2016)  
| BRCA-mutated or HRD-positive:  
| Niraparib (2019)  |
| **Germline BRCA-mutated, HER2-negative:** | Olaparib (2018)  
| Talazoparib (2018)  |

Abbreviation: HRD = homologous recombination deficient.
With the HR pathway restored, cancer cells can repair DNA double-strand breaks that are induced by PARPi, thereby conferring a PARPi-resistant phenotype. A recent study of patients with known germline or somatic BRCA mutations showed that detection of BRCA reversions mutations in circulating cell-free DNA prior to treatment was correlated with decreased progression-free survival and found more commonly among platinum-resistant or -refractory cancers. We performed targeted next-generation sequencing of circulating cell-free DNA (cfDNA) used prospectively, this could become a means of choosing appropriate candidates prior to initiating PARPi therapy.

Another resistance mechanism that has been identified is upregulation of genes that encode for drug efflux pumps, which can lead to decreased intracellular levels of PARPi and thus less drug effect. Increased levels of proteins such as SLFN11 in tumors may augment the effects of PARPi, so low levels in tumors could eventually be used as a biomarker to predict PARPi resistance. Novel approaches are being developed to reverse resistance to PARPi by modulating these pathways.

**MAINTENANCE THERAPY**

Maintenance therapy is becoming ubiquitous in ovarian cancer care. The first FDA approval was in 2016, for the antiangiogenic agent bevacizumab after chemotherapy in patients with recurrent ovarian cancer. Since then, bevacizumab has also been approved as frontline maintenance therapy, to be given after primary treatment. PARPi are now approved for use as maintenance in some patients in both settings (Table 1). The question remains whether to administer maintenance therapy to all patients, and how to choose the most appropriate agent.

All three PARPi that are FDA-approved for use in ovarian cancer have indications for maintenance therapy in recurrent disease. Although these are irrespective of BRCA mutation or HRD tumor status, the magnitude of the benefit differs substantially by these factors, including sensitivity to the prior platinum chemotherapy treatment. The number of disease-free months gained with PARPi use (compared to placebo) approaches 15 months in patients with a BRCA mutation, while this benefit is up to 9 months for those with HRD tumors and just 3 months in patients with HR-proficient disease (Table 2). Among PARPi, only olaparib is approved for frontline maintenance therapy.

### Table 2.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial (drug)</th>
<th>BRCA-mutated</th>
<th>BRCA wild-type, HRD-Positive</th>
<th>BRCA wild-type, HRD-Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontline maintenance</td>
<td>SOLO-1 (olaparib)</td>
<td>36 months*</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>PRIMA (niraparib)</td>
<td>11.2 months</td>
<td>11.4 months</td>
<td>2.7 months</td>
</tr>
<tr>
<td>Recurrent maintenance</td>
<td>SOLO-2 (olaparib)</td>
<td>13.6 months</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>ARIEL-3 (rucaparib)</td>
<td>11.2 months</td>
<td>5.5 months</td>
<td>2.9 months</td>
</tr>
<tr>
<td></td>
<td>NOVA (niraparib)</td>
<td>15.5 months</td>
<td>9.1 months</td>
<td>3.1 months</td>
</tr>
</tbody>
</table>

Value in months calculated as the median disease-free survival in patients treated with PARPi inhibitor minus median disease-free survival in patients receiving placebo.

*Median disease-free survival not yet reached in the olaparib group. Benefit listed is estimated from a sensitivity analysis.

**Abbreviation:** HRD = homologous recombination deficient. Numerical references to be found online.
therapy, and is specifically for patients who harbor germline \textit{BRCA} mutations. Veliparib and niraparib have been investigated in this setting as well with promising results, although the indication currently is not FDA-approved. Interestingly, the combination of bevacizumab and olaparib as frontline maintenance led to significant prolongation of the disease-free interval for patients with \textit{BRCA} mutations and HRD tumors.\footnote{7}

\textbf{Conclusion}

With an abundance of recent data in ovarian cancer, the role of PARPi is rapidly evolving, and new standards of care are being developed. The paradigm for deciding which, if any, PARPi to give to a patient is complicated by the availability of bevacizumab as an alternative for maintenance therapy and traditional chemotherapy for treatment of recurrence. Although the benefits of PARPi are clear in delaying disease recurrence among many patients with \textit{BRCA}-mutated and HRD tumors, there is much to be learned about predictors of response and resistance to PARPi. Furthermore, the associated cumulative AEs and their impact on overall survival is not yet known, and some patients and providers may be reluctant to use a PARPi for this reason.

Nonetheless, the addition of PARPi to the landscape of treatments for ovarian cancer represents an exciting breakthrough in the age of personalized medicine. Patients can safely be given PARPi for extended periods of time and maintain a high quality of life. With knowledge of AE profiles, PARPi can be selected for a given patient based on their pre-existing symptoms and comorbidities, as these will impact the tolerability of specific PARPi. Differential insurance coverage for each PARPi may further determine what is feasible for a given patient. With the anticipation of more FDA-approved indications for PARPi in ovarian cancer, it is hoped that these drugs can become more accessible to everyone.

\textbf{PARPi AFTER PRIOR PARPi USE}

In the near future, many patients with recurrent ovarian cancer will have already been exposed to a PARPi as frontline maintenance therapy or as treatment for a prior breast cancer, and they could potentially be candidates for repeat PARPi use. Little is known about the efficacy and tolerability of PARPi in this setting. The ongoing OReO trial (NCT03106987) is evaluating the potential benefit of repeat exposure to olaparib maintenance therapy in patients with recurrent, platinum-sensitive ovarian cancer who have previously been treated with olaparib, regardless of \textit{BRCA} mutation status. MOLTO (NCT02855697) is also investigating the impact of repeat olaparib exposure, but it is limited to patients with germline \textit{BRCA} mutations.

Patients can safely be given PARPi for extended periods of time and maintain a high QOL.

\begin{itemize}
\item \textbf{INVITATION} \\
\item \textbf{PEER REVIEW} \\
\item \textbf{REVISION} \\
\item \textbf{PUBLICATION}
\end{itemize}

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Currently, 38 states and the District of Columbia have enacted dense breast notification (DBN) laws mandating that mammogram results include language informing women of risks related to dense breasts. However, new research from the *Journal of General Internal Medicine* shows that these laws are not associated with an increased understanding of the clinical implications of breast density.

The study assessed the association of residing in a state with a DBN law and a woman’s awareness and knowledge about breast density through survey responses. The survey also looked at breast cancer anxiety. The internet survey was conducted in 2018 with participants in KnowledgePanel®, an online research panel. Participants were English-speaking women between ages 40 and 59 without a personal history of breast cancer who had received at least one screening mammogram (N = 1928; survey completion rate 68.2%). The four main measures of the survey were: 1) reported history of increased breast density; 2) knowledge of the increased risk of breast cancer from dense breasts; 3) knowledge of the masking effect of dense breasts on mammography; and 4) breast cancer anxiety.

Based on weighted analysis, 41.3% of women reported a history of increased breast density. A much higher proportion of survey participants who lived in states with DBN reported having increased breast density compared with women who reported living in states with no law (43.6% vs 32.7%, \( P < 0.01 \)). In multivariable regression, women residing in a DBN state were more likely to report increased breast density (OR 1.70, 95% CI 1.34-2.17), as were older women, women with a high school education or higher, and with public or private insurance (compared with no insurance).

Black and Hispanic women were less likely than white women to report having increased breast density. Only 23.0% of women overall knew that increased breast density was associated with higher risk of breast cancer and 68.0% of women understood that dense breasts decreased the sensitivity of mammography. However, the authors found no difference between women from DBN and non-DBN states for these outcomes, or for breast cancer-related anxiety.

Based on their findings, the authors suggest that state DBN laws are not associated with increased understanding of the clinical implications of breast density. Furthermore, they found that women with lower education may be less likely to benefit from DBN laws. Ultimately, the authors believe that the clinical implications of a dense breast finding are “complex and personalized and require a conversation between a woman and her provider.”

Ben Schwartz is the associate editor for Contemporary OB/GYN.

**SOURCE**


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**GBC in breast MRI: What ob/gyns need to know**

Experts review the latest data to support counseling of patients who may have repeated exposure.

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AUGS CONSENSUS STATEMENT

Cystoscopy at the time of prolapse repair

The American Urogynecologic Society (AUGS) has issued guidelines on cystoscopy at the time of prolapse repair.

ABSTRACT
Injury to the urinary tract can occur during surgical repair of anterior and apical pelvic organ prolapse. Cystoscopy at the time of surgical prolapse repair is a low-risk procedure that can identify genitourinary tract injury by inspecting the bladder and urethra as well as by visualizing the ureters and ureteral efflux. There are several techniques to assist with visualization of ureteral efflux. Identifying injury intraoperatively can mitigate the morbidity of the injury. Universal cystoscopy should be performed at the time of all pelvic reconstructive surgeries, with the exception of operations solely for posterior compartment defects.

Iatrogenic injury to the lower genitourinary tract can occur during pelvic organ prolapse reconstructive surgery including anterior vaginal wall, vaginal vault (with or without concomitant hysterectomy), and obliterator repairs. Identifying lower genitourinary tract injuries intraoperatively decreases morbidity. Failure to identify lower genitourinary tract injury at the time of surgery can lead to serious complications including peritonitis, fistula formation, and loss of renal function.1,2

Cystoscopy is useful in assessing bladder integrity and ureteral patency. Surgeons should perform intraoperative cystoscopy during any pelvic organ prolapse reconstructive surgery with risk to the bladder or ureters, as cystoscopy provides a mechanism by which iatrogenic lower genitourinary tract injury can be recognized and, in most cases, immediately managed, thereby minimizing morbidity.

RECOMMENDATIONS
- Cystoscopy can identify lower genitourinary tract injury intraoperatively and prevent patient morbidity.
- Ureteral efflux should be confirmed when cystoscopy is performed during pelvic organ prolapse reconstructive surgery; multiple agents exist to aid with this if needed.
- Universal cystoscopy should be performed at the time of all pelvic organ prolapse reconstructive operations, with the exception of operations solely for posterior compartment defects.

FOR REFERENCES VISIT contemporaryobgyn.net/AUGScystoscopy

This was created in partnership with the American Urogynecologic Society (AUGS). AUGS was established in 1979 and represents more than 1,900 members, including practicing physicians, nurse practitioners, physical therapists, nurses and health care professionals, and researchers from many disciplines.

On August 27 at 11:40 p.m., the plaintiff was transferred from Defendant Hospital A to Defendant Hospital B with an admitting diagnosis of injury to the bladder and urethra and open wound. The admitting physician was Defendant ob/gyn B, who attempted conservative management; for 48 hours, the patient was stable without any issues. On August 29, a decision was made to perform a cystoscopy to further evaluate the bladder injury. Defendant ob/gyn B’s operative report indicated that informed consent was obtained. A cystogram was performed using 200 mL of fluid without obvious contrast extravasation. The plaintiff’s Foley catheter was removed and the two previously placed double-J stents were identified and noted to be in good position. A cystoscopy then was performed, and at the level of the trigone in the posterior portion of the bladder, an area consistent with the intraoperative injury was found. The same was noted to have granulating tissue but no obvious tear or extraperitoneal leak was seen. As a consequence, Defendant ob/gyn B decided “to not proceed with a formal repair” and instead, decided to continue to conservatively manage the plaintiff. The Foley catheter was replaced and the report concluded with a comment that the patient was to follow up in the office within the next 2 weeks for a repeat cystoscopy and removal of the double-J stents that had been placed. In the Postoperative Acute Care Unit, she received 2 units of blood. Discharge was on August 30.

A day later, the plaintiff was readmitted to Defendant Hospital B complaining of no urine output from the Foley catheter for 12 hours, lower abdominal pain, and difficulty breathing. The catheter was changed in the ER without relief of symptoms, so the plaintiff was admitted. On U/S, her bladder was small with fluid...
around it. A computed tomography (CT) scan showed that the Foley catheter was out of the bladder and in the peritoneum. The catheter was repositioned and conservative management was attempted. However, the patient had desaturations in oxygen to the 80s and was found to have bilateral pulmonary embolisms (PEs). Dopplers came back negative for deep vein thrombosis. Because of the woman’s history of PEs, a removable inferior vena cava filter was placed by vascular surgery. An intravenous (IV) heparin drip also was started. The plan was to stabilize the patient medically and then take her to the operating room (OR) for an open bladder repair.

On September 3, repair surgery was undertaken by Defendant ob/gyn B. The procedure was described as an open complex cystorrhaphy with a repair of bladder injury and placement of a suprapubic tube. Per the OR report, “due to the location of the injury at the level of the trigone, a decision was made to perform an intravesical repair.” As a result, a cystotomy was performed in the dome of the bladder. The injury was noted to be at the trigone between both ureteral orifices. A suprapubic catheter was placed and the plan was to monitor the patient, transition her back to a heparin drip and eventually warfarin, with the hopes of discharging her a few days thereafter. Postoperatively, the plaintiff had bouts of tachycardia. She remained on a heparin drip. Transthoracic echocardiography showed evidence of some right heart strain. Heparin was changed to enoxaparin sodium. The suprapubic tube eventually drained clear urine and the patient was discharged on September 6 with the suprapubic tube to the Foley catheter and a three-way, 24-French Foley to leg bag.

On September 13, the plaintiff followed up with Defendant ob/gyn B at his office. On exam, the doctor found her to be doing well with a suprapubic tube and the Foley catheter in place. He planned to keep the catheters in for the next 2 weeks and the note indicated she would be following up with her PCP regarding management of her warfarin level. Defendant ob/gyn B planned to perform a cystogram at the next visit and perhaps remove the Foley catheter but he intended to leave the suprapubic tube in for another few weeks. The plaintiff went to her PCP on September 24 for complaints of a UTI with abrupt onset. Diagnosis was acute cystitis, UTI and she was started on sulfamethoxazole/trimethoprim.

A note written by Defendant ob/gyn B about the patient’s return visit on September 27, repeated the history and said that the patient is “doing well with no complaints other than minimal pain from the Foley.” A cystogram was performed and no evidence of extravasation was noted. The Foley catheter was removed but the suprapubic tube was left in place. When plaintiff returned to Defendant ob/gyn B’s office a week later, a cystogram showed no evidence of extravasation and the suprapubic tube was removed. The bilateral stents were left in place and the patient was directed to return in 3 weeks for their removal. In addition, she was placed on more antibiotics as a result of a complaint of dysuria.

On October 8, the plaintiff was seen by her PCP for a complaint of 4-day lumbar radicular syndrome, pain 4/10. She also reported frequent urination, incontinence, dribbling, and painful urination. She reported that the pain started after the catheter was removed. The plan was that she return to the urologist for catheter placement versus further evaluation. On October 10, the plaintiff was transferred to Defendant Hospital B with complaints of nausea, vomiting, and flank pain and a diagnosis of pyelonephritis. A Foley catheter was placed and she was started on IV antibiotics. A CT scan showed bilateral moderate hydronephrosis with left perinephric stranding.

On October 12, Defendant ob/gyn B brought the patient back to the OR for a cystoscopy, during which he removed the bilateral stents. A cystogram was performed and again no contrast extravasation was seen. Thereafter, a cystoscopy was performed. The report noted that the “entire mucosa was extensively observed” and in the area of the previous repair, debris and granulation tissue were noted. Both ureteral orifices were easily identified, and both the right and left ureteral stents were noted to be calcified with debris. It was decided to remove the bilateral stents and she was discharged home with a suprapubic tube.
Though easily screened for, prevented and treated, tuberculosis is a leading cause of non-obstetrical death worldwide in reproductive age women, and significantly increases risk of maternal and fetal morbidity and mortality for women who are pregnant.

In this Contemporary OB/GYN® podcast, Lee P. Shulman, MD, FACMG, FACOG, discusses screening selectivity to reach high-risk populations, advantages of using an in-vitro blood test based on interferon-gamma release assay over a skin test with purified protein derivative, and appropriate treatment steps for patients testing positive.

Go to: contemporaryobgyn.net/tb-screening
On October 30, the woman saw her PCP for complaints of bladder discomfort.

The purpose of the visit was for a new onset of urinary incontinence. In his note, Defendant ob/gyn B recited the woman’s history of the complex bladder injury and repair, the pulmonary embolus. He also mentioned her “bleeding issues” (hypercoagulability), for which she was under the care of a hematologist. The plaintiff reported that she had been feeling well over the preceding 6 months and it was only 2 weeks prior when she started to notice the urinary incontinence. She denied any other urinary issues but did report that she was having some pelvic pain. A urine dipstick done in the office was within normal limits and the patient was scheduled for further evaluation with flexible cystoscopy. She did not return.

On October 30, the woman saw her PCP with complaints of bladder discomfort and UTI symptoms. She did not feel her complaints were socially unacceptable, but had leaking when she laughed, sneezed, and coughed. She also reported urinary frequency but no pain with incontinence. The diagnosis was UTI, acute cystitis. The plan was to start antibiotics.

The plaintiff went back to her PCP on February 27, 2016. His note reported that she presented for urinary incontinence and indicated that the woman was status-post multiple bladder procedures with new incontinence. The plan was to reorder medication for incontinence and that she should follow up with urology and urological studies. On July 18, the woman was seen by her primary care physician for lesions found on her rib cage via a CT chest. She had no complaints of dysuria, frequency, urgency, nocturia, hematuria or incontinence. Her exam was normal. The PCP referred the plaintiff for a bone scan to rule out metastatic disease, which was performed on July 28. On July 29, The PCP notified the woman that the results were normal.

Allegations

The plaintiff argued that the defendants delayed diagnosing a fibroid uterus, menorrhagia, and anemia and delayed treating fibroids and performing a hysterectomy. The plaintiff’s side further alleged that the defendants negligently performed a laparoscopic hysterectomy, delayed timely treatment of complex bladder injury, failed to diagnose said injury intraoperatively, failed to diagnose and treat or prevent bladder damage, delayed surgery, failed to have appropriate surgical specialists available, failed to assess risk factors for a PE, caused a PE, and failed to properly place a Foley catheter.

They contended that the bladder injury was diagnosed by defendants just after the hysterectomy was completed and during the cystoscopy of August 29, 2013. They argued that good and accepted medical practice required immediate repair of the hole in the plaintiff’s bladder. They contended that the delay placed the plaintiff at risk further complications including the worsening of her condition, worsening of the hole, reopening of the hole, incomplete closure, additional procedures, infection, increased risk of urinary incontinence and/or frequency and pain.
Discovery

Our firm only represented ob/gyn B in this matter. Our urology expert was able to defend Defendant ob/gyn B. The plaintiff’s injury, the cystotomy, occurred during the hysterectomy on August 26, 2013. He confirmed that any delay in performing surgery to repair the cystotomy did not cause further injury to the woman. Moreover, incontinence—her alleged injury—pre-existed the surgery. Therefore, any complaint that she was now at an increased risk because she was treated conservatively made no medical sense. In fact, she would be at an increased risk if she had surgery. Furthermore the repair itself was undertaken in a standard fashion and expertly performed.

The gynecology expert advised that the approximate 2-day delay in repairing the patient’s bladder injury made no difference. On August 29, Defendant ob/gyn B performed a cystogram and a cystoscopy to assess the extent of the plaintiff’s injury. The cystogram showed no evidence of leakage and the cystoscopy confirmed the finding. While some healing tissue was found, no perforation was found and there was no extravasation of dye. Defendant ob/gyn B directly visualized the area, and it appeared to be healing. Given the complexity of the repair that would have been necessary due to the injury’s location, Defendant ob/gyn B decided to treat the plaintiff conservatively. Our expert opined that the prudent course was to let her continue to heal as she appeared to be healing on her own, and not subject her to a further complicated surgery. As a general matter, although there is variation from patient to patient, but if a patient does not have a leak and is healing, treatment is conservative. Waiting for evidence of a leak for 2 days did not cause or contribute to subsequent urinary issues.

At Defendant ob/gyn B’s deposition, it became evident that the plaintiff really had no claims against him and was hoping, by naming him as a defendant and taking his deposition, that he would implicate the co-defendants. To the extent that the plaintiff found it necessary to have him testify that the injury to the bladder occurred at the prior institution, he accomplished his purpose. To the extent he had hoped that ob/gyn B would offer comment that the injury to the bladder was caused by negligence, he was unsuccessful. In fact, he testified that he had no knowledge of how the injury occurred other than learning that it happened during the surgery undertaken at the codefendant Hospital.

Result

The case settled as to co-defendant ob/gyn A prior to trial. Ob/gyn B was given a voluntary discontinuance.

ANALYSIS

This case was interesting because we essentially knew from the time of our client’s deposition forward that the plaintiff was not focusing on his actions or inactions and that so long as we maintained our defense posture, we were likely to extract him from the case if and when our codefendant settled. We were certainly prepared to defend his care at trial if it came to that. Sometimes things work out that way, but it is imperative to have the case fully worked up and evaluated to ensure you are in your best position to defend whatever allegations—credible or otherwise—are advanced. Ob/gyn B was prepared to not only defend his care but also not to offer opposing counsel any testimony that could implicate his codefendants and further the plaintiff’s somewhat spurious claims.

Was this prolapse properly managed?

In a case with multiple defendants, coordinating defenses should be the primary objective for trial.

The importance of intervention: When was this baby in trouble?

In this case, the question of fetal well-being as demonstrated on the FHR tracing is significant.
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CAREERS

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Did delay in bladder repair cause urologic issues?

Allegations in this complex case include negligence in performing laparoscopic hysterectomy and delaying treatment of bladder injury.

Facts
The 46-year-old plaintiff first presented to her primary care physician (PCP) on April 23, 2013, for a cough that had lasted 3 days. She reported incontinence, dribbling, and an inability to hold her urine after heavy menstruation. She also reported abdominal pain. Her PCP urged her to go to an ob/gyn for a work-up, with the differential possibly being endometriosis versus ruptured cyst. The impression was that the patient had recurrent stress urinary incontinence but the ob/gyn was concerned that it could turn into physical incontinence, given the woman’s gynecologic issues and age. The plan was to send her for an ultrasound (U/S) of the pelvis, which was performed on May 1, 2013. The U/S revealed a very large uterine fibroid (7x7 cm).

On May 5, 2013, the plaintiff presented to nonparty hospital with complaints of lower abdominal pain and vaginal bleeding that had lasted for 2 days. She reported bright red blood with multiple clots that increased throughout the day and her diagnosis with a 7x7-cm uterine fibroid by her PCP but said she did not have an ob/gyn. On exam, she reported that she had a history of heavy menses secondary to the fibroid. Transvaginal (TVUS) confirmed multiple fibroids, the largest being 8.7 cm, and an enlarged uterus (8.5 x 12.2 cm). The impression was leiomyoma of the uterus.

An interoperative cystoscopy confirmed a 2-cm tear near the vaginal cuff.

The woman was sent home in stable condition that night because she felt better, with a directive to follow up with an ob/gyn that week.

The plaintiff saw her PCP on July 23, 2013, for the start of preoperative medical clearance for a hysterectomy. She was cleared for surgery. Importantly, she reported incontinence and dribbling and that she could not hold her urine after menstruating. The assessment was vaginal bleeding, with abdominal pain secondary to the abdominal fibroids.

On or about August 26, 2013, the plaintiff presented to Defendant Hospital A for a laparoscopic hysterectomy by Defendant ob/gyn A, secondary to bleeding fibroids. The plaintiff’s history included a cesarean delivery, open cholecystectomy, bilateral breast reduction, and treatment for a miscarriage. During the hysterectomy, she sustained a bladder injury. An intraoperative cystoscopy confirmed a 2-cm tear near the vaginal cuff. Two double-J ureteral stents were placed by Defendant urologist, who recommended that she be transferred to Defendant Hospital B. The woman’s bladder was not repaired intraoperatively; instead she was transferred after Defendant ob/gyn A spoke with Defendant ob/gyn B.

FOR MORE LEGALLY SPEAKING
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Andrew I Kaplan, Esq is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP in New York City, specializing in medical malpractice defense and healthcare litigation. This case was handled by one of his partners.
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Rx Only
This Brief Summary does not include all the information needed to use SOLOSEC® safely and effectively. See full Prescribing Information for SOLOSEC.

SOLOSEC (secnidazole) 2g oral granules
Single oral dose
Initial U.S. approval: 2017

INDICATIONS AND USE
SOLOSEC is a nitroimidazole antimicrobial indicated for the treatment of bacterial vaginosis in adult women.

DOSEAGE AND ADMINISTRATION
Administer a single 2-gram packet of granules once orally, without regard to the timing of meals. Sprinkle entire contents of packet onto yogurt, applesauce, or pudding and consume all of the mixture within 30 minutes without chewing or crunching the granules. A glass of water may be taken after the administration of SOLOSEC to aid in swallowing. SOLOSEC is not intended to be dissolved in any liquid.

CONTRAINDICATIONS
Hypersensitivity. SOLOSEC is contraindicated in patients with a history of hypersensitivity to secnidazole, other ingredients of the formulation, or other nitroimidazole derivatives.

WARNINGS AND PRECAUTIONS
Vulvovaginal Candidiasis. The use of SOLOSEC may result in vulvovaginal candidiasis and may require treatment with an antifungal agent.

Potential Risk for Carcinogenicity. Carcinogenicity has been seen in mice and rats treated chronically with nitroimidazole derivatives, which are structurally related to secnidazole. It is unclear if the positive tumor findings in lifetime rodent studies of these nitroimidazoles indicate a risk to patients taking a single dose of SOLOSEC to treat bacterial vaginosis. Avoid chronic use of SOLOSEC.

Drug Resistance. Prescribing SOLOSEC in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide any benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS
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 practice.

The safety data described below reflect exposure to 589 patients, of whom 518 received a 2g dose of SOLOSEC. SOLOSEC was evaluated in 3 clinical trials of patients diagnosed with bacterial vaginosis: 2 placebo-controlled trials (Trial 1 n=215, Trial 2 n=189) and 1 uncontrolled safety trial (Trial 3 n=521).

All patients received a single oral dose of study medication or placebo. Trial 1 evaluated a 1g dose (this dose is not approved) dose (n=71) and a 2g dose (n=72) of SOLOSEC. Trial 2 evaluated 4 a 2g dose (n=125). The population was female, aged 15 to 54 years. Patients in the placebo-controlled trials were primarily Black or African American (54%) or Caucasian (41%). There were no deaths in the trials. Two patients in Trial 3 discontinued due to vulvovaginal candidiasis in the SOLOSEC-treated arm.

Most Common Adverse Reactions
Among 197 patients treated with a single 2g dose of SOLOSEC in the 2 placebo-controlled trials, Trial 1 and 2, adverse reactions were reported by approximately 29% of patients. Table 1 displays the most common adverse reactions (≥2% in SOLOSEC-treated patients) in these 2 trials.

Among the 321 patients in an uncontrolled trial, Trial 3, adverse reactions were reported in 30% of patients. Vulvovaginal candidiasis (8.4%), nausea (5.3%), abdominal pain, headache, and vomiting (2.5%) and dysgeusia (3.4%) were the most common adverse reactions reported in this trial.

Postmarketing Experience. The following adverse reactions have been reported during use of other formulations of secnidazole 2g 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. Reported adverse reactions were nausea, dysgeusia, abdominal pain, headache, and vomiting.

DRUG INTERACTIONS
Oral Contraceptives. There was no clinically significant drug interaction between secnidazole and the combination oral contraceptive, ethinyl estradiol plus norethindrone. SOLOSEC can be co-administered with combination oral contraceptives (eg, ethinyl estradiol plus norethindrone).

USE IN SPECIFIC POPULATIONS
Pregnancy. Limited available data with SOLOSEC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. In animal reproduction studies, there were no adverse developmental outcomes when secnidazole was administered orally to pregnant rats and rabbits during organogenesis at doses up to 4 times the clinical dose.

Lactation. Breastfeeding is not recommended. Discontinue breastfeeding for 96 hours after administration of SOLOSEC.

Pediatric Use. The safety and effectiveness of SOLOSEC in pediatric patients below the age of 18 years have not been established.

Geriatric Use. Clinical studies with secnidazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nitroimidazoles, which have similar chemical structures to secnidazole, have been associated with tumors affecting the liver, lungs, mammary, and lymphatic tissues in animals after lifetime exposures. It is unclear if these positive tumor findings in lifetime rodent studies of these nitroimidazoles indicate a risk to patients taking a single dose of secnidazole to treat bacterial vaginosis. Secnidazole was positive in the bacterial reverse mutation assay, but was negative for the rat micronucleus test and mouse lymphoma test.

In a rat fertility study, females were dosed for 2 weeks prior to mating until Day 7 of gestation with males that were dosed for a minimum of 28 days before cohabitation. No parental toxicity or adverse effects on mating performance, estrous cycles, fertility or conception was observed at doses of up to the maximum tolerated dose (300 mg/kg/day, approximately 1.4 times the recommended dose based on AUC comparisons).

PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information).

Manufactured for and Distributed by: Lupin Pharmaceuticals, Inc.
Baltimore, MD 21202
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NP-SOL-0004

Table 1: Adverse Reactions Occurring (≥2% SOLOSEC-Treated Patients) in the Pooled Placebo-Controlled Trials 1 and 2 in Adult Women with Bacterial Vaginosis

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SOLOSEC N=197 n (%)</th>
<th>Placebo N=136 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>19 (9.6)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (3.6)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (3.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (2.5)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (2.0)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Vulvovaginal pruritus</td>
<td>4 (2.0)</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>

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NP-SOL-0004
Solosec® (secnidazole) delivers a full course of bacterial vaginosis (BV) treatment in one oral dose¹

- Solosec demonstrated statistically and clinically significant efficacy in a pivotal trial²
  - Clinical response rate in Study 1 was 67.7% for Solosec, compared to 17.7% for placebo (p<0.001).²
  - Study 1 enrolled 215 non-pregnant female patients aged 19 to 54 years. Efficacy was assessed by clinical outcome evaluated 21-30 days following a single dose of Solosec.²
- Solosec has no alcohol restriction*¹
  *In vitro drug alcohol studies show Solosec does not interact with aldehyde dehydrogenase.¹
- Patients may pay as little as $25† for treatment with the Solosec Savings Program
  †Excluding Medicaid, Managed Medicaid, and Medicare. Terms and conditions apply. Visit solosechcp.com/savings for details.

Visit solosechcp.com to learn more and access the savings card

INDICATION
SOLOSEC® (secnidazole) 2 g oral granules is a 5-nitroimidazole antimicrobial agent indicated for the treatment of bacterial vaginosis in adult women.

IMPORTANT SAFETY INFORMATION
- SOLOSEC is contraindicated in patients with a history of hypersensitivity to secnidazole, other ingredients of the formulation, or other nitroimidazole derivatives.
- Vulvo-vaginal candidiasis may develop with SOLOSEC and require treatment with an antifungal agent.
- Potential risk of carcinogenicity is unknown and has not been studied. Carcinogenicity has been seen in rodents chronically treated with nitroimidazole derivatives, which are structurally related to secnidazole. Chronic use should be avoided.
- Breastfeeding is not recommended. Patients should discontinue breastfeeding for 96 hours after administration of SOLOSEC.
- Most common adverse reactions observed in clinical trials (incidence ≥2%) were vulvovaginal candidiasis, headache, nausea, dysgeusia, vomiting, diarrhea, abdominal pain, and vulvovaginal pruritus.

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-844-SOLOSEC (1-844-765-6732) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of Prescribing Information on Adjacent Page

References:
PERSPECTIVES ON

Outpatient Cervical Ripening Across Borders
Panelists

Eliane Shore, MD, MSc, FRCSC, is a member of the Division of Gynecologic Surgery and Pelvic Medicine at St. Michael’s Hospital in Toronto, Ontario, Canada. She is also an assistant professor at the University of Toronto and actively involved in the university residency program. Dr. Shore has a diverse practice that focuses on low-risk obstetrics, advanced gynecologic surgery, colposcopy, and management of vulvar disorders. Her research interests include surgical simulation, surgical education, resident selection, and clinical gynecology.

Mara Sobel, MD, MSc, FRCSC, is a member of the Division of Obstetrics and Gynecology at Mount Sinai Hospital in Toronto, Ontario, Canada, and an assistant professor at the University of Toronto. Her practice focuses on low-risk obstetrics, fibroids in pregnancy, and advanced gynecologic surgery, including surgical management of endometriosis. Her research interests include medical education and optimization of perioperative care.

Richard M. Burwick, MD, MPH is an assistant professor of obstetrics and gynecology and associate fellowship director in maternal-fetal medicine at Cedars Sinai Medical Center in Los Angeles, CA. He was among the first clinicians in the world to treat preeclampsia and HELLP syndrome using complement blockade. Dr. Burwick has clinical and research expertise in complement disorders such as atypical hemolytic uremic syndrome, and specializes in blood, kidney, and immune disorders in pregnancy. He is an expert in cervical cerclage and pessary to prevent premature delivery.

Rodney K. Edwards, MD, MS, is professor and chief of the Section of Maternal-Fetal Medicine, MFM Fellowship Program Director, and Presbyterian Health Foundation Endowed Chair of Perinatal Research at the University of Oklahoma Health Sciences Center in Oklahoma City. He is board certified in obstetrics and gynecology and in maternal-fetal medicine. Dr. Edwards has contributed to more than 85 scientific publications, including more than 65 original research articles. His research interests include infections in pregnancy, abnormal labor, obesity, and the interaction between those areas.

Disclosures

All faculty, planning committee members, editors, managers, and other individuals who are in a position to control content are required to disclose any relevant relationships with any commercial interests related to this activity. The existence of these interests or relationships is not viewed as implying bias or decreasing the value of this publication.

Rodney K. Edwards, MD, MS, has disclosed the following relevant financial relationship specific to the subject matter of the content included in this educational activity: Ferring (consultant, advisory board, investigator-initiated clinical trial)

Richard M. Burwick, MD, MPH, has disclosed that he has no relevant financial relationships specific to the subject matter within the last 12 months.

Eliane Shore, MD, MSc, FRCSC, has disclosed that she has no relevant financial relationships specific to the subject matter within the last 12 months.

Mara Sobel, MD, MSc, FRCSC, has disclosed that she has no relevant financial relationships specific to the subject matter within the last 12 months.

Scott Kober, MBA (Medical Writer), has disclosed that he has no relevant financial relationships specific to the subject matter within the last 12 months.

Commercial Support

This promotional supplement was developed by Contemporary OB/GYN with support from Ferring Pharmaceuticals.
Perspectives on Outpatient Cervical Ripening Across Borders

Induction of labor is a common process, occurring in approximately 25% of all term pregnancies.\(^1\)\(^2\) Cervical ripening is often the first component of labor induction in women with an unfavorable cervix, and is used to facilitate the softening and thinning of the cervix.

While cervical ripening was primarily initially confined to the inpatient setting, outpatient cervical ripening has now become the standard of care in many countries. It has, however, been more slowly adopted in the United States. In this supplement, four ob/gyn experts—two in Canada and two in the United States—discuss the reasons for the divergent perspective and offer insight into why outpatient cervical ripening may or may not be appropriate for today’s pregnant women. >>
Cultural differences in the approach to cervical ripening

Moderator: How do perspectives on outpatient cervical ripening differ between the United States and Canada?

Mara Sobel, BScH, MSc, MD, FRCS: At both Mount Sinai Hospital and St. Michael’s Hospital in Toronto Canada, the default is outpatient cervical ripening.

Eliane Shore, MD, MSc, FRCS: Based upon our experiences at other hospitals within Ontario, I think it’s fair to assume that most Canadian sites are using a combination of outpatient and inpatient cervical ripening.

Richard M. Burwick, MD: Certainly, outpatient cervical ripening is not as common in the United States as it is in Canada. Over the years, I’ve worked at a number of hospitals that did not offer outpatient cervical ripening to patients.

Moderator: Why is outpatient cervical ripening looked upon more favorably in Canada than in the United States?

Dr. Burwick: There are a variety of reasons. Some physicians are worried about medical and legal issues that may be involved, but I think a lot of it simply has to do with changing our mindset. Many hospitals have historically only offered inpatient induction, so convincing both physicians and patients that outpatient induction is a safe and reasonable option is challenging. Raising awareness has been the first step for us at Cedars-Sinai as we’ve worked on adopting an outpatient induction protocol.

Rodney K. Edwards, MD: There are a lot of physicians in the United States who are not yet convinced that the advantages of outpatient cervical ripening are proven, and when there is an absence of such evidence, people are going to be slow to change their practice. I would also agree that the medicolegal climate in the United States plays a role. In a setting where there is even a tiny likelihood of increased risk of complication with an unproven clinical benefit, the risk tolerance is very low.

Choosing the right patient

Moderator: How do you determine when a patient is a suitable candidate for outpatient cervical ripening?

Dr. Shore: At St. Michael’s, we schedule three inductions a day, but it’s not divided into inpatient or outpatient slots. Generally, the decision about keeping the patient in the hospital versus sending them home is up to the most responsible physician on that day. When the patient first arrives, they have a nonstress test (NST). We assess them, check their history, the fetal indication, maternal indications, and do a bimanual examination to determine the Bishop score. We then either determine what method of cervical ripening we are going to use (ie, progesterone gel, dinoprostone, Foley catheter) or, if their cervix is already ripe, admit the patient for artificial rupture of membranes and oxytocin as needed. For those patients who do qualify for cervical ripening, generally they are discharged home unless there is a maternal or fetal indication for admission. We also take into account the distance the patient has to travel to and from our hospital as well as social circumstances that may affect outpatient induction (eg, patients who are underhoused).

Dr. Edwards: Our group at the University of Oklahoma doesn’t generally support outpatient cervical ripening and certainly would not advocate an outpatient induction. There is an important difference between those two that I would like to highlight.

There are some people who advocate the administration of a dose of misoprostol as an outpatient procedure and consider it a procedure to “avoid” a labor induction. In my mind, however, misoprostol is both an induction and cervical ripening agent. If one is considering outpatient cervical ripening, I think that it would be preferable to choose an agent that will change the cervix but won’t necessarily induce labor. Although our hospital does not prohibit outpatient cervical ripening, it’s not something our physicians perform in a widespread fashion.

Moderator: Do any of you have a formal protocol in place at your institution for outpatient induction?

Dr. Burwick: I helped write our facility’s outpatient induction protocol with the Foley catheter. It’s been in place for less than 2 years. Because we didn’t previously have the option for outpatient induction, we started conservatively, developing a protocol for low-risk women, between 39 and 41 6/7 weeks’ gestation, with singleton pregnancies. Eligible women are those opting for an elective induction of labor. We are not yet permitting outpatient inductions for medical indications, such as hypertension or fetal growth restriction.

Dr. Sobel: At our institution, most patients are selected for outpatient induction unless there is an indication that the patient will require maternal or fetal surveillance throughout the process. As long as maternal and fetal well-being are reassuring, the patient will receive outpatient cervical ripening. Patients with maternal or fetal concerns, or those whose cervix is already favorable, are designated for an inpatient induction spot.

Moderator: How do you define a “favorable cervix”?

Dr. Sobel: We primarily look at the Bishop score, with a score
greater than 6 as favorable. A cervix with a Bishop score of >6 is typically amenable to artificial rupture of membranes.

Moderator: What is the benefit of outpatient cervical ripening?

Dr. Shore: The typical induction process is lengthy, so as long as patients are located close enough to the hospital that it’s easy for them to get back to us in a short amount of time, we find they are more comfortable in the early stages of induction at their own home. They know they can come back in at any time. They don’t need to wait for us to tell them it is time to return. We make sure they are reassured when we send them home that if anything comes up, they can call and speak to one of the nurses on labor and delivery or they can just come in. I think knowing that they are not abandoned at home makes outpatient induction an acceptable option for patients.

Moderator: What does the current medical literature say about the general efficacy of outpatient cervical ripening?

Dr. Shore: In 2013, a Cochrane review was published looking at the efficacy and safety of the three most common methods used for cervical ripening: prostaglandin gel, dinoprostone, and Foley balloon catheter. It compared results in the inpatient versus outpatient setting. The authors found equivalent results regardless of the induction method. They did, however, note that there were limited data in the outpatient setting and that it was not yet possible to determine whether induction of labor was safe and effective in the outpatient setting. One important feature was noted in the OPRA study, a 2015 trial comparing inpatient versus outpatient results following the use of prostaglandin E2 gel. That trial attempted to randomize patients to one of the two groups, but several of the patients randomized to the outpatient group either couldn’t proceed as outpatients due to maternal or fetal concerns or simply because they didn’t want to go home. That speaks to the importance of setting up appropriate expectations prior to the initial induction visit, so patients know what to expect.

Dr. Edwards: I would classify the data surrounding outpatient cervical ripening as mixed. I was a coauthor of a recent paper that looked at whether outpatient cervical ripening with a transcervical Foley catheter in parous women undergoing elective induction of labor shortens the total duration of time from admission to delivery. We did not find a significant difference. There have been other papers, however, that did show a time benefit. So from my perspective, mixed results.

I’m certainly more conservative about this topic than other members of this panel, and maybe that is because I’m the only one here with gray hair, but I don’t think we are ready to roll out outpatient induction at my center based on the current evidence. That said, there certainly are opportunities to investigate methods of care in terms of resource utilization. For example, what if we started evaluating beginning labor inductions that required cervical ripening in hospital units other than labor and delivery, since resources there are often strained? That could be interesting.

Moderator: What about any safety issues related to outpatient cervical ripening?

Dr. Shore: Very few safety concerns have been identified in clinical trials. One 2001 study looked at the use of dinoprostone in a simulated outpatient setting and found that more than 25% of patients required removal of the insert within 12 hours, usually due to regular contractions. The authors concluded that it therefore was not a good idea to send patients home with the dinoprostone insert, but I’m not sure I agree with that conclusion. The whole point of the procedure is to induce labor. It didn’t sound like the insert was removed for any concerning features, only because the women in the study were uncomfortable. I would not consider that a safety concern.

The OPRA study did note one adverse event about which the ob/gyn community should be mindful. In that study, one patient treated with prostaglandin gel had a baby with an undiagnosed growth restriction that necessitated delivery in a compromised state. The trial was actually temporarily halted while that case was reviewed, and eligibility criteria were tightened to exclude women from the outpatient induction group who had a baby with gestational age <10th percentile in the third trimester. But that was the only notable adverse event in the entire trial of 827 women.

Dr. Sobel: The general theme in most papers about this topic that I have read is that outpatient cervical ripening is safe in the appropriately selected patient.

Moderator: What questions or concerns do patients raise when you are talking to them about outpatient induction?

Dr. Sobel: We spend a lot of time explaining what our outpatient induction process will look like. Our outpatient induction slots are scheduled between 4:30 and 5:30 pm, and we send patients home overnight after an assessment of maternal/fetal well-being as long as there are no contraindications to doing so. It’s important to explain to patients that they might experience some uterine cramping and that, in the case of a Foley catheter, it might fall out.

Patients are given careful instructions on when to come back. If they are having painful contractions or their water

Outpatient cervical ripening: efficacy and safety
Perspectives on Outpatient Cervical Ripening Across Borders

Breaks, they should return to the hospital. We have a nurse-staffed phone line 24 hours a day for patients if they have any questions or concerns.

Dr. Shore: Especially for women in their second or third pregnancy who have kids at home, not having to be away from them for potentially several days during the labor and delivery process is also appealing. The biggest pushback I get from patients comes from those who might not have their own method of transportation. For instance, they may not have a car, so they’re looking at taxis or public transportation. We do take this into account when deciding about inpatient versus outpatient induction.

Current standards of care

Moderator: In patients that you do send home for outpatient induction, which of the three common cervical ripening methods do you prefer?

Dr. Sobel: At Mount Sinai, our default approach for inductions is the Foley catheter. It tends to cause less uterine contractions and is economical, which is always a concern in a publicly-funded health care environment. One downside to the Foley catheter is that it can be uncomfortable to insert and, in some cases, the patient won’t tolerate it. In these patients, we use prostaglandins in an outpatient setting.

Dr. Shore: Our approach at St. Michael’s is similar. The nice thing about Foley catheters and dinosprostone inserts are that they are removable methods. The Foley catheter will fall out. Dinoprostone inserts can be removed by the patient if they are suffering excessive pain or if they start having regular contractions. Another benefit is that neither method requires frequent reassessment, unlike prostaglandin gel, which requires patients to come back every 6 hours for reassessment.

Dr. Burwick: We have not yet started offering prostaglandins as part of our outpatient induction protocol and solely rely on Foley catheters, although prostaglandins do seem like a reasonable option. I did work at one center that offered misoprostol as part of an outpatient induction protocol, and I found it to be safe and effective in low-risk pregnancies.

In the past few years, I have seen a big change in our mindset regarding elective inductions at 39 weeks. Traditionally, the mindset was to avoid elective inductions in nulliparous women with an unfavorable cervix, but that’s beginning to change. As our inpatient labor floors are becoming fuller, there has been increased attention to outpatient induction protocols.

Impact of the ARRIVE trial

Moderator: In 2018, the ARRIVE trial was published showing that induction of low-risk, nulliparous women at 39 weeks was linked to a lower rate of cesarean section compared to those assigned to expectant management and a reduced chance of developing pregnancy-induced high blood pressure.8 What effect, if any, have the results of that trial had on your practice?

Dr. Edwards: To me, the ARRIVE trial results gave us a clear indication that induction of low-risk, nulliparous women is a viable option. However, we have not seen as brisk a rise in elective inductions in the last 2 years as I might have expected. Some patients simply don’t want to deliver at the 39-week stage via induction and want to carry the pregnancy for as long as necessary until spontaneous labor.

Dr. Burwick: We’ve noticed a big change at our hospital. Prior to the ARRIVE trial, we did not routinely offer elective induction in nulliparous women with an unfavorable cervix due to a variety of factors, including unclear benefit and a high demand for medically indicated induction of labor. We have a large unit with 20 active labor rooms and 7 induction slots per day, but most are prioritized for women with a medical indication. That said, we have seen an uptake in 39-week elective inductions based on the results of the ARRIVE trial, which encouraged us to develop an outpatient option for our patients.

Dr. Shore: We’ve certainly had a number of women come in with questions about the ARRIVE trial and what it means for them. Unfortunately, it’s a matter of resources. We only have three induction slots available each day, so if there are patients with medical indications for an induction such as post-term, preeclampsia, or intrauterine growth restriction, they will trump any woman who asks for an elective induction.

Moderator: One thing several of you have said is that the current demand for elective induction outstrips the number of available slots in your institutions. Have there been discussions about increasing the number of slots available for induction to accommodate the rising demand?

Dr. Shore: Not really. The reason why we don’t have more spots is because we can’t safely accommodate more patients on any given day. We don’t have the financial resources to hire more nurses and other staff right now. What I suspect will happen is that there will be a shift over time as fewer patients need to be induced post term. We just have not seen that shift yet.
Future perspectives

Moderator: What advice would you give to centers in the United States that are interested in developing an outpatient induction protocol or expanding opportunities for elective inductions? What are some of the pitfalls to avoid?

Dr. Sobel: Certainly, the adoption of protocols from other centers that have succeeded previously can be helpful. Getting buy-in from the various parties who will be affected—including ob/gyns, nurses, midwives, patients and others—is key. Everyone needs to understand the primary components of the new protocol and be allowed to offer their input.

It can be helpful to start your outpatient induction protocol by only including the healthiest, lowest-risk patients until your team gets comfortable with the process. We initially only included healthy, post-term women as outpatients, but now, as we have gained experience, we’re even including women with stable high blood pressure or other medical concerns as outpatients if they have reassuring findings in the pre-induction assessment.

Dr. Burwick: I agree that staff buy-in is key. We have numerous provider groups that deliver at Cedars Sinai, and thus we tried to reach out to stakeholders from all groups as we developed our protocol.

The hardest part comes during actual rollout of the new protocol and seeing, “OK, we’ve talked about this and put the protocol down on paper, but when push comes to shove, will people be willing to recommend it to their patients?” We’re currently tracking and analyzing our post-implementation data to see how we are doing.

It’s also important to allow providers some flexibility within the boundaries of the protocol. For example, we have some providers who prefer to place the Foley catheter in the office as opposed to in the labor-and-delivery triage setting within the hospital. We also noticed that providers had different preferences specific to the Foley catheter. In our initial protocol, we called for a 16-French Foley catheter, but we learned that there were many providers in the hospital setting who used a 22 or 24 French. You need to allow for some flexibility so that your protocol works for the entire team.

Moderator: This has been a terrific discussion. We want to thank you all for your insights. I hope that our audience can take away some helpful information from our discussion to inform their practice’s approach to outpatient cervical ripening and induction of labor. ■

References
11th Annual
INTERNATIONAL SYMPOSIUM ON
OVARIAN CANCER
AND OTHER GYNECOLOGIC MALIGNANCIES®

SATURDAY,
MAY 2, 2020

Program Co-Chairs:

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Professor and Executive Director
Cancer Network Research
Ann Rife Cox Chair in Gynecology
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
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Creighton University School of Medicine
St. Joseph’s Hospital and Medical Center
Medical Director, US Oncology Network – Gynecologic Oncology Research
Phoenix, AZ

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• Network with gynecological experts and colleagues
• Discuss evidence-based approaches to mitigate adverse events
• Apply latest approved agents and companion diagnostic tests

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Overview:

The 11th Annual International Symposium on Ovarian Cancer and Other Gynecologic Malignancies® is a 1-day, educational and scientific meeting that will focus on key clinical topics in the management of ovarian cancer, as well as endometrial, uterine, and cervical malignancies. Join leading experts as they debate and discuss the latest diagnostic, therapeutic, and supportive care strategies for patients with gynecologic cancers. The field has seen breakthroughs in treatment options in recent years, including the integration of targeted therapies and immunotherapeutics into clinical practice. Optimal implementation of surgery, chemotherapy, PARP inhibitors, antiangiogenesis agents, checkpoint blockade, as well as combination and other therapeutic strategies, will be analyzed and discussed both in frontline and recurrent disease settings. Case-based presentations will allow for vibrant discussion of the practical concerns of treating patients in the real world. Promising novel agents currently undergoing clinical trial evaluation will also be highlighted.

What You Will Learn:

- Understand the design, efficacy, and safety data of clinical trials investigating novel compounds and strategies for the management of gynecologic malignancies
- Apply the new findings and recently presented data in clinical context, and understand their therapeutic implications for the management of gynecologic malignancies
- Potentiate trial enrollment for eligible patients in order to evaluate new agents or strategies in the treatment of gynecologic malignancies

Registration Fees:

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<tr>
<th>Role</th>
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<tr>
<td>Physicians</td>
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<td>Fellows*</td>
<td>$50</td>
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<td>Nurses, PAs, other HCPs</td>
<td>$50</td>
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<td>Industry**</td>
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## Agenda

### 8:00 AM
Welcome, Introductions, and Presession Survey

**Bradley J. Monk, MD, FACOG, FACS**

### OVARIAN CANCERS

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>8:15</td>
<td>Genetics, Genomics, and Precision Medicine: Efficient Integration of Powerful Tools in Ovarian Cancer</td>
<td>Michael Birrer, MD, PhD</td>
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<tr>
<td>8:40</td>
<td>Advances in Frontline Treatment Options for Patients With Ovarian Cancer</td>
<td>Kathleen Moore, MD</td>
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<tr>
<td>9:05</td>
<td>Mechanisms of Development and Strategies for Overcoming PARP Resistance</td>
<td>Gottfried Konecny, MD</td>
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<td>9:30</td>
<td>Incorporating Combination Therapy in an Evolving Treatment Landscape</td>
<td>Susana M. Campos, MD, MPH</td>
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<td>9:55</td>
<td>Break</td>
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<tr>
<td>10:25</td>
<td>Immunotherapeutic Updates in Ovarian Cancer</td>
<td>Ursula A. Matulonis, MD</td>
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<tr>
<td>10:50</td>
<td>Future Directions: Where Are We Headed?</td>
<td>Maurie Markman, MD</td>
</tr>
<tr>
<td>11:15</td>
<td>MXF-Treatment Sequencing in a Patient With Newly Diagnosed Ovarian Cancer: Role of VEGF Inhibition</td>
<td>Bradley J. Monk, MD, FACOG, FACS</td>
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<td>11:40</td>
<td>Cases and Q&amp;A Session</td>
<td>Ursula A. Matulonis, MD</td>
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<tr>
<td>12:05</td>
<td>Keynote Lecture—Precision Medicine in Ovarian Cancer: When Understanding the Biology Cuts Deeper Than Surgery</td>
<td>Robert L. Coleman, MD, FACOG, FACS</td>
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### CERVICAL CANCERS

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<tr>
<td>1:45</td>
<td>Impact of Biomarker Testing on Precision Medicine for Cervical Cancer</td>
<td>Ritu Salani, MD</td>
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<tr>
<td>2:10</td>
<td>What, When, Where: Sequencing Therapies for Cervical Cancer</td>
<td>Debra Richardson, MD, FACOG, FACS</td>
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<tr>
<td>2:35</td>
<td>Future Directions: Emerging Therapies in Cervical Cancer</td>
<td>Bradley J. Monk, MD, FACOG, FACS</td>
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### ENDOMETRIAL CANCERS

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<td>Can Biomarker Testing Inform Treatment Decision Making in Endometrial Cancer?</td>
<td>Ramez Eskander, MD</td>
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<td>4:20</td>
<td>Future Directions: Novel Agents and Treatment Strategies in Endometrial Cancer</td>
<td>Shannon N. Westin, MD, MPH</td>
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<td>4:45</td>
<td>Interactive Cases and Expert Discussion in Cervical and Endometrial Cancer</td>
<td>Robert L. Coleman, MD, FACOG, FACS</td>
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<tr>
<td>5:10</td>
<td>Closing Remarks and Adjournment</td>
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Meet the Faculty

Michael J. Birrer, MD, PhD  
Vice Chancellor, UAMS  
Director, Winthrop P. Rockefeller Cancer Institute  
Director, Cancer Service Line  
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Fellowship Director  
Associate Residency Program Director  
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President, Medicine & Science  
Cancer Treatment Centers of America  
Clinical Professor of Medicine  
Drexel University College of Medicine  
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Associate Director, Clinical Research  
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Stephenson Cancer Center  
Associate Professor, Section of Gynecologic Oncology  
Director, Gynecologic Oncology Fellowship  
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