TREATING INFERTILITY

Shared decision-making approach to effective outcomes

Amanda Kallen, MD & Sandra Ann Carson, MD

OBSTETRICS
 Imaging approach to early pregnancy failure

VULVOVAGINAL DISEASE
 Rare vulvar infection in patient with acute myeloid leukemia

CONTRACEPTION
 Choosing the right pill

WELL WOMAN
 Advocating for changes in the compounded bioidentical hormone industry

LIFE TRANSITIONS
 Prior depression may worsen in perimenopause

GYNECOLOGY
 Recurrence of high-grade cervical dysplasia
INDICATION
ORILISSA® (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.
INDICATIONS AND USAGE
ORILISSA is indicated for the management of moderate to severe pain associated with premenstrual dysphoric disorder (PMDD) in premenopausal women without a past history of endometriosis.

DOSE AND ADMINISTRATION
Important Dosing Information
• Exclude pregnancy before starting ORILISSA or start ORILISSA within 7 days of the onset of menses.
• 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 responses (see Warnings and Precautions).
• Limit the duration of use because of bone loss (see Table 1) (see Warnings and Precautions).

Recommended Dose and Duration of Use

Dosing Regimen | Maximum Treatment Duration | Conceding Condition
--- | --- | ---
Inhibit treatment with ORILISSA 150 mg once daily | 30 months | None
Consider withdrawing treatment with ORILISSA as tolerated | 6 months | Osteopenia
Inhibit treatment with ORILISSA 150 mg once daily or 200 mg twice daily is not recommended. | 6 months | Moderate hepatic impairment (Child-Pugh Class B)

Impairment
No dosage adjustment of ORILISSA is required in women with mild hepatic impairment (Child-Pugh A).

Limitation of Use because of Bone Loss
- Moderate hepatic impairment
- Severe hepatic impairment (Child-Pugh C)

Oral Contraceptive Use
- Concomitant use of ORILISSA and oral contraceptives is not recommended. (See Drug Interactions and Warnings and Precautions).

Food
- There is no effect of food on the absorption of ORILISSA (see Clinical Pharmacology).

TABLE 1. Recommended Dose and Duration of Use

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Maximum Treatment Duration</th>
<th>Conceding Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit treatment with ORILISSA 150 mg once daily</td>
<td>30 months</td>
<td>None</td>
</tr>
<tr>
<td>Consider withdrawing treatment with ORILISSA as tolerated</td>
<td>6 months</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>Inhibit treatment with ORILISSA 150 mg once daily or 200 mg twice daily is not recommended.</td>
<td>6 months</td>
<td>Moderate hepatic impairment (Child-Pugh Class B)</td>
</tr>
</tbody>
</table>

Hepatic Impairment
No dosage adjustment of ORILISSA is required in women with mild hepatic impairment (Child-Pugh A).

- Compared to women with normal liver function, those with moderate hepatic impairment had approximately 2- to 3-fold higher ORILISSA exposure and those with severe hepatic impairment had approximately 7- to 8-fold higher ORILISSA exposures. Because of these increased exposures and risk for bone loss:
  - ORILISSA 150 mg once daily is recommended for women with moderate hepatic impairment (Child-Pugh B) with the duration of treatment limited to 6 months. Use of ORILISSA 200 mg twice daily is not recommended for patients with moderate hepatic impairment (see Use in Specific Populations).

- The patient who 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).
- Who are nursing (see Use in Specific Populations).
- With known or suspected pregnancy (see Use in Specific Populations).
- With concurrent use of strong organic cation transport polypeptide (OCTP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil) (see Drug Interactions).

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 reversed by temporarily 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 weakness, and the use of 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, administration of these 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 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 endometriomas clinical trials. ORILISSA subjects had a higher incidence of depression and mood changes compared to placebo, and ORILISSA subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history (see Adverse Reactions). Promptly evaluate patients with depressive symptoms to determine whether the risk of continued therapy outweighs the benefits (see Adverse Reactions). 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 medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORILISSA if such events occur.

Hepatic Transaminase Elevation
In clinical trials, dose-dependent elevations of serum alanine aminotransferase levels over the upper limit of the reference range occurred with ORILISSA. Use the lowest effective dose of ORILISSA and carefully monitor patients for signs of or symptoms that may reflect liver injury, such as jaundice. Promptly evaluate patients with abnormal transaminase levels to determine whether the benefits of continued therapy outweigh the risks (see Adverse Reactions).

Reduced Efficacy with Estrogen-Containing Contraceptives
Based on the mechanism of action of ORILISSA, estrogen containing contraceptives should not be used concurrently with ORILISSA. The presence of progesterone-only contraceptives on the efficacy of ORILISSA is unknown. Advise women to use non-hormonal contraceptives during treatment with ORILISSA and for one cycle after discontinuing ORILISSA (see Use in Specific Populations).

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 clinical practice.

The safety of ORILISSA was evaluated in two six-month, randomized, double-blind, placebo-controlled clinical trials (EM-1 [NCT01650238] and EM-2 [NCT01719301]) in which a total of 1,162 adult women with moderate to severe PMDD were treated with ORILISSA 150 mg once daily and 200 mg twice daily and placebo. In the first 1-month treatment period, one unplanned extended trial was reported by 55%, 91% and 96% of women within 1, 2, and 6 months respectively. After 12 months of therapy, women were receiving ORILISSA or within 30 days after stopping ORILISSA. In Study EM-3, if a subject had BMD loss of more than 1.5% at the lumbar spine or more than 2.5% at the total hip at the end of treatment, follow-up DXA was performed at 2 years. In Study EM-4, all subjects were required to have a follow-up DXA 6 months off treatment regardless of change in BMD. In some subjects, DXA was performed more than 6 months after stopping ORILISSA. In Study EM-3, if a subject had BMD loss of more than 1.5% at the lumbar spine or 2.5% at the total hip at the end of treatment, follow-up DXA was performed at 2 years. In Study EM-4, all subjects were required to have a follow-up DXA 6 months off treatment regardless of change in BMD. In some subjects, DXA was performed more than 6 months after stopping ORILISSA.

Table 2. Percentage of Subjects in Studies EM-1 and EM-2 with Treatment-Related Adverse Reactions Occurring in At Least 5% of Subjects (except ORILISSA Dose Group) and at a Greater Incidence than with placebo

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>% (N=477)</th>
<th>% (N=734)</th>
<th>% (N=477)</th>
<th>% (N=734)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORILISSA 150 mg Once Daily</td>
<td>0.4</td>
<td>0.4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ORILISSA 200 mg Twice Daily</td>
<td>0.4</td>
<td>0.4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORILISSA 150 mg Once Daily</td>
<td>0.4</td>
<td>0.4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ORILISSA 200 mg Twice Daily</td>
<td>0.4</td>
<td>0.4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The use of ORILISSA 150 mg once daily or ORILISSA 200 mg twice daily for up to 12 months and when then followed after cessation of therapy for an additional 6 months. Partial recovery of BMD was seen in these subjects (Figure 1). In Study EM-3, if a subject had BMD loss of more than 1.5% at the lumbar spine or more than 2.5% at the total hip at the end of treatment, follow-up DXA was performed after 6 months off treatment. In Study EM-4, all subjects were required to have a follow-up DXA 6 months off treatment regardless of change in BMD. In subjects with BMD loss of more than 1% at the lumbar spine or more than 2% at the total hip at the end of treatment, follow-up DXA was performed after 6 months off treatment. Figure 2 shows the changes in lumbar spine BMD for the subjects in Study EM-2 (N=188) who completed 12 months of treatment with ORILISSA and who had a follow-up DXA 12 months off treatment.

Figure 1. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up DEXA 6 Months off Therapy in Studies EM-2/N-EM-4

Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up DEXA 6 Months off Therapy in Studies EM-2/N-EM-4
Suicidal ideation, Suicidal behavior and Attemptation of Mass Disorders

In the placebo-controlled trials, one subject withdrew due to suicidal ideation. This subject had a history of depression.

Among the 2500 subjects exposed to ORILISSA in the endometriosis Phase 2 and Phase 3 studies, there were four reports of suicidal ideation. In addition to the two subjects in Table 2, there were two additional reports of suicidal ideation: one subject on 75 mg once daily, and one in a Phase 2 study (75 mg once daily, unapproved dose). Three of these subjects had a history of depression. Two subjects discontinued ORILISSA and two completed the clinical trial treatment periods.

Adverse Reactions

Table 6. Mean Change and Maximum Increase from Baseline in Serum Lipids in Studies EM-1 and EM-2

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Placebo (N=734)</th>
<th>ORILISSA 150 mg once daily (N=183)</th>
<th>ORILISSA 200 mg twice daily (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>137</td>
<td>107</td>
<td>122</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>48</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>113</td>
<td>113</td>
<td>113</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>Concomitant Use of ORILISSA</th>
<th>Effect of ORILISSA on Drug Metabolism</th>
<th>Clinical Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Antimycobacterial</td>
<td>Increase maximum daily dose of omeprazole in subjects taking elagolix (P-gp inhibitor)</td>
<td>Reduce elagolix dose at 150 mg daily</td>
<td>Titrate omeprazole to a lower dose based on clinical assessment</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Antiarrhythmic</td>
<td>Increase mean Cmax of digoxin</td>
<td>Reduce the dose of digoxin</td>
<td>Consideration of the individual patient’s needs</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Oral midazolam</td>
<td>Increase Cmax and Tmax of midazolam</td>
<td>Reduce the dose of midazolam</td>
<td>Consideration of the individual patient’s needs</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antimicrobial</td>
<td>No effect on the pharmacokinetics of rifaximin</td>
<td>No effect on the pharmacokinetics of rifaximin</td>
<td>Consideration of the individual patient’s needs</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Antineoplastic</td>
<td>No effect on the concentration of hydroxyurea</td>
<td>No effect on the concentration of hydroxyurea</td>
<td>Consideration of the individual patient’s needs</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Immunosuppressant</td>
<td>No effect on the concentration of azathioprine</td>
<td>No effect on the concentration of azathioprine</td>
<td>Consideration of the individual patient’s needs</td>
</tr>
<tr>
<td>P-glycoprotein inhibitors</td>
<td>Metabolite inhibition</td>
<td>No effect on the concentration of P-glycoprotein inhibitors</td>
<td>No effect on the concentration of P-glycoprotein inhibitors</td>
<td>Consideration of the individual patient’s needs</td>
</tr>
</tbody>
</table>

Use in Specific Populations

**Pregnancy**

Pregnancy Exposure Registry

There is no information on the occurrence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on reproduction or fertility. There are no adequate animal data on the secretion of ORILISSA in milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s need to avoid breastfeeding. Milk feeding at the lowest estimated exposure in humans is unknown.

**Lactation**

There is no information on the occurrence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on reproduction or fertility.

**Females and Males of Reproductive Potential**

Based on the mechanism of action, there is a risk of early pregnancy loss in women who are administered to a pregnant woman (see Data on Specific Populations).

**Programmed Testing**

Include pregnancy before initiating treatment with ORILISSA. Perform pregnancy testing if pregnancy is suspected during treatment with ORILISSA (see Warnings and Precautions and Drug Interactions).

**Contraception**

Advise women to use effective non-hormonal contraception during treatment with ORILISSA and for one week after discontinuing ORILISSA (see Warnings and Precautions and Drug Interactions).

**Pediatric Use**

Safety and effectiveness of ORILISSA in patients less than 16 years of age have not been established.

**Renal Impairment**

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

**Hepatic Impairment**

No dosage adjustment of ORILISSA is required for patients with mild hepatic impairment (Child-Pugh B). Only the 150 mg once daily regimen is recommended for women with moderate hepatic impairment (Child-Pugh B) and the duration of treatment should be limited to 6 months. ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) (see Contraindications).

**OVERDOSAGE**

In case of overdose, monitor the patient for any signs or symptoms of adverse reactions and initiate appropriate supportive treatment, as needed.

**NONCLINICAL TOXICOLOGY**

Carcinogenesis, Mutagenesis, Impairment of Fertility

In the two 2-year carcinogenicity studies conducted in mice (90, 150, or 200 mg/kg/day) and rats (150, 300, or 500 mg/kg/day) that administered ORILISSA at doses up to 10-fold, there was no evidence of a clastogenic effect on the bone marrow of rats. Although the duration of total exposure was limited in ORILISSA clinical trials, there were no apparent decreases in birth weights associated with ORILISSA in comparison to placebo.

Animal Data

A method of potential developmental study in rats, elagolix was given in the diet to achieve doses of 0.100 and 300 mg/kg/daily (25 per cent dose per group) from gestation day 4 to lactation day 20. There was no evidence of maternal toxicity. At the highest dose, two dams had total litter loss, one and one dose failed to deliver. The suckled was weaned was not different between groups. Overall, there was no difference in postnatal body weight gain between groups. ORILISSA 150 mg once daily and the estimated fetal exposure to ORILISSA was 1.2% of the maternal exposure. The developmental and health benefits of breastfeeding should be considered along with the mother’s need to avoid breastfeeding. Milk feeding at the lowest estimated exposure in humans is unknown.
male and female (and liver 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.
  - 300 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.
CHAIRMAN’S LETTER

Age of anxiety

The practitioner’s role is to care for others, but what happens when they are facing burnout and have no time to care for themselves? It is a common theme we are hearing from physicians across the specialties we cover. As the pandemic goes on, the issue of mental health has been coming to the forefront. In her editorial that begins on page 8, Editor-in-Chief Catherine Y. Spong, MD, gives us a glimpse into her antepartum rounds and the number of women she is seeing who struggle with mental illness and substance abuse. According to the Centers for Disease Control (CDC), national rates of anxiety have increased four-fold from one year ago. Why wouldn’t that be the case? Life as we know it has been upended. The ability to socialize and feel of community have changed, and economic and life stressors are compounded. In caring for others during this time, physicians also must remember to know their own limits. Last month, we included an article on physician burnout. You can access that article at contemporaryobgyn.net/burnout. For ob/gyns, professional organizations such as the American College of Obstetricians and Gynecologists (ACOG) have additional resources. There are numerous resources available. As Dr. Spong points out, one of her colleagues’ practices has biweekly meetings with a psychologist. These are trying times for everyone. Do not leave yourself out. Let us know what you are doing for self-care, or what programs are being implemented at your institutions or hospital facilities by emailing Senior Editor Angie DeRosa at aderosa@mjhlifesciences.com.

Mike Hennessy, Sr.
Chairman and Founder, MJH Life Sciences
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54 Was this a failure to diagnose ovarian failure? ANDREW I. KAPLAN, ESQ

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My antepartum rounds reflect the impact of the pandemic - women struggling with substance abuse and mental illness fill the beds. One patient, wearing her designated green hospital gown that signals “at-risk” status and assigned a one-on-one sitter, explained, “Isn’t it appropriate to have bad thoughts now? I have three kids at home – two I try to make the computer work for so they can attend school, a 1-year-old, and here I am pregnant again. We lost our jobs, tensions are high, we cannot visit or see anyone, we have no help… At times it all just boils up and I explode. Then I think life is not worth living. I get over it, but yes, I have bad thoughts.”

As demonstrated by my patients, the very measures used to prevent the spread of COVID-19 increase the risk of depression and suicidal thoughts: economic stress, social isolation, decreased access to community, barriers to mental health treatment, and illness.¹

**FIGURE 1. SERIOUSLY CONSIDERED SUICIDE IN THE PRIOR 30 DAYS**

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.7%</td>
</tr>
<tr>
<td>Age 18-24</td>
<td>25.5%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18.6%</td>
</tr>
<tr>
<td>Black</td>
<td>15.1%</td>
</tr>
<tr>
<td>Essential workers</td>
<td>21.7%</td>
</tr>
</tbody>
</table>

According to the Centers for Disease Control and Prevention (CDC), the national rates of anxiety increased nearly four-fold from one year ago. In 1999, national rates of anxiety in adults were 8.2%, whereas data from August 19-31, 2020, are 31.4%. Similarly, rates for anxiety or depression have increased from 11.0% to 36.4%. All are higher in women, those with less education, and Black, Hispanic and multiple other races.² A separate survey in June found similar rates of anxiety or depression (30.9%). In addition, 10.7% of the respondents reported “having seriously considered suicide in the prior 30 days” – these were significantly higher among those aged 18-24 (25.5%), minority racial and ethnic groups (Hispanic 18.6%; Black 15.1%) and essential workers (21.7%)(Figure 1).³

Beyond its impact on our patients, it is vital to realize its effect on us as caregivers. As the impact of the pandemic continues, our ob/gyn practices and families are affected. Eighty-three percent of obstetrics and gynecology residents are female – the highest percentage of any specialty⁴ – and they are often playing a dual role as the family’s primary caregiver in addition to practicing medicine. Setting aside the burden of virtual schooling for both caregivers and children, the effects of social isolation and decreased access to mental health support are critical during pandemic times.
to community are also affecting our children. They also mirror increased rates of anxiety and depression, yet may not have the access or resources for identification and treatment.

So what to do, what to do? In our practices, departments, and families, providing an opportunity for open communication and a safe space to share feelings without judgment is essential. Proactively, one of my colleagues’ practices meets biweekly with a psychologist. All of the providers gather and discuss both practice and personal stressors. Although predating the pandemic, this has been especially beneficial with an ongoing opportunity for open communication to discuss and identify solutions. These sessions help to identify feelings, conflicts, and provide strategies to communicate them effectively. They also allow a platform to discuss complications and poor patient outcomes, serving as a forum to process these deeply traumatizing events and rise, rather than stagnate, or worse, fall. We as physicians need this type of forum in order to heal ourselves.

Our patients and families deserve similar support and we should strive to help them get it. We need to provide opportunities for open communication in a safe space. Referrals to our colleagues in psychiatry and psychology are essential to ensure appropriate care. Although there is always a shortage of therapists, these at-risk populations need to be prioritized. Furthermore, we need to be on the alert for signs and symptoms of anxiety and depression in not only ourselves but also in our colleagues, families, and patients.

Catherine Y. Spong

Dr. Spong, editor in chief, is Professor and Vice Chair in the Department of Obstetrics and Gynecology and Chief of the Division of Maternal-Fetal Medicine at UT Southwestern Medical Center in Dallas. She holds the Gillette Professorship of Obstetrics and Gynecology.

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REFERENCES
Recurrence of high-grade cervical dysplasia

by BOB KRONEMYER

Women with high-grade cervical dysplasia are much less likely to have recurrence after primary conization if they undergo laser conization than a loop electro-surgical excision procedure (LEEP), according to a 5-year follow-up study.

The Italian retrospective multi-institutional study in the journal Gynecologic Oncology found that the 5-year recurrence rate was 8.1% for LEEP and 4% for laser conization ($P = 0.023$).

Patients undergoing LEEP are more likely to be diagnosed with positive margin, which is defined as a histological finding of the cervical intraepithelial neoplasia (CIN) along the specimen margin, in comparison with patients undergoing laser conization.

However, the risk of having persistent human papillomavirus (HPV) was similar between the two groups: 15.0% for LEEP vs. 11.6% for laser conization ($P = 0.256$).

"Many studies have been conducted to investigate the predictors of persistent/recurrent cervical dysplasia," said principal investigator Giorgio Bogani, MD, PhD, a professor of ob/gyn at Fondazione IRCCS Istituto Nazionale dei Tumori in Milano, Italy. "A positive margin after conization and HPV persistence are well-defined predictors of persistent/recurrent disease."

Dr. Bogani said that treatment of recurrent disease might significantly impact a patient’s health. "In addition, the second conization might have a detrimental impact on fertility and might be associated with an increased risk of preterm delivery and premature rupture of membranes" he said. “Therefore, studies aiming to reduce cervical dysplasia recurrence are of paramount importance.”

The current study evaluated the medical records of 2,966 patients with high-grade cervical dysplasia who underwent primary conization at Dr. Bogani’s institute and in 21 other centers in Italy between 2010 and 2014. The median patient age was 40 years (range 18 to 89). During the study period, 20% of patients had laser conization and 80% had LEEP. The reason for conization was CIN2 in 32.7% of patients and CIN3 in 66.9% of patients. Overall, 175 women received a second conization within the first 5 years after primary treatment, for a recurrence rate of 6%. The median time to recurrence was 18 months, ranging from 5 to 52 months, with most patients developing recurrence within the first 2 years. Women with a diagnosis of CIN3 were nearly four times as likely to have recurrence, whereas women with HPV persistence were almost twice as likely.

"To overcome the biases related to the retrospective nature of the study, we applied a propensity-matched algorithm, from which we selected 500 patients undergoing laser conization and 1,000 undergoing LEEP for analysis," Dr. Bogani said. After applying a propensity-matched algorithm, LEEP was associated with an increased risk of recurrence in comparison to laser conization.

One reason laser conization is associated with a lower rate of recurrence than LEEP is that "similar to cold knife with conization, laser allows us to perform a step-by-step conization, following the geometry of the lesions, thus tailoring the radicality of the procedure," Dr. Bogani said.

The extensive vaporization of the surgical margins caused by laser CO₂ might also provide a higher rate of local control than diathermocoagulation.

HPV persistence was the only factor associated with 5-year recurrence after either laser conization ($P = 0.003$) or LEEP ($P = 0.001$). "This finding highlights the importance of HPV persistence as one of the main prognostic factors for recurrence," Dr. Bogani said.

The author and colleagues are now studying the long-term effect of vaccination against HPV in women who undergo conization. "We anticipate that vaccination against HPV in adolescent and young adults will reduce the burden of HPV-related diseases," Dr. Bogani said.

DISCLOSURES Dr. Bogani reports no relevant financial disclosures.

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

FOR REFERENCES VISIT contemporaryobgyn.net/dysplasia
Multimodal pain management with EXPAREL provided significantly better pain control after C-section vs multimodal protocols alone\(^2\) 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.

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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.

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**References:**


Bupivacaine is contraindicated for obstetrical paracervical block anesthesia. Bupivacaine is contraindicated for obstetrical paracervical block anesthesia.

Other than bupivacaine as noted above, EXPAREL should not be admixed with other local anesthetics or with nonsteroidal anti-inflammatory drugs (NSAIDs) or other anticholinergics.

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Do not dilute EXPAREL with water or other hypotonic agents, as it will result in dilution of the liposomal bupivacaine and reduced drug efficacy.

Acute emergencies from local anesthetics are generally related to high plasma concentrations of bupivacaine which can persist for 96 hours after local infiltration and 120 hours after epidural administration.

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The background on the risk of maternal death and miscarriage for the indicated population is unknown. However, the background risk in the US population of major birth defects is 2.4% and of miscarriage is 15-20% of clinically recognized pregnancies.

The toxic effects of local anesthetics are additive and their co-administration with other local anesthetics increases the possibility of systemic toxicity and death.

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Toxic effects of local anesthetics are additive and their co-administration with other local anesthetics increases the possibility of systemic toxicity and death.

Use suspensions of EXPAREL diluted with preservative-free normal saline or lactated Ringer’s solution within 4 hours of preparation in a syringe.

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If not treated immediately, both cardiovascular and neurovascular collapse may result in hypotension, acidosis, bradycardia, arrhythmias and cardiac arrest if cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

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Endotracheal intubation, employing drugs and techniques familiar to the anesthesiologist, should be performed if needed.

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Bupivacaine is rapidly cleared from the plasma, and when used for epidural, caudal, or peripheral block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity.

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The incidence and degree of toxicity depend upon the concentration, duration of drug administration. Adverse reactions in the parturient, fetus, and neonate procedure performed, the type, and amount of drug used, and the technique

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Perplexing condition in patient who underwent bone marrow transplant

This vulvar infection rarely is seen, but presents intriguing case.

**by** NATALIE A. SAUNDERS, MD, JUN HU, MD, ROSALYN MABEN-FEASTER, MD, KATHRYN C. WELCH, MD, EBONY PARKER-FEATHERSTONE, MD, RAJAL PATEL, MD, ANTHONY OPIPARI, MD, AND HOPE K. HAEFNER, MD

**Presentation**
A 55-year-old woman presented to her hematologist/oncologist 56 days after a bone marrow transplant for acute myeloid leukemia (AML). The patient was immunosuppressed with methotrexate and tacrolimus to prevent graft versus host disease (GVHD). She complained of poor appetite, weight loss, and diarrhea. She was found to have elevated liver function tests and bilirubin and hospitalized for evaluation, which included esophagogastroduodenoscopy (EGD) and flexible sigmoidoscopy. The patient was diagnosed with GVHD of the colon and started on intravenous (IV) steroids for treatment of acute GVHD. Chest x-ray was concerning for pneumonia. She was started on piperacillin/tazobactam. She was found to have cytomegalovirus viremia and was started on ganciclovir.

Two weeks after admission, the patient developed vulvar pain. Vulvar examination showed small ulcerations measuring 3 mm in the largest diameter. One day later, the lesions enlarged to 1 to 3 cm, with subepithelial hemorrhage on the labia majora and labia minora (Figure 1). The patient’s vulva was exquisitely tender. Her feet contained large bullae. Figure 2 shows a ruptured bulla in the medial aspect. The patient was afebrile, with normal vital signs. Laboratory investigation revealed a normal white blood cell count. She was anemic (hemoglobin 8.8 g/dL) and thrombocytopenic with a platelet count of 20 K/µL, secondary to previous bone marrow transplant.

**Diagnosis**
A yeast culture and aerobic culture were obtained. A punch biopsy of the vulva was performed for histologic evaluation and tissue culture. Two days later, the yeast culture grew Rhizopus. The organism also was identified on pathology staining from the patient’s punch biopsy, which showed abundant fungal elements morphologically consistent with Rhizopus infection (Figure 3).

**Management**
The patient was placed on IV amphotericin B. Unfortunately, the appearance of her vulva worsened rapidly—becoming edematous, with subcutaneous hemorrhage progressing to necrotic tissue. A decision was made to proceed to the operating room secondary to rapid deterioration. A partial vulvectomy was performed and the excision was carried down to the fascia to remove all of the necrotic tissue (Figure 4). An adequate margin of normal tissue was taken to ensure that the area of disease was effectively debrided. Platelets were administrated intraoperatively for thrombocytopenia. The patient’s estimated blood loss was 100 cc. Pathology revealed abundant fungal elements morphologically consistent with the previously cultured Rhizopus specimen.

Postoperatively, the patient’s dress-
ing was changed twice a day with 4x4 gauze soaked with amphotericin B. Her wound was healing well. However, on postoperative Day 4, multiple new erythematous, tender lesions (similar in appearance to the initial vulvar lesions) were noted on the patient’s left upper extremity, left scapula, and bilateral lower extremities (Figure 5). A punch biopsy of her leg lesions was consistent with a deep fungal infection morphologically consistent with Rhizopus. A computed tomography scan indicated potential fungal infection in the kidneys and interval development of nodular opacities in the lungs. The dose of amphotericin B was increased to 10 mg/kg and micafungin was added secondary to the dissemination of Rhizopus, likely due to hematogenous seeding of the lesions. The patient’s condition continued to deteriorate and she died 9 days after surgery.

Discussion

Rhizopus is the most common species of the order Mucorales.1 Mucormycosis occurs most often in immunocompromised patients, including individuals with hematological malignancies. It has also been associated with diabetes.1,2 Epidemiological studies suggest that the incidence of mucormycosis has significantly increased in the past 30 years.3,4 A high mortality rate is reported across studies, which may be secondary to a lack of antifungal agents with adequate activity against the class zygomycetes. Vulvar mucormycosis is a rare entity; only three cases of Rhizopus infection on the vulva have been reported previously.5-7

Hematopoietic stem cell transplant recipients run a high risk of developing invasive fungal infections during the immediate post-transplant and the pre- and post-engraftment periods, as well as up to 3 months after transplantation.8 This was the case with our patient, who presented with Rhizopus infection of the vulva 56 days after a bone marrow transplant for AML. A re-
view of 929 mucormycosis cases revealed skin as the third most common site infected, representing 19% of mucormycosis infections, whereas 39% were located in the sinuses and 24% in the lungs. Cutaneous mucormycosis typically results from direct spore inoculation or exposure of compromised skin (e.g., burns or trauma). Cutaneous mucormycosis can present as pustules, bullae, nodules, ulcers, necrotizing cellulitis, granulomatous pyoderma, bulls-eye cutaneous infarcts, and, rarely, zosteriform lesions. The hallmark of disease is tissue necrosis resulting from angioinvasion and subsequent thrombosis. Black necrotic eschars are common in affected tissues, which can extend into deep fascia and muscle layers. Necrotizing fasciitis has also been reported in association with this condition.

A high index of suspicion is required for rapid and timely diagnosis of invasive mucormycosis. Even if the cutaneous location observed upon mycological examination and/or pathologic analysis facilitates diagnosis, this rare condition is often not initially considered. Fungal growth alone is insufficient, as it may represent colonization or contamination; histopathological evidence of invasive disease is required. So far, there has not been enough evidence that identification of mucormycosis to the genus and/or species level helps guide antifungal treatment. Rapid and exact diagnosis by both morphology and molecular techniques is crucial for starting early treatment of fungal infection.

Invasive disseminated Rhizopus infections develop in around 25% of patients who present with localized infection. Although hematogenous dissemination to the skin is rare, cutaneous infections are often complicated by deep extension or dissemination by secondary vascular invasion. In a review by Roden et al., 78 of 176 cases (44%) of cutaneous mucormycosis showed extension to bone, tendon, or muscle—or even hematogenous dissemination. Dissemination of infection resulted in an increase in overall mortality that approached 90%, compared to approximately 30% in localized cutaneous mucormycosis. Due to the invasive aspect of the infection and the potential for disseminated disease, imaging should be performed promptly to detect other possible sites of infection independent of the initial location. In our case, the later involvement of lung and kidneys classifies it as a case of disseminated infection.
The European Society for Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology have released comprehensive guidelines for the management of mucormycosis. Whenever possible, early and aggressive surgical debridement is strongly recommended to be combined with immediate first-line antifungal treatment, because the procedure yields greater than a 1.5-fold increase in survival rates. The rapid reversal of predisposing conditions, such as using granulocyte colony-stimulating factor in patients with ongoing neutropenia, controlling hyperglycemia and ketoacidosis in diabetic patients, and limiting glucocorticosteroids to the minimum dose required, may be useful. This is an aggressive infection that targets and destroys local vasculature, preventing the delivery of systemic antimicrobial/antifungal therapy. If treatment is delayed, proliferation and dissemination of angioinvasive Mucorales will result in thrombotic necrosis of tissues, thus limiting adequate delivery of antifungal agents to the sites of infection. This is especially true when the infected cutaneous site is highly vascularized, such as the vulva.

Multiple procedures may be necessary, and the need for skin grafting or other wound closure techniques should be individualized. Zimmermann et al. presented a case of mucormycosis of decubitus ulcers, which demonstrated that intraoperative analysis of frozen section slides was a valuable tool for assessing skin and soft tissue margins for fungal infection (68.4% sensitivity and 100% specificity). However, in our case, surgical debridement in addition to amphotericin B resulted in local improvement, but the patient died 9 days after her surgery due to her underlying disseminated Rhizopus infection. Amphotericin B is clinically effective for treatment of these infections, with response rates of 39% to 71%. However, the potential for long-term nephrotoxicity remains a concern.

The current guidelines from the European Conference on Infections in Leukemia state that first-line treatment should be initiated with lipid formulations of amphotericin B. The recommended dose is 5 mg/kg/day for patients without central nervous system (CNS) involvement and 10 mg/kg/day for patients with CNS involvement, for at least 6 to 8 weeks. The optimal dose or duration of therapy remains debatable in the absence of prospective comparative studies. It can be continued for weeks until a positive clinical outcome and/or negative mycological culture results occur. There is also some evidence to suggest that posaconazole and isavuconazole are best reserved for de-escalation, refractory cases, or patients intolerant to amphotericin B. A combination of amphotericin B and echinocandins may be beneficial after failure of first-line treatment. Antifungal susceptibility testing is important in understanding susceptibility patterns, although most data come from morphologically identified isolates.

The prognosis of patients with mucormycosis is poor. Mortality rates up to 94% have been reported in patients with hematogenous dissemination. This underscores the importance of early aggressive therapy. In our patient, early dissemination was present, which significantly lowered the chance of survival.

Photos are courtesy of Dr. Hope Haefner
For references visit contemporaryobgyn.net/Rhizopus

Take our quiz!

Rhizopus is an opportunistic infection caused by a:
A. Virus
B. Bacteria
C. Fungus

Treatment for Rhizopus includes:
A. Intravenous medications such as amphotericin B
B. Surgical debridement
C. Both A&B

Mortality rate of Rhizopus infection with hematogenous spread is:
A. <10%
B. 50%
C. >90%

For answers visit contemporaryobgyn.net/Rhizopus
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Annovera: The First Long-Lasting, Reversible Contraception that is Patient Controlled and Procedure Free
Providing a Long-Lasting Supply of Contraception May Lead to More Consistent Use and Reduction in Unintended Pregnancies

Of all unintended pregnancies, 41% are due to the inconsistent use of contraceptives. The Centers for Disease Control and Prevention recommend that women be provided with a 1-year supply of birth control. Birth control pills, patches, one-month rings, and injections are typically dispensed in only 1- or 3-month supplies, making additional trips to a clinic or pharmacy a potential barrier to consistent use. Women who receive a 1-year supply of birth control have been found to be 30% less likely to have an unintended pregnancy compared with women receiving a 1- to 3-month supply. Long-acting reversible contraception (LARC) methods such as intrauterine devices (IUDs) and implants must be administered by a healthcare professional and require a procedure for insertion and removal.

Annovera (segesterone acetate and ethinyl estradiol vaginal system)

The segesterone acetate and ethinyl estradiol vaginal system was developed to address the needs of women who desire a long-lasting form of birth control without requiring a procedure for insertion and removal coupled with the patient control and immediate reversibility aspect of short-acting products (Figure).

It is a soft, flexible vaginal ring that is self-administered and does not require a procedure. Although the overall diameter is roughly the same as

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NuvaRing (etonogestrel/ethinyl estradiol vaginal ring), the increase in its width was purposeful because it is composed of a “squishy” silicone elastomer to make it soft and flexible for easy insertion and removal while remaining comfortably in place throughout daily activities including sex.\textsuperscript{5,6} It is inserted into the vagina and remains in place for 21 days and then removed for 7 days each cycle. It can be used for up to a full year or 13 menstrual cycles.\textsuperscript{5} It is also as effective as a pill without the daily commitment. In clinical trials, the 13-cycle (1-year) cumulative probability of not becoming pregnant was 97.3\%\textsuperscript{5}. Unlike other contraceptive vaginal rings, it does not require refrigeration at any time.

**Created with a novel hormonal profile**
This ring-shaped vaginal system contains two active hormones, releasing one of the lowest daily doses of ethinyl estradiol (13 mcg/day) and a nonandrogenic progestin, segesterone acetate. Unlike the other progestins contained in combination hormonal contraceptives that are all derived from testosterone, segesterone acetate is derived from natural progesterone. Segesterone acetate is of the highest anti-ovulatory potency and unlike other progestins, it demonstrates no androgenic or glucocorticoid activity that can be responsible for changes in weight and acne.\textsuperscript{7,8} Based on the residual amount of drug in the product used in clinical trials over 13 cycles, approximately 40\% (41.2 mg) of segesterone acetate and 20\% (3.48 mg) of ethinyl estradiol were released over this period.\textsuperscript{5}

**Cycle control – Bleeding profile**
In clinical trials of 2070 women, 98\% of women had scheduled bleeding with amenorrhea occurring in 2.6\% to 4.9\% of women per cycle.\textsuperscript{9} The mean number of bleeding-only days averaged 3.3 days.\textsuperscript{8} Unscheduled bleeding or spotting occurred in 5\% to 10\% of women and lasted for an average of 1 day or less per cycle.\textsuperscript{9}

**Patient acceptability**
Overall satisfaction with this form of contraception was approximately 90\%.\textsuperscript{10,11} No clinically relevant increase in weight or other androgenic side effects were observed.\textsuperscript{8,11} Its use did not increase the risk of vaginal infection nor did it affect the vaginal microbiome.\textsuperscript{12} There were no increases in bacterial vaginosis, candidiasis, or trichomoniasis throughout the study.\textsuperscript{12}

**Adverse reactions**
Safety was demonstrated in 3 open-label, 13-cycle (1-year) clinical trials that enrolled 2308 women.\textsuperscript{11}

Adverse events occurred most frequently within the first days of the first cycle and were both mild and self-limiting (Table). Expulsion occurred primarily in the first few weeks as women were getting used to the product and resulted in 1.4\% discontinuation.

<table>
<thead>
<tr>
<th>Adverse reactions reported by ≥ 5% of patients in the 1-year study</th>
<th>Adverse reactions leading to discontinuation by ≥ 1% of patients in the 1-year study</th>
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<tbody>
<tr>
<td>•  Headache including migraine</td>
<td>•  Metrorrhagia/amenorrhea (1.7%)</td>
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<tr>
<td>•  Nausea/vomiting</td>
<td>•  Headache, including migraine (1.3%)</td>
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<tr>
<td>•  Vaginal infections</td>
<td>•  Vaginal discharge/vulvovaginal infections (1.3%)</td>
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<tr>
<td>•  Abdominal pain</td>
<td>•  Diarrhea</td>
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<tr>
<td>•  Dysmenorrhea</td>
<td>•  Gential pruritus</td>
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**How to start**
- Women not using hormonal contraception should start between days 2 and 5 of their menstrual cycle—no back-up contraception is needed.\textsuperscript{5}
- Women consistently using the pill, patch, or ring can switch at any time, provided there has been no break in usage without requiring a back-up method.\textsuperscript{5}
- Women switching from a progestin-only method, including pill, IUD, injection, or implant, may switch at any time, but a back up method should be used for the first 7 days of use.\textsuperscript{5}

**Patient types**
The segesterone acetate and ethinyl estradiol vaginal system is ideal for women who want to be in control
of both their fertility and menstruation with a 21/7 cyclical, self-administered, long-lasting product with immediate reversibility. It should be considered for adolescents or anyone who does not want to take a product every day and does not want a procedure. It is appropriate for nulliparous women and those not in a monogamous relationship who in the past may have been denied LARCs; women who are birth spacing and in-between children who do not want to commit to a contraceptive of longer duration; college women with unpredictable schedules who do not want a daily-use product or worry about getting their monthly refills; women in the military who want control of fertility and menstruation for 1 year; and women who are approaching menopause and still want contraception. It represents a single contraceptive product amenable for most patient and prescriber types.

Conclusion
The segesterone acetate and ethinyl estradiol vaginal system is the only long-lasting reversible contraception that is procedure free, used for 21/7 day cyclical dosing for 1 year (13 cycles), empowering women to be in control of their fertility and menstruation.5 It contains a nonandrogenic progestin, segesterone acetate, with the highest anti-ovulatory that has no androgenic or glucocorticoid effects at contraceptive doses.7,8* It also has one of the lowest average daily releases of ethinyl estradiol (13 mcg/day), and users report high patient satisfaction (~90%).5,10† Women should be counseled about its unique features when discussing their birth control options.

To learn more about the segesterone acetate and ethinyl estradiol vaginal system, visit annoverahcp.com.

Please see brief summary of Full Prescribing Information, including BOXED WARNING, on the following page or visit annovera.com/pi.pdf.

*Based on pharmacologic studies in animals and in vitro studies. The clinical significance of these data is not known. †A phase 3 study, a product acceptability questionnaire was administered and completed at the end of Cycle 3 (n=1036). Results were based on data from 905 subjects in the areas of ease of use, expulsion, side effects, and sex/intercourse. Vulvovaginal infections and vaginal discharge were common adverse reactions. For a full list of common adverse reactions, see table on previous page or review the Full Prescribing Information.

References
ANNOVERA® (segesterone acetate and ethinyl estradiol vaginal system)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information that you need to use ANNOVERA safely and effectively. Please visit ANNOVERA.com/pi.pdf for Full Prescribing Information (PI).

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 and particularly in females 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 smoke.

INDICATIONS AND USAGE

ANNOVERA is indicated for females by females of reproductive potential to prevent pregnancy.

Limitations of Use: ANNOVERA has not been adequately studied in females with a BMI ≥29 kg/m2.

DOSEAGE AND ADMINISTRATION

One ANNOVERA vaginal system is inserted into the vagina. The vaginal system must remain in place continuously for 21 days (1 cycle) followed by 7 days (1 week) of vaginal system-free interval. One new ANNOVERA vaginal system is inserted every 21 days (1 cycle) of use. The first system should be inserted within 72 hours of the start of menses.

Contraceptive efficacy of ANNOVERA may be reduced if a woman deviates from the recommended use. If ANNOVERA is not used out of the vagina for more than 2 continuous hours or more than 2 cumulative hours during the 21 days of continuous use, then back-up contraception, such as male condoms or spermicide, should be used until the vaginal system has been in the vagina for the 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: smoke, if over age 35; have current or history of deep vein thrombosis or pulmonary embolus; have cerebrovascular disease; have coronary artery disease; have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with vascular 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 end-organ damage, or diabetes mellitus of >20 years duration, have headaches with focal neurological symptoms, or have headaches with aura, or aura of over 24 hours with any migraine headaches. • Current or history of breast cancer or other estrogen- or progesterone-sensitive cancer. • Liver tumors, including hepatocellular carcinoma, or biopsy-proven pseudo–Hepatitis C. • Undiagnosed abnormal uterine bleeding. • Hypersensitivity to any of the components of ANNOVERA. Hypersensitivity reactions reported include: throat constriction, facial edema, urticaria, hives, and wheezing. • Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. ANNOVERA can be restarted 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

Hypertension

ANNOVERA is contraindicated in females with uncontrolled hypertension or hypertension with vascular disease for 30 years, for both females with and without diabetes who are over 35 years of age. Consider the presence of underlying risk factors that may increase the risk of hypertension and prevent starting ANNOVERA. ANNOVERA is contraindicated in females with uncontrolled hypertension and should not be used in females with hypertension, including women with diabetes, if CHC use is contraindicated.

Age-Related Considerations

The risk for cardiovascular disease and prevalence of risk factors for cardiovascular disease increases with age. Certain CHCs are associated with CHC use. ANNOVERA may be at an increased risk for CHC-related cholesterol.

Adverse Reactions Leading to Discontinuation

Among subjects using ANNOVERA for contraception, 12% of females experienced adverse reactions occurring in ≥1% of subjects: • Cough (7.7%). • Lower back pain (6.9%). • Headache, including migraine (1.3%). • Vaginal discharge (1.2%). • Nausea (1.2%). • Myalgia (1.1%). • Syncope (1.1%). • Vomiting (1.1%). • Vaginal irritation (1.1%). • Migraine headache without aura (1.0%). • Vomiting, nausea (1.0%). • Cough, upper respiratory tract infection (1.0%). • Cough, bronchitis, pharyngitis (1.0%). • Headache, including migraine (1.0%). • Nausea/vomiting (1.0%). • Abdominal pain, lower (1.0%). • Abdominal pain, upper (1.0%). • Nausea (0.9%). • Headache, upper (0.9%). • Nausea (0.9%). • Abdominal pain, lower (0.9%). • Abdominal pain, upper (0.9%).

Rupture of hepatic adenomas may cause death through acute liver failure. ANNOVERA is contraindicated in females with benign or pre-existing hepatic adenomas. Females with a history of pregnancy-related cholestasis have a higher risk of hepatic adenomas. Use of CHCs may also increase the risk of hepatic adenomas and may worsen existing gallbladder disease. A past history of CHC-related cholestasis predicts an increased risk with subsequent CHC-use. Females with a history of pregnancy-related cholestasis may be at an increased risk for CHC-related cholestasis. Adverse Carbohydrate and Lipid Metabolic Effects

Hyperglycemia

ANNOVERA is contraindicated in diabetic females over age 35, or females who have diabetes with hypertension, nephropathy, retinopathy, neuropathy, other vascular disease, or females with diabetes of ≥20 years duration. ANNOVERA may decrease glucose tolerance. Carefully monitor prediabetic and diabetic females who are taking ANNOVERA.

Dyslipidemia

Consider alternative contraception for females with uncontrolled dyslipidemia. ANNOVERA may cause adverse lipid changes. Females with hyperlipidemia with a history thereof, may be at an increased risk of pancreatitis when using ANNOVERA.

Headache

ANNOVERA is contraindicated in females with certain headaches. Evaluate new or significant changes in headaches, including migraines, and discontinue ANNOVERA if indicated.

Bleeding Irregularities and Amenorrhea

Females using ANNOVERA may experience unscheduled bleedings (breakthrough bleeding and spotting, during especially the first month of use. If unscheduled bleeding occurs or persists, check for causes such as pregnancy or malignancy. Based on subject diaries from two of the clinical efficacy trials of ANNOVERA, 5–10% of females experienced unscheduled bleeding per 28-day cycle. A total of 41 subjects (1.7%) discontinued use due to breakthrough bleeding including: metrorrhagia, menorrhagia, and abnormal withdrawal bleeding. Females who are not pregnant and use ANNOVERA may experience amenorrhea. Based on subject data from diary reports for 2 clinical trials for up to 13 cycles, amenorrhea occurred in 3–5% of females per cycle using ANNOVERA and in 0.9% of females in all 13 cycles. If scheduled bleeding does not occur, consider the possibility of pregnancy.

Depression

Carefully observe females with a history of depression and discontinue ANNOVERA if depression recurs to a serious degree.

Cervical Cancer

Some studies suggest that CHCs are associated with an increase in the risk of cervical neoplasia, including cervical intraepithelial neoplasia.

Effect on Binding Globulins

The estrogen component of ANNOVERA may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

Hereditary Angioedema

In females with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

Chloasma

Chloasma may occur with ANNOVERA use, especially in females with a history of chloasma gravidarum. Advise females who tend to develop chloasma to avoid exposure to the sun or ultraviolet light while using ANNOVERA.

Toxic Shock Syndrome (TSS)

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 vaginal coitus during and after use of ANNOVERA. Couples 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 infection. Vaginal or 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 by ≥5% of ANNOVERA-treated subjects include: headache, including migraine (38.6%); nausea/vomiting (25.0%); vulvar/vaginal mycosis/vaginal candidiasis (14.5%), abdominal pain/upper (13.3%); dysmenorrhea (12.5%); vaginal discharge (11.8%); UTI/cystitis/peyroniitis/gonitric tract infection (10.0%); breast pain/breast tenderness (10.0%); breast mass (2.9%); hyperglycemia (1.7%); diabetes mellitus (1.7%); hyperuricemia (1.7%); and genital pruritus (5.5%).

Adverse Reactions Leading to Discontinuation

Among subjects using ANNOVERA for contraception, 12% of females experienced adverse reactions occurring in ≥2 subjects were: VTEs (deep venous thrombosis, cerebral vein thrombosis, pulmonary embolism); psychiatric events; 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 osimertinib/paritaprevir/ritonavir, with or without dasabuvir, due to potential for AEs for all 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 18 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 Use

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 due to 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.

Body Mass Index (BMI)/Body Weight

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

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The path that led to American women favoring compounded bioidentical hormone therapy (cBHT) is rooted in several important historical factors. The Dietary Supplement Health and Education Act of 1994 specifically exempted compounded hormones from being considered pharmaceuticals; instead, they were put into the same category as dietary supplements. This designation requires far less rigor in terms of quality control, no need for adverse event reporting, and carries no requirements for potential conflicts of interest disclosures. Penalties for false advertising are rare.

In 2002, the Women’s Health Initiative (WHI) showed that estrogen and progesterone were ineffective as preventives for cardiovascular disease for women and confirmed that ‘conventional,’ FDA-approved forms of hormone therapy carried health risks. Overall, hormone therapy caused net harm or gave no benefit to most of the women who had been taking it for treatment other than for symptoms. As a result, millions of women abruptly abandoned their hormone therapy. Many doctors who had prescribed it for preventive purposes were loath to accept the WHI data. The information gap was filled by cBHT. Because cBHT products were now dietary supplements, they were not subject to FDA approval; they had no restraints on proof of claim or efficacy; and had no adverse event reporting requirements. Moreover, the claim that cBHT, which contained ‘natural’ – as opposed to ‘synthetic’ hormones used in research such as the WHI—developed great resonance in the consumer sphere. The concept that naturally occurring hormones were harmless began to be promulgated and provided women with a new, alternative treatment that seemed to be superior.

Although many naturally occurring hormone products got approved by the FDA during and immediately after the WHI and rapidly became widely available, the cBHT industry effectively used internet-based marketing and repetition of partial truths to garner a significant portion of the dwindling hormone therapy market. The mythology that the hormones used in the WHI were simply the ‘wrong’ hormones, and alternative cBHT products had no such side effects or risks and would, indeed, prevent aging, was widely and
successfully marketed such that current estimates are that one-third to half of the national use of menopausal hormone therapy is cBHT. ‘Natural’ hormones have become highly desired by consumers, and are incorrectly viewed as without risk, in comparison to FDA-approved ‘synthetics’ used in many research trials.

Many cBHT prescribers and compounders have financial interest in prescribing and continuing therapy. Consumers may be recommended to use a proprietary cBHT formulation as well as a panel of ‘customized’ proprietary blood or saliva tests to follow hormone levels, with no requirement for patient disclosure. Prescribing proprietary cBHT preparations for a profit creates an overt conflict of interest and may violate professional ethics.

Due to several concerns raised by these ongoing practices, the National Academies of Sciences, Engineering, and Medicine (NASEM) conducted an 18-month review of the field, gathering data and taking in-person testimony from pharmacists, practitioners, and patients. Their recommendations recently have been released and are supported by the North American Menopause Society (NAMS). The chief recommendations relevant to many ob/gyns are summarized below and offer an excellent starting point to rein in potentially harmful medical practice in our field.

**NASEM Recommendations**

1. Review select bioidentical hormone therapies and dosage forms as candidates for the FDA Difficult to Compound list. Drugs considered ‘difficult to compound’ are defined as ‘drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs.’ The NASEM report suggests the Pharmacy Compounding Advisory Committee (PCAC) review the following cBHT hormones as candidates for this list: estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate. They also recommend that all cBHT in pellet form be added to this list.

2. Improve education for prescribers and pharmacists who market, prescribe, compound and dispense cBHT preparations. NASEM recommends that State medical boards and professional medical societies advocate for state-level certification for those who want to begin or continue prescribing. Additionally, professional societies (AMA, NAMS) that are not-for-profit could help establish evidence-based recommendations and guidelines. Education from industry is discouraged. Education would include identification of safe formulations and contraindications to treatment, description of conflicts of interest, and reasoning for when to consider cBHT over FDA-approved products. Although prescribers are responding to patient demand, this does not supersede practice informed by evidence. Given this breach in obligation to patient safety, it is possible that prescribers could face consequences including invalidation of malpractice insurance, personal liability or possible criminal charges.

3. Additional federal and state-level oversight should be implemented to better ad-
dress public health and clinical concerns regarding the safety and effectiveness of compounded cBHT.

The report calls on the National Association of Boards of Pharmacy (NABP) and state boards of pharmacy to expand and improve oversight and standardization. Among the most significant suggested measure is that cBHT products include an insert containing critical details about the preparation, including active ingredients and a statement that the preparation is not FDA approved and therefore lacks the rigorous dosage, safety and efficacy data required by the FDA. Pharmacies are called upon to disclose their good manufacturing practices or United States Pharmacopeia (USP) designation, and to include contact information for the pharmacy and those responsible for quality and safety.

Boxed warnings for adverse effects identical to that required for FDA-approved estrogens, androgens and progestins was recommended. Pharmacies providing cBHT were also called upon to create a robust methodology for surveillance and data collection of adverse events, as well as make that information available to the public. There is no current insight into the prevalence of such events as they are not reported or available to the consumer. NASEM calls for required adverse event reporting of cBHT to state boards of pharmacy as well as to MedWatch and the FDA Adverse Event Reporting System. This would allow states to respond to these issues locally.

Lastly, all states should adopt USP standards to meet minimum quality standards for sterile and non-sterile cBHT preparations.

4. Collect and disclose conflicts of interest. cBHT is often sold directly by the prescriber, which violates professional ethical conduct and is a clear example of conflict of interest (COI). Many providers of cBHT are physicians and advanced practice providers with credentials that patients believe mean that they are well informed and practicing safe medicine. Disclosures of COI should be publicly available and disclosed to patients at the point of care. NASEM also recommends that state licensing boards collect and make public financial relationships so that these COIs are easily accessible to all consumers.

5. Strengthen and expand the evidence base on the safety, effectiveness, and use of cBHT preparations.

NASEM calls for increased engagement in research to generate a comprehensive evidence base for cBHT use. Assuming patient interest is here to stay, we need to provide consumers with the same breadth of safety data and industry accountability that the FDA-approved meds possess. This goal will require funding and clinical research with high quality trials, generation of bioavailability data of active ingredients and adverse event reporting. These trials should be approved and registered by the Institutional Review Board (IRB).

6. Restrict the use of cBHT preparations.

There are select scenarios in which compounding is helpful. Some people may have an allergy to an active ingredient in all possible appropriate FDA approved formulations, and this is the most common reason to use compounded drugs in all categories. Other users may also require a dosage unavailable via FDA approved formulation. cBHT use should be limited to these select scenarios. When prescribing, it should be made clear that compounded formulations are not FDA approved and thus have limited safety and efficacy data. Of importance, the report is very clear that patient preference alone should not be a reason to prescribe cBHT. We understand there is patient demand, but educated decision making and doing no harm must take precedence.

The 350-page NASEM report recommends long-overdue measures that will protect consumers from unsafe health outcomes. Prescribers and pharmacies alike have a duty to provide the safest treatments, and to do so requires significantly more data and regulation than is currently present. Without evidence, oversight and reporting systems in place, patients are poorly equipped to make informed and safe decisions. “When statements about cBHT are inaccurate or misleading, informed consent cannot take place.” All healthcare providers take an oath to do no harm, but without more education, data, oversight and patient education, harm is not only possible, but likely. We can do better, and NASEM provides excellent recommendations to help us to take steps in the right direction.

FOR REFERENCES VISIT contemporaryobgyn.net/hormones

Watch contemporaryobgyn.net for a video interview with Dr. Santoro who will provide highlights from the North American Menopause Society’s annual scientific program.
This letter first appeared in USA Today. The threat to women’s health cannot be understated, which is why I share the same message with you.

Susan G. Komen founder:

New Cervical Cancer Screening Guidelines Dismiss Best Practices

Nancy G. Brinker
Founder, Susan G. Komen Foundation and The Promise Fund of Florida

The American Cancer Society issued at the end of July new guidelines for cervical cancer screening that call for fewer women to be tested and stand in direct opposition to recommendations from leading scientific organizations. As someone who has devoted their life to fighting for better and more accessible health care for women, I know that the disservice these changes will have on society, and woman specifically, could not come at a worse time.

The global health crisis we are living through right now is a stark reminder of just how dangerous a course of action the American Cancer Society’s new guidelines may set in motion. In fact, while COVID-19 and cervical cancer are vastly different diseases, there are three important lessons related to the rollout and implementation of testing we should be learning in real time. The American Cancer Society’s new guidelines ignore them all.
Test like lives depend on it. They do.

First, if the experience of the coronavirus has taught us anything, it’s that testing—widespread, science-driven and accessible testing—is crucial to understanding and combating disease. The more accurate testing we offer people, the better. Testing allows earlier detection and diagnoses and, when necessary, treatment. We know that while companies have been able to significantly ramp up production, the challenges people had in getting access to testing for COVID-19 in the early months likely intensified the crisis.

Where the current cervical cancer screening guidelines advise the Pap test for women starting at age 21, the new American Cancer Society guidelines advise delaying testing altogether until women turn 25, and then, preferably, solely with the HPV test every five years thereafter. This is despite the fact we know that the HPV test alone is less effective than co-testing along with the Pap test.

Not only does the American Cancer Society threaten the use of the life-saving Pap test, and recommend phasing it out entirely, but that four-year wait likely means fewer women cumulatively will be tested. If just having a cervix puts women at risk of a potentially fatal disease, it’s a wait most women may prefer to avoid.

Secondly, one of the most demoralizing responses to the current pandemic has been the disregard in some quarters for science, data, facts and the hard-won insights of the health care community. That the American Cancer Society, an organization I have long admired, should now fall into this category with its new guidelines is especially disheartening. Let’s look at the science.

In a highly diverse and the largest cervical cancer screening study ever, the results of which were released in early July, co-testing with the Pap test and HPV test identified 94.1% of cervical cancer cases and 99.7% of pre-cancer cases in women who would be diagnosed within 12 months.

Co-testing remains the most effective strategy for detecting cervical cancer and precancer in women, but it is listed as an inferior choice by the new guidelines. Furthermore, that study demonstrates the use of HPV testing alone, which the American Cancer Society now recommends, misses twice as much cervical cancer as co-testing. We cannot disregard the science; we must follow it.

Finally, mixed messages around coronavirus testing have sown confusion about who should get tested, and when. It has introduced uncertainty where there should be certainty and has led patients and even some health care professionals to question aspects of the system they rely on and trust. This isn’t a result we want to replicate when it comes to cervical cancer screening.

Follow the science.

The American Cancer Society guidelines stand at odds with the previous guidelines that have helped drive a decrease in cervical cancer rates by 70% since the Pap test was introduced more than 50 years ago. They may introduce confusion about which tests to get and when, which in effect is building another barrier between women and the health care they deserve. The current challenges posed by testing in the time of COVID-19 has shown us just how dangerous such barriers can be.

An estimated 4,300 women will die in the United States from cervical cancer this year. Clarity drives trust and trust is essential to making progress in fighting this cancer.

With racial disparities in health care finally receiving the attention they deserve, and given what we are living through with the pandemic, it would be a tragedy if we do not at the very least learn from it. With a little tweak, George Santayana’s admonition that “those who cannot remember the past are condemned to repeat it” can provide the most important insight of all. When it comes to the American Cancer Society’s new guidelines on cervical cancer screening, it’s not lessons from the past I’m worried we’re ignoring, but lessons from the here and now.

A failure to acknowledge the lessons of this moment by loosening commonsense screening guidelines will almost surely reverse the progress we have made in combating cancer in recent years. If we allow this to be our future then we have learned nothing, and more women may die because of it.

If the pandemic has taught us anything, it’s the more testing, the better. So why is the American Cancer Society recommending women get fewer tests?
Choosing the right pill

Oral contraceptive pills are a popular choice for many; providers should understand the options to guide patients effectively.

by CHARISSE LODER, MD MSC, MONICA ROSEN, MD, AND CHELSEA CHASE, MS4

Oral contraceptive pills are the most commonly used method of hormonal contraception in the United States. According to the National Survey of Family Growth conducted in 2015-2017, 80.5% of reproductive-aged women who had ever been sexually active had used oral contraceptive pills (OCPs) at some point. A survey of reproductive-aged women who have ever been sexually active found that 12.6% currently use pills.1 There are two general types of OCPs—combined oral contraceptives (COCs), which contain both ethinyl estradiol (EE) and progestin, and progestin-only pills (POPs). Current COCs offer a range of doses and progestins to choose from.2

How well do oral contraceptives work?
COCs are a moderately effective method of contraception. They have a perfect use failure rate of <1% and a typical use failure rate of 9%.3 Several clinical trials have quoted failure rates of POPs between 1-13% in the first year.4-7 Little data is available directly comparing the efficacy of different types of progestins; however, a few studies suggest no difference.8 It is likely that typical use failure rates are higher in POP users due to the strict dosing timeframe, including recommendations to take the pill within a 3-hour window.3

Mechanisms of action
EE and progestin each work separately, as well as synergistically, to provide contraceptive benefit. EE mainly works by suppressing the release of follicle-stimulating hormone (FSH) from the pituitary, which hinders folliculogenesis. EE also causes endometrial edema, which affects implantation. EE has an added benefit of stabilizing the endometrium, which reduces spotting—a favorable effect. As EE potentiates the effects of progestin, smaller doses of progestin may be used in COCs.8

Progestin works in three major ways:
1) it suppresses GnRH release from the hypothalamus, decreasing LH and FSH release; 2) it prevents the LH surge from the pituitary, which prevents ovulation; and 3) it thickens cervical mucus, which impedes sperm entry into the uterus. There may be some inhibition of peristalsis and tubal mobility as well. Progestin causes endometrial atrophy, which impairs implantation. Each progestin has a different potency and dose for which it blocks ovulation. POPs rely on these multiple mechanisms to prevent pregnancy.8

Who shouldn’t use oral contraceptives?
Although oral contraceptives are a great choice for many women, it is important to understand the conditions that may increase risk for the user. We will outline some of the risks below and the CDC Medical Eligibility Criteria chart can be referenced for more information.7 It is important to remember that the risks and benefits must be weighed for each woman individually and that in most cases

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cases, pregnancy is more dangerous than pill use. In patients who have conditions in which pregnancy would increase their risk of adverse health outcomes (Table 1), long-acting reversible contraception (LARC) may be the best choice to avoid unintended pregnancy. It is also important to review a patient’s medication history, as there may be drug interactions that reduce efficacy of COCs and POPs.

EE is pro-coagulable and is contraindicated in a number of situations. Progestin also has risks to the user. Providers should screen for personal or family history of venous thromboembolism, as this increases coagulation risk in COC users. Additionally, because of hypercoagulability in the postpartum state, COCs should not be used until 6 weeks after childbirth. Women who smoke and are over age 35, women with migraine with aura, or those who have uncontrollable hypertension or vascular disease are at increased risk of stroke and should not use estrogen-containing methods. There are self-screening tools available to check for COC eligibility, such as the one used in a study by Grossman et al, which showed a sensitivity of 83.2% and specificity of 88.8% in patients using the survey to determine true contraindications to COC use.

These tools can be helpful to both providers and patients, particularly as we increase use of telemedicine (Table 2).

### Shared decision-making

As with any medical decision, it is exceptionally important to utilize shared decision-making in choosing the right contraceptive method for each patient, which should improve satisfaction, encourage compliance, and reduce unintended pregnancy. Shared decision-making involves the patient and provider working together to make a decision through discussion of all options while taking patient preference into account. Because there are many contraceptive options available, it is important to discuss values (including the acceptability of an unplanned pregnancy if there is a contraceptive failure), beliefs, dosing frequency, financial considerations, and risks and benefits of each method. Other considerations include how often women want to have withdrawal bleeding, and desired benefits such as improvement in dysmenorrhea, acne, and mood symptoms. All women should be provided with a multiple-month prescription to improve medication adherence.

As with any method, there are side effects of COCs and POPs that are important to discuss with patients as they decide which method is best for them. Of women who have ever discontinued using COCs or POPs, 34% reported that they were dissatisfied and 64.4% stopped due to side effects. Some common side effects to discuss with women are breast tenderness, nausea, bloating, and breakthrough bleeding—all of which often improve or completely resolve after the first several months.

Women may not always discuss their choice to stop taking COCs or POPs, making it essential for clinicians to ask about the experience of past side effects, as well as to provide preventive guidance about the possibility of side effects before starting a new method.

### How to choose the right pill

Once a woman and her provider have decided on using COCs, there are multiple options. Patients desiring a withdrawal bleed may prefer a pill pack with

| Medical conditions associated with increased risk of adverse health problems due to pregnancy |
|---------------------------------|---------------------------------|
| Breast cancer                   | Ischemic heart disease          |
| Complicated valvular heart disease | Gestational trophoblastic disease |
| Cystic fibrosis                 | Hepatocellular cardiomyopathy   |
| Diabetes (insulin dependent; nephropathy, retinopathy, neuropathy or other vascular disease; or has had diagnosis for >20 years) | Schistosomiasis with fibrosis of the liver |
| Endometrial or ovarian cancer   | Severe (decompensated) cirrhosis |
| Epilepsy                        | Sickle cell disease             |
| Hypertension (SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg) | Solid organ transplantation within the past 2 years |
| History of bariatric surgery within the past 2 years | Stroke |
| HIV (not clinically well or not receiving antiretroviral therapy) | Systemic lupus erythematosus |
|                                 | Thrombogenic mutations          |
|                                 | Tuberculosis                    |

Adapted from Curtis
monthly placebo pills, while patients desiring fewer menses prefer continuous use without placebo pills and may opt for extended cycle use. Additionally, providers may identify other co-existing conditions that may be treated with COCs such as acne, undesired facial hair growth, bloating, and/or headaches. COCs can also help reduce risk of ovarian cysts, fibroids, and benign breast disease.14

As mentioned earlier, all COCs have a progestin and EE component and doses differ by pill type. COCs have a range of EE between 10-35 mcg. A systematic review showed higher discontinuation rates for COCs with lower doses of EE, due to side effects such as breakthrough bleeding. To reduce estrogenic risks, it is reasonable to start at 20 mcg EE and increase if necessary,15 although for adolescents, data supports using a dose of 30 mcg EE or greater as lower doses of EE have been associated with impaired bone acquisition.16,17

Providers should consider the progestin component of the COC, or which progestin to use on its own in a POP, as this may result in undesired side effects.2,18-20 Some progestins are noted to have androgen-like effects, with users reporting oily skin, facial hair growth, or acne. Of note, all COCs have been shown to help with acne, but it is reasonable to choose a pill with a less androgen-like progestin and/or higher estrogen content if this is a concern.19,21,22 First-generation progestins have a lower potency and half-life, which can result in breakthrough bleeding. While second-generation progestins are more potent with a longer half-life, they may have an androgen-like effect. Third-generation progestins maintain a high potency but have lower androgen-like effects. Some third-generation formulations are even approved to treat mild to moderate acne. Finally, the only fourth-generation progestin, drospirenone, has both anti-mineralocorticoid and anti-androgenic properties and is newly available in a progestin-only pill.18,19 It has an improved bleeding profile while matching COCs in efficacy, as well as extending the missed-pill window to 12 hours for ease of use23 (Table 3).

Many of the common side effects of COCs will resolve on their own in the first few months. Thus, in the absence of severe side effects, patients should be encouraged to continue their pills for an initial 3-month interval. If these side effects continue or are particularly bothersome, Table 4 shows some options providers can use to approach them.16,24

In addition to bleeding patterns and progestin options, COCs can be monophasic or multiphasic. We recommend that most providers start with a monophasic preparation for ease of use and ability to extend to continuous use, although some data show that triphasic preparations—specifically those with newer progestins—help reduce acne, irregular bleeding, and menorrhagia.25

Table 2. Screening tool for appropriate use of COCs

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you currently pregnant?</td>
<td>No</td>
</tr>
<tr>
<td>Have you had a baby within the past 3 weeks?</td>
<td>No</td>
</tr>
<tr>
<td>If you’ve had a baby within the past 6 months: are you currently breastfeeding?</td>
<td>No</td>
</tr>
<tr>
<td>Have you ever had a blood clot or DVT (deep vein thrombosis)?</td>
<td>No</td>
</tr>
<tr>
<td>If &gt;35 years old: do you smoke?</td>
<td>No</td>
</tr>
<tr>
<td>Have you ever had a migraine headache?</td>
<td>No</td>
</tr>
<tr>
<td>Do you have high blood pressure or vascular disease?</td>
<td>No</td>
</tr>
<tr>
<td>Have you ever had a stroke or heart attack?</td>
<td>No</td>
</tr>
<tr>
<td>Do you have heart disease?</td>
<td>No</td>
</tr>
<tr>
<td>Do you have diabetes?</td>
<td>No</td>
</tr>
<tr>
<td>Do you have liver disease or a history of liver cancer?</td>
<td>No</td>
</tr>
<tr>
<td>Do you have gall bladder disease?</td>
<td>No</td>
</tr>
<tr>
<td>Have you ever had breast cancer?</td>
<td>No</td>
</tr>
<tr>
<td>Do you take medication for high cholesterol?</td>
<td>No</td>
</tr>
<tr>
<td>Do you take medication for seizures or tuberculosis?</td>
<td>No</td>
</tr>
</tbody>
</table>

*If patient checks any of the boxes, combined oral contraceptive pills may not be appropriate for her

Table 3. Benefits of the new drospriene-only POP

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-mineralocorticoid effects</td>
<td>Can decrease dysmenorrhea</td>
</tr>
<tr>
<td>Anti-androgenic</td>
<td>Can decrease BP in patients with hypertension</td>
</tr>
<tr>
<td>Can decrease dysmenorrhea</td>
<td>No effects on coagulation</td>
</tr>
<tr>
<td>Can decrease BP in patients with hypertension</td>
<td>Missed pill window</td>
</tr>
<tr>
<td>No effects on coagulation</td>
<td>Equal effectiveness to COCs</td>
</tr>
<tr>
<td>Missed pill window</td>
<td>Less breakthrough bleeding</td>
</tr>
</tbody>
</table>

Non-contraceptive benefits: dysmenorrhea and menorrhagia

In addition to contraception, COCs have non-contraceptive benefits that can be advantageous to patients. One of these benefits is helping to improve menstruation, reduce pain, and improve blood loss. Dysmenorrhea is the most common
menstrual symptom complaint, affecting up to 90% of women. COCs have been shown to reduce dysmenorrhea by 60%, and in those with severe dysmenorrhea even further (90%). This reduces absences for school or work, as well as a patient’s need for pain medication. In women who suffer from dysmenorrhea, it can be especially helpful to be on extended or continuous COC preparations to further decrease pain. The desogestrel-only POP has also been shown to help improve dysmenorrhea.

Menorrhagia is less common, yet still problematic, for patients, as it can lead to iron-deficiency anemia. COCs are particularly helpful for normalizing bleeding patterns and decreasing both amount and duration of bleeding. However, other forms of contraception, such as hormonal intrauterine devices, can have similar effects—enhancing the need for shared decision-making with a patient when deciding which hormonal method is right for her. Additional benefits to COCs include the ability to allow a woman to predict her bleeding episodes and skip them if desired. While older generations of POPs often caused abnormal bleeding patterns in patients, new drospirenone-only pills have a more favorable bleeding profile.

Non-contraceptive benefits: PMS and PMDD
COCs can also improve premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). A study looking at both POPs and COCs and their effect on premenstrual mood found that use of either one of these pills did not affect mood in over 71% of women. The remaining women were split as to whether their mood was improved or worsened. Having a history of premenstrual mood changes prior to starting a POP or COC was a strong predictor of the ability to improve mood, as was onset of premenstrual mood disturbance at a younger age. However, those with a history of depression prior to pill use were twice as likely than those without a history to have mood deterioration. Studies have also shown that in women being treated for depression, COCs containing drospirenone can improve mood deterioration in the premenstrual period, as well as reduce both physical and behavioral symptoms of PMDD. Another way to reduce PMS and PMDD symptoms is with extended or continuous cycles and reduction of withdrawal bleeding.

Non-contraceptive benefits: Endometriosis
COCs can also be very useful to women who suffer from endometriosis. COCs have been shown to reduce pain associated with endometriosis and continuous cycles are often even more beneficial for pain reduction. However, it is important to remember that COCs work by causing endometriotic implants to undergo atrophy and become inactive. Upon discontinuation of COCs, the implants become active again, resulting in return of pain and other symptoms. Initiation of COCs after surgery for endometriosis can reduce recurrence rates of endometriomas, as well as the size and growth rates of those that do recur. For women who cannot take COCs but suffer from endometriosis, desogestrel-containing POPs have been shown to be equally effective in reducing endometriosis pain.

Conclusion
Oral contraceptive pills are a widely used form of contraception and nearly all providers in all specialties will encounter patients who are taking them. While different variations between pills can seem complicated, thereby making it hard to choose a pill, it is important to tailor the decision to each patient’s needs and desires. Sometimes it can take several adjustments to find the best OCP for a particular patient. As long as the provider and patient continue to work together through shared decision-making, many women will be able to satisfactorily find a reliable form of contraception while also taking advantage of the many non-contraceptive benefits that pills offer.

Table 4: Common side effects and how to approach them

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakthrough bleeding</td>
<td>Increase EE or change progestin to norethindrone</td>
</tr>
<tr>
<td>Breast tenderness or nausea</td>
<td>Decrease EE dose</td>
</tr>
<tr>
<td>General Headaches</td>
<td>Decrease EE and progestin dose</td>
</tr>
<tr>
<td>Acne or hirsutism</td>
<td>Increase EE or switch to progestin with less androgenicity</td>
</tr>
<tr>
<td>Catamenial symptoms</td>
<td>Switch to continuous or extended-cycle formulations</td>
</tr>
</tbody>
</table>

EE = ethinyl estradiol
Co-testing with the Pap test and HPV test together is the preferred screening strategy in the United States among both healthcare providers and women, and it has greatly contributed to saving lives. Real-world data demonstrated through several large domestic studies have found that co-testing detects more pre-cancerous lesions and cervical cancer cases than either test alone. Additionally, one study has shown that screening with the HPV test alone, as the ACS recommends, could miss a cancer diagnosis in 20 percent of women.

The ACS guidelines admit that Black women have significantly higher rates of cervical cancer, yet by limiting screening options these guidelines will widen the racial disparity gap even further. Health care disparities among Black women result from systemic racism, less access to health care, and receiving lower-quality care as compared with white women. Black women are passionate about their health and actively involved in caring for themselves. But many must make decisions to forgo or delay screenings due to concerns about cost and the lack of health care coverage. The current “one-size-fits-all” approach fails to consider the needs of each individual and it ignores the science. This is why access to affordable and comprehensive screening is imperative in ensuring the early detection and treatment of cervical cancer in Black women.

The ACS owes women and healthcare providers an answer as to why they would remove support for trusted testing options when preventive healthcare is already fragile due to the COVID-19 pandemic. They have lost sight of their responsibility to put choice, access, and proven science at the forefront, instead making decisions that are odds with their stated mission to “lead the fight for a world without cancer.” We strongly urge the ACS to reconsider their new guidelines and vision for the future. Far too many women die needlessly from cervical cancer. However, we have the tools, the data and the ability to make a difference, especially in this country.

We invite ACS to join us in preserving all options for women so we can eradicate this disease together.

Black women in the United States die from cervical cancer at more than two times the rate of white women. Also, because of delays in screening, Black women are more likely to be diagnosed with advanced cervical cancer than any other racial group.

The Black Women’s Health Imperative (BWHI) is the only national non-profit organization dedicated to advancing health equity and social justice for Black women, across lifespan, through policy, advocacy, education, research and leadership development. The organization identifies the most pressing health issues that affect the nation’s 22 million Black women and girls and invests in evidence-based strategies and best-in-class organizations to accomplish its goals.

At a time when the US health care community should be reaffirming its commitment to preventing cervical cancer, the American Cancer Society (ACS) has released new screening guidelines that fail to preserve access to the most accurate and effective cervical cancer screening options and threatens to put lives at risk.

The new guidelines from the ACS recommend against continued routine use of the Pap test, instead suggesting that women ages 25–65 undergo primary HPV testing every five years. Additionally, the guidelines remove a recommendation to screen women under age 25 altogether. These changes represent a staggering departure from established current clinical practice and screening guidelines from other professional societies.
Co-testing with the Pap test and HPV test together is the preferred screening strategy in the United States among both healthcare providers and women, and it has greatly contributed to saving lives. Real-world data demonstrated through several large domestic studies have found that co-testing detects more pre-cancerous lesions and cervical cancer cases than either test alone. Additionally, one study has shown that screening with the HPV test alone, as the ACS recommends, could miss a cancer diagnosis in 20 percent of women.

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Prior depression may worsen in perimenopause

by BOB KRONEMYER

Perimenopausal women with prior depression exhibit significantly more depressive symptoms, more menopausal symptoms, and more sleep disturbances than perimenopausal women without prior depression, according to a study from Switzerland. The research in the Journal of Affective Disorders was part of the Swiss Perimenopause Study: a large prospective, 1-year longitudinal research project conducted at the Department of Clinical Psychology and Psychotherapy at the University of Zurich.

The population-based sample for the cross-sectional analysis consisted of 135 perimenopausal women, aged 40 to 56 years, who participated in the study. Subjects were recruited between June 2018 and December 2019 through various channels, such as mailing lists, social media, and newsletter articles.

A good-to-excellent self-reported health status at study enrollment was required. Among the 135 women, 43.7% were early perimenopausal and 56.3% were late perimenopausal. In addition, slightly more than half of the cohort (56.3%) was married. All women were either Swiss (n = 105), German (n = 8) or Austrian (n = 1). However, despite efforts to recruit women from different socioeconomic backgrounds, participants were overall well-educated, with 54.5% reporting an academic degree, compared with 44.5% in the Swiss population, and had a higher socioeconomic status.

A history of depression was surmised if a woman had been previously diagnosed by a mental health expert such as a psychiatrist or a psychotherapist, or as a self-report complying with the criteria for major depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

A wide range of validated psychosocial questionnaires were used to compare women with and without prior depression. Overall, 40% of the study group had experienced at least one depressive episode in the past, whereas 60% did not indicate a history of depression.

Women with prior depression showed significantly more depressive symptoms (Mann-Whitney U-test \[U = 1215.5; \ P < 0.01\]), more menopausal symptoms \((U = 1395.0; \ P < 0.01)\) and more sleep disturbances \((U = 1583.5; \ P < 0.05)\) than women without prior depression.

Women with a history of depression also rated their own mental health worse \((U = 1573.0; \ P < 0.05)\) and felt more isolated \((U = 1524.0; \ P < 0.05)\) than those without prior depression.

“We assumed that females with prior depression would struggle significantly more during the menopausal transition, as reflected by greater levels of suffering in the perimenopause, more frequent negative health outcomes and limited subjective well-being,” wrote the authors.

However, there were no significant differences in perceived stress, coping or self-esteem between women with and without prior depression.

Noteworthy, though, is that women with prior depression reported higher scores on instrumental social support compared with women without prior depression; hence, social isolation and helplessness during past depressive episodes might have increased the perceived social support.

The study’s findings underscore the need to consider a woman’s mental health history during evaluation, education, and treatment of symptoms linked to the menopausal transition.

Moreover, because a woman’s sensitivity to hormonal changes has been suggested as an influential factor in the relationship between depression and perimenopause, endocrinological factors as predictors of depressive symptoms should be considered for future research, according to the authors.

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

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Infertility treatment begins with shared decision-making with the couple. Besides the usual risks, benefits, and alternatives, the couple’s desire for a biologic child, their resources, and their insurance coverage will govern subsequent therapy. Accurate diagnosis from a basic infertility evaluation often results in an easy therapeutic recommendation. Based on their diagnosis, a couple may be offered a variety of treatments: often simple, sometimes very complex. Genetic testing of couples or their embryos will also provide additional opportunities in family building. Donor gametes, donor embryos, and adoption are often the most cost-effective route to having a child.

**Ovulation induction**

Clomiphene citrate is a synthetic estrogen receptor modulator. By blocking the estrogen receptor at the level of the hypothalamus and pituitary, the negative feedback of estrogen is eschewed and gonadotropin-releasing hormone (GnRH) pulses increase follicle-stimulating hormone (FSH) and luteinizing hormone (LH) production. These elevated gonadotropins stimulate early follicle development, increase estradiol production, and mature the oocyte. Clomiphene is most often administered as a daily oral dose for 5 days in the early follicular phase (e.g., beginning between day 3 and day 5 of the menstrual cycle), beginning at 50 mg/day. Clomiphene citrate causes FSH and LH to rise; after discontinuation, gonadotropins fall and allow the normal estrogen feedback of a developing follicle to return. Thus, when the oocyte is mature, an LH surge is triggered by the ovary, or an exogenous human chorionic gonadotropin hormone (hCG) trigger can be administered, and ovulation ensues. Adverse effects (AEs) of clomiphene citrate include hot flashes, thickened cervical mucus, vaginal dryness, scotomata, pelvic “heaviness,” and headaches. Hyperstimulation of the ovaries is rare. Because clomiphene citrate may cause thickened cervical mucus, it is often used in combination with in-

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**by AMANDA KALLEN, MD, AND SANDRA ANN CARSON, MD**

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**DR. CARSON** is a professor of Obstetrics, Gynecology, and Reproductive Sciences in the Division Chief, Division of Reproductive Endocrinology and Infertility within the Department of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine, Yale University.
trauterine insemination, especially in treatment of unexplained infertility.²

Aromatase inhibitors act in a similar fashion to clomiphene citrate, although by a different mechanism. These medications block aromatase, the enzyme which converts androgens to estrogens; estrogen is decreased to menopausal levels. The low concentration of estrogen results in increased GNRH pulses and stimulates gonadotropin release from the pituitary. Aromatase inhibitors are given orally, starting at 2.5 mg per day from day 3 to 8 of the cycle. AEs include hot flashes, vaginal dryness, nausea, muscle aches, and headaches. Data from meta-analyses, registry studies, and retrospective cohort studies do not appear to suggest increased risk of birth defects with either clomiphene citrate or letrozole.³,⁴

Patients treated with clomiphene citrate or aromatase inhibitors may use an ovulation predictor kit to measure the LH surge and time their intercourse accordingly. Ovulation occurs an average of 7 days after discontinuation of clomiphene citrate and approximately 34 to 40 hours after detection of the LH surge. Thus, patients may start testing their urine with an ovulation predictor kit on day 11 of their cycle and have intercourse on the day of the surge and the day after. Both clomiphene citrate and aromatase inhibitors have a multiple pregnancy rate of less than 10%, the majority of which are twin pregnancies,¹⁵ compared with 3% of the general population.

Gonadotropins (LH and FSH) directly stimulate the ovarian follicles and have been used in the treatment of anovulation related to eugonadotropic hypogonadism (eg, polycystic ovary syndrome), when clomiphene citrate or aromatase inhibitors fail, as well as for women with hypogonadotropic hypogonadism who will typically not respond to clomiphene or letrozole. This requires serial dilution of the ejaculate,²⁸ centrifugation, and reconstitution with media. The washed, concentrated sperm is placed into the uterus with a catheter 24 to 36 hours after an endogenous LH surge or the exogenous ovulation trigger. The sperm will be waiting in the Fallopian tube to fertilize the oocyte after ovulation. For unexplained infertility in the absence of male factor, IUI alone does not increase pregnancy rates over expectant management; therefore, IUI should be utilized in combination with OS in these instances.²⁷ If severe male factor infertility exists (eg, less than 4 million total sperm, or the strict morphology reveals less than 4% normal forms), the pregnancy rate with in vitro fertilization (IVF) is higher than with IUI.²⁸

Intrauterine insemination

Intrauterine insemination (IUI) is used in the treatment of mild male factor infertility, cervical factor infertility, and, along with ovarian stimulation, in the treatment of unexplained infertility. This requires serial dilution of the ejaculate,²⁸ centrifugation, and reconstitution with media. The washed, concentrated sperm is placed into the uterus with a catheter 24 to 36 hours after an endogenous LH surge or the exogenous ovulation trigger. The sperm will be waiting in the Fallopian tube to fertilize the oocyte after ovulation. For unexplained infertility in the absence of male factor, IUI alone does not increase pregnancy rates over expectant management; therefore, IUI should be utilized in combination with OS in these instances.²⁷ If severe male factor infertility exists (eg, less than 4 million total sperm, or the strict morphology reveals less than 4% normal forms), the pregnancy rate with in vitro fertilization (IVF) is higher than with IUI.²⁸

Ovarian stimulation

Ovarian stimulation (OS) may be used to treat unexplained infertility, male factor infertility, or hypogonadotropic hypogonadism. When OS is started, the patient is ovulating, she has the same chance of conceiving that fertile patients of similar age have, unless another infertility factor is present. Therefore, after 4 to 6 ovulatory cycles without pregnancy in an anovulatory patient, the patient should be evaluated for other causes of infertility, if a workup has not already been completed.²⁷
hypogonadism, and may be performed with clomiphene citrate, aromatase inhibitors, or gonadotropins. The premise of OS is to allow for 2 or 3 oocytes to be ovulated and increase the statistical chance of conception that might occur in any 1 cycle. Pregnancy rates with OS depend on the diagnosis, choice of therapy, sperm viability, and ovarian response. OS in combination with IUI is largely used in the treatment of unexplained infertility or male factor infertility; particularly for unexplained infertility, neither clomiphene nor letrozole is more effective than expectant management when combined with timed intercourse alone.\textsuperscript{17} Pregnancy rates with OS-IUI depend on the diagnosis, sperm viability, and ovarian response. With respect to OS with gonadotropins, the Fast Track and Standard Treatment Trial randomized women aged less than 40 years with unexplained infertility to treatment with clomiphene-IUI followed, if unsuccessful, by (1) gonadotropins-IUI or (2) IVF; results showed that the time to pregnancy was significantly shorter in the clomiphene to IVF group.\textsuperscript{19} Therefore, in most cases, it is generally recommended that unsuccessful trials of OS with oral medications be followed by IVF rather than gonadotropins. Additionally, multiple pregnancies, as well as OHSS, represent serious consequences of OS with gonadotropins, and their use to treat unexplained infertility is not recommended.\textsuperscript{17}

### FERTILITY DRUGS AND CANCER

Infertile women may be at an increased risk of invasive ovarian, endometrial, and breast cancer, but fertility drugs do not appear to increase this risk significantly.\textsuperscript{20,21} Small cohort studies suggest that infertility medications may increase the risk of borderline ovarian cancer slightly in infertile women treated with infertility drugs, but the absolute risk is small. However, it appears that this risk does not occur unless clomiphene is given for an extended time, and it has not been shown with aromatase inhibitors.\textsuperscript{22}

### In Vitro Fertilization

IVF, initially used for the treatment of tubal factor infertility in 1978, has been extended to treat a variety of causes of infertility.

<table>
<thead>
<tr>
<th>Cause of infertility</th>
<th>Risks</th>
</tr>
</thead>
</table>
| Polycystic ovary syndrome | Obesity  
Insulin resistance/type 2 diabetes  
Dyslipidemia  
Metabolic syndrome  
Obstructive sleep apnea  
Nonalcoholic steatohepatitis  
Depression/anxiety  
Endometrial hyperplasia/endometrial cancer |
| Abnormal uterine bleeding | Hypothyroidism/hyperthyroidism  
Hyperprolactinemia  
Hypogonadotropic/hypergonadotropic hypogonadism  
Coagulopathies |
| Structural uterine anomalies | Hypothyroidism/hyperthyroidism  
Hyperprolactinemia  
Hypogonadotropic/hypergonadotropic hypogonadism  
Coagulopathies |
| Premature ovarian insufficiency | Osteoporosis  
Cardiovascular disease  
Urogenital atrophy/sexual dysfunction  
Depression/anxiety  
Adrenal insufficiency  
Hypothyroidism  
Karyotypic abnormalities  
Fragile X premutation carrier |
| Endometriosis | Pelvic pain; dyspareunia  
Heavy menstrual bleeding |
| Male factor | Hypogonadotropic/hypergonadotropic hypogonadism  
Chromosomal abnormalities (Klinefelter syndrome; Y chromosome microdeletion)  
Retrograde ejaculation  
Ejaculatory duct obstruction/congenital absence of the vas deferens  
Varicocele |
infertility; IVF is also used by noninfertile individuals pursuing fertility preservation. Indeed, IVF allows women without oocytes or a uterus and men without sperm in the ejaculate to have a biological child. IVF is indicated in cases of severe oligospermia or azoospermia, untreated tubal factor, or infertility in women 40 years and older, and it may also be utilized in women with endometriosis, anovulation, or unexplained infertility when ovulation induction and IUI have been unsuccessful. IVF is also utilized when genetic screening of embryos is planned.

IVF protocols vary depending on the indication, patient age, treatment history, and other considerations. A typical IVF cycle involves, first, ovulation induction to stimulate multiple ovarian follicles, followed by oocyte aspiration using a transvaginal ultrasound-guided needle. Collected oocytes are fertilized in vitro by mixing them with spermatozoa (IVF) or by injecting selected spermatozoa directly into the oocyte cytoplasm (intracytoplasmic sperm injection). Embryos are cultured under carefully controlled conditions, optimizing oxygen concentration, embryo culture media, and other modifications to promote the development of high-quality embryos. The embryos are then transferred into the uterus through a catheter under ultrasound guidance. In the case of severe male factor infertility, sperm retrieval from the epididymis or testis may also be performed. Embryos not transferred may be cryopreserved to transfer in a later cycle (frozen embryo transfer).

Preimplantation genetic testing (PGT) is a procedure in which cultured embryos can be biopsied and tested in order to select the most appropriate embryos for transfer. Prior to transfer, PGT can be used to screen for euploid embryos for transfer (PGT-aneuploid [PGT-A]); however, specific groups of infertility patients most likely to benefit from PGT-A have not been clearly defined. PGT may also be utilized to identify embryos with a single gene disorder (PGT-monogenic or preimplantation genetic diagnosis); this would be used, for example, if both partners are carriers for the same autosomal recessive condition, such as cystic fibrosis.

It is important to note that once a patient is ovulating, she has the same chance of conceiving that fertile patients of similar age have, unless another infertility factor is present.

DONOR GAMETES AND SURROGACY

Donor gametes may be considered when either partner has severe defects in gamete quality or quantity. For males, such situations may include severe oligospermia, azoospermia, failure of fertilization in prior IVF cycles, ejaculatory dysfunction, or other severe male factor infertility (ie, after gonadotoxic chemotherapy). Donor oocytes or embryos may be used when a woman’s oocyte reserve is low (ie, advanced reproductive age or diminished ovarian reserve) or oocyte quality is poor, when multiple attempts at IVF with her own oocytes have failed, or when a condition such as premature ovarian insufficiency makes the likelihood of conceiving with her own gametes extremely low. Donor gametes may also be utilized when either partner has a significant genetic defect, or if there is a family history of a genetic condition for which carrier status cannot be determined. Females without male partners, same-sex couples, or males without female partners may also utilize donor gametes, either anonymously from donor gamete banks or known donors.

A gestational carrier (GC) is defined as a woman who carries a pregnancy and is not sexually intimate with the genetic parents or gamete donors. A GC may be used when a medical condition prevents a woman from carrying a pregnancy or when she has a congenital or surgical absence of a uterus. A GC may also be indicated if a pregnancy would pose significant risk to a woman’s health or life, or if there is a biological inability to carry a pregnancy, as with single males or gay male couples. Lastly, uterine transplant is an emerging option for individuals without a uterus; it is currently available only in the setting of clinical research trials.

Conclusions

Although legal adoption has allowed couples to build a family for more than a century, modern technology now allows for effective therapy for infertility in many cases, guided by accurate diagnosis and shared decision-making. The basic evaluation of an infertile couple has been supplemented with an evaluation of related health issues, as our knowledge has advanced to include surveillance beyond the reproductive system (Table). The primary care practitioner is vital in not only initiating the evaluation, surveying for related health problems, and referring to specialty care, but also longitudinally, following patients for possible disease processes harbingered by infertility.
ANNOVERA® IS
ANNUAL BIRTH CONTROL
OWNED AND OPERATED BY HER¹*

Meet the innovative contraception designed to empower women

Created for her control: Long-lasting, reversible, and procedure-free¹
Created for her comfort: Soft and flexible for easy insertion and removal¹²
Created with a novel hormone profile: Purposefully designed to release a combination of a non-androgenic progestin and a low-dose estrogen daily for 1 year (13 cycles)¹³

*ANNOVERA is inserted for 21 continuous days and removed for 7 days for 13 cycles.

ANNUAL. COMFORTABLE. CONTROLLABLE.

IMPORTANT SAFETY INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning.
• 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.

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 (segesterone acetate and ethinyl estradiol vaginal system) 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.
• 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.

Limitations of Use: ANNOVERA has not been adequately studied in females with a body mass index >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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WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptives (CHCs). This risk increases with age, particularly in females over 35 years of age, and with the duration of female smoking. For this reason, CHCs should not be used by females who are over 35 years of age and smoke.

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 in females with a BMI >27 kg/m².

DOSEAGE AND ADMINISTRATION
One ANNOVERA is inserted in the vagina. The vaginal system must remain in place continuously for 3 weeks (21 days) followed by 1 week (7 day) vaginal system-free interval. One vaginal system provides contraception for thirteen 28-days cycles (1 year). Follow instructions for starting ANNOVERA, including switching from other contraceptive methods, and users should be advised to discontinue use if pregnancy occurs, or if the vaginal system is removed, discarded, or lost. [see How to Start ANNOVERA (2.2) in PI]

Contraceptive efficacy of ANNOVERA may be reduced if a woman stops using the system before the end of the 21-day estrogen withdrawal period. ANNOVERA is out of the vagina for more than 24 hours or more than 2 cumulative hours during the 21 days of continuous use, then back in the vagina for 21 days or longer, this may cause a male condom or spermicide 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 thromboembolic diseases. Examples include females who are known to have severe obesity (BMI >35); have a current or recent 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 hyperension with vascular disease; have diabetes mellitus and are over age 35, diabetes mellitus with hypertension or vascular disease, or other end-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 migraine headaches. • Current or history of breast cancer or other estrogen or progesterin-sensitive cancer. • Liver tumors, hepatic tumors, or severe (decompensated) liver disease. • Undiagnosed abnormal uterine bleeding. • Hypersensitivity to any of the components of ANNOVERA. Hypersensitivity reactions reported include urticaria, rash, angioedema, facial edema, hives, and swelling. • Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. ANNOVERA may be restarted 2 weeks following completion of treatment with the Hepatitis C combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir. ANNOVERA can be restarted 2 weeks after stopping ANNOVERA if depression recurs to a serious degree. • Deperson

DEATH
ANNOVERA is not indicated for use in females who are known to be at high risk of arterial or venous thromboembolic disease. 

BLOOD Pressures
ANNOVERA increases blood pressure in postmenopausal females using ANNOVERA and in 0.9% of females in the placebo group. 

ADVERSE REACTIONS
ANNOVERA is contraindicated in females with a BMI >27 kg/m².

Body Mass Index (BMI)/Body Weight
ANNOVERA® (segesterone acetate and ethinyl estradiol vaginal system) is associated with lower systemic exposure of SA and EE.

CONTRAINDICATIONS
ANNOVERA is contraindicated in females with a BMI >27 kg/m².
An imaging approach to early pregnancy failure

Ultrasound technology can be an indispensable tool for the management of suspected early pregnancy loss.

by BRYANN BROMLEY, MD, AND THOMAS D. SHIPP, MD

Introduction
Early pregnancy loss (miscarriage) is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without cardiac activity within the first 12 6/7 weeks of gestation.¹ The cessation of development occurs in approximately 10-20% of clinically recognized pregnancies, increasing with advancing parental age.¹ ² ³ With the adoption of early home pregnancy testing, women are commonly referred for sonographic evaluations very early in gestation to determine pregnancy location and viability. Although we believe ultrasound to be indispensable for the management of suspected early pregnancy failure, if performed too early or without strict adherence to guidelines, it may lead to inconclusive results or an incorrect diagnosis of an early pregnancy loss.⁴

Ultrasonography (usually transvaginal) in combination with β-hCG and clinical history is instrumental for making the diagnosis of a nonviable pregnancy with certainty. Historically, these criteria were based on small studies; a CRL of ≥ 5mm and mean sac diameter of ≥ 16-17 mm without an embryo were considered diagnostic for an early pregnancy loss.¹,⁵ Over the last decade, the reliability of these thresholds has been called into question.⁶,⁷ In 2013, the Society of Radiologists in Ultrasound (SRU) convened a multispecialty panel on early first trimester diagnosis of miscarriage and exclusion of a viable intrauterine pregnancy (cannot result in the birth of a live baby) and published a more conservative approach to defining a pregnancy as nonviable.³ This change was made with the expectation of a diagnostic specificity of 100% (no false positives), while accounting for intra and interobserver variability in measurements as well as a range in practice conditions and experience.⁶,⁷

Inadvertent misclassification of potentially viable pregnancy as nonviable with resultant medical or surgical intervention resulting in the iatrogenic termination of a desired pregnancy has significant consequences to the family and may be an inciting factor in malpractice cases.⁸,⁹

The cessation of development occurs in approximately 10-20% of clinically recognized pregnancies, increasing with advancing parental age.

This article will focus on the criteria for the sonographic diagnosis of a nonviable intrauterine pregnancy early in gestation, those sonographic findings that are suspicious to result in an early pregnancy loss, and the vital role of ultrasound in these frequent clinical scenarios. The sonographic findings are only one part of the puzzle in determining if a preg-
nancy is nonviable. In order to apply the findings to a clinical situation, the obstetric care provider must take other clinical factors into consideration, such as accounting for the certitude of menstrual dating, the woman’s desire to continue the pregnancy until the definitive diagnosis is made along with logistical challenges such as the possibility of heavy bleeding leading to emergency room visits, unexpected passage of products of conception or unscheduled surgical procedures. On another note, when diagnosing a complete miscarriage, care must be taken that an intrauterine pregnancy has previously been confirmed. If not, serial β-hCG should be performed so as to not miss the diagnosis of an ectopic pregnancy.

Embryologic development in early pregnancy is quite linear and follows a dependable and fairly tight timetable (Figs. 1A, B, C, D). Ultrasound can reliably characterize the progression of a normally developing pregnancy from very early in gestation. The gestational sac is first identified at approximately 5 weeks, the yolk sac is visible at approximately 5.5 weeks and an embryo with cardiac activity located in close proximity to the yolk sac should be evident at approximately 6 weeks gestation. Embryonic cardiac activity is often seen when the embryo is first identified, measuring as little as 2 mm in length. The mean sac diameter is the average of three orthogonal diameters of the fluid portion of the gestational sac but is not as accurate as crown rump length for gestational dating. Nomograms for development of embryonic length, heart rate, gestational sac diameter and yolk sac diameter are available.

Transvaginal sonographic findings diagnostic of an early pregnancy loss

Given the newer, more conservative guidelines that are now well-accepted, a single transvaginal ultrasound identifying an embryo with a crown rump length of 7 mm or greater without cardiac activity or a gestational sac with a mean sac diameter of 25 mm or greater without an embryo are considered definitive proof that a pregnancy is nonviable (Figs. 2 and 3). These metrics have also been validated in a prospective observational multicenter study to have a specificity of 100%.

Given the expected linear development of normal early pregnancies, the definitive diagnosis of an early pregnancy loss can also be made based on sequential transvaginal ultrasound scans over a specified time interval (Figure 4). In a normally developing viable pregnancy, an embryo with cardiac activity must be demonstrated ≥11 days after a gestational sac with a yolk sac or ≥14 days in which a gestational sac without a yolk sac was identified by transvaginal sonography. The lack of cardiac activity after that interval of observation is definitive evidence for an early pregnancy loss. A shorter interval of observation with no embryonic heart motion would raise suspicion for an early pregnancy loss, however, it is not definitive. Predictably, patients are anxious when the results of an indeterminant status of viability are disclosed, and the rationale behind the recommended time interval for follow up of the sonographic evaluation should be communicated.

Transvaginal sonographic findings suspicious (but not diagnostic) for early pregnancy loss

If an embryo is seen with a crown-
rump length of <7 mm and without cardiac activity, it is suspicious for an early pregnancy loss (Figure 5). Similarly, a gestational sac with a mean sac diameter of 16-24 mm and no embryo is suspicious for an early pregnancy loss. The development of gestational sac landmarks is progressive and therefore the sonographic finding of an amnion with an adjacent yolk sac and without a visualized embryo is suspicious for an early pregnancy loss (Figure 6). It is important not to mistake a second yolk sac for the amnion as may be seen with early monochorionic diamniotic twins. If ascertainment of viability is indeterminant based on a suspicious finding, it is generally appropriate to repeat the ultrasound examination in 7-10 days.5,13

Sonographic signs concerning for an increased risk of early pregnancy loss
In embryos in which cardiac activity is demonstrated, there are additional sonographic features that may signal an increased risk for early pregnancy loss. These include findings such as embryonic bradycardia, a small gestational sac, a large yolk sac, and a subchorionic hematoma.

Embryonic or fetal bradycardia
In normal pregnancies, the embryonic heart rate progressively increases up to 8 weeks’ gestation. It has been 25 years since the seminal paper by Dubbilet and Benson in which the rate of first trimester pregnancy loss was directly correlated with embryonic heart rate14 (Figure 7). These investigators evaluated 1,185 early pregnancies and provided pregnancy loss rates stratified by the degree of bradycardia and gestational age. The slower the heart rate, the higher the risk of pregnancy loss (Table 1).

A recent systematic review and diagnostic accuracy meta-analysis evaluating the prediction of miscarriage found that the most predictive factor for early pregnancy loss was embryonic/fetal heart rate.16 This predictive effect was even more pronounced among those with bleeding in early pregnancy. In their hierarchical summary receiver operating characteristic model curve, the authors found that bradycardia had a sensitivity of 68.4%, specificity of 97.8%, positive likelihood ratio of 31.7, and negative likelihood ratio of 0.32 for predicting early pregnancy loss. For those with bleeding the sensitivity of heart rate to predict miscarriage increased further (sensitivity, 84.2%, specificity, 95.7%, positive likelihood ratio, 19.51, and negative likelihood ratio, 0.16). The authors found that the best cut-off for heart rate was \( \leq 110 \) bpm for the prediction of miscarriage. A heart rate of >134 bpm at seven weeks’ gestation and a heart rate of >158 bpm at 8 weeks’ gestation were predictive of on-going pregnancies. These data highlight the importance of assessing embryonic heart rate by M-mode while performing an early ultrasound, as it is the most predictive sign of pregnancy loss. It must be recognized, however, that in an embryo of less than 6 weeks gestation, the very
initiation of cardiac pulsations may be reflected in a slower rate, which underscores the value of a repeat scan. A bradycardic heart rate should prompt a follow-up sonographic examination to assess embryonic viability, whereas a normal heart rate provides considerable reassurance for the patient.

Small gestational sac in relation to crown-rump length
On occasion, an embryo with a normal heart rate will appear sonographically ‘crowded’ within the gestational sac (Figure 8), a finding which has been associated with an increased risk of early pregnancy loss. Objectively, this has been characterized as a mean sac size - crown rump length (MSS-CRL) of < 5 mm. Bromley et al. demonstrated that the risk of miscarriage was 94% with a small gestational sac in the first trimester despite a normal cardiac rate. In a larger and more recent study of patients conceiving via IVF, the early pregnancy loss rate among patients with a MSS-CRL of < 5 mm was approximately 44% compared with a referent population with a MSS-CRL of 5-9.9 mm in whom the loss rate was 15.8% (P < .0001). Of note, there is no appreciable increase in the risk of early pregnancy loss between those conceiving using assisted reproductive technology compared with spontaneously conceived pregnancies. The sonographic finding of an embryo in a small gestational sac should prompt follow-up sonography to assess persistence of development.

Yolk sac size
The yolk sac is the first structure that is identifiable within the gestational sac by transvaginal ultrasound when the gestational sac reaches 8-10 mm. Abnormalities in size and appearance of the yolk sac have been reported to be associated with an increased risk of pregnancy loss, although not all studies have found this to be a useful metric for predicting pregnancy loss. A yolk sac of greater than 7 mm has been suggested as a concerning threshold for an increased risk of pregnancy loss, although methods of measurement have been inconsistent. Recent data suggests yolk sac diameter does not improve the prediction of miscarriage over bradycardic heart rates and limited embryonic/fetal crown-rump length. One should be very cautious in the use of this sonographic sign, especially as an isolated finding, for prediction of first trimester pregnancy loss until stronger guidance from the literature is available.

Crown-rump length
In a well dated pregnancy, a small crown-rump length for gestational age may reflect early growth disturbance and is associated with an increased risk of aneuploidy as well as early pregnancy loss. Among an IVF population with clear gestational age determination, those with a crown-rump length of < 10% had an increased risk of miscarriage as compared to those...
normally grown, 17.2% vs. 6.6%, $P = 0.005$, OR = 2.93, 95%CI 1.2, 6.7). Should a much smaller than expected crown-rump length be encountered in the first trimester, especially those that would lead to a change in pregnancy dating, a follow up evaluation to assess interval growth in 2 weeks should be considered.

**Subchorionic hematoma**

Bleeding in early pregnancy is common, and a subchorionic hematoma can be sonographically identified in this setting (Figure 9). Subchorionic hematoma has been associated with an increased rate of pregnancy loss, especially if the hematoma is large, associated with bleeding or the patient is 35 years of age or older.24 The method of assessing the size of the subchorionic hematoma has been controversial, but it appears that in one study, the subjective assessment of hematoma size based on the fraction of the gestational sac size correlates best with first trimester pregnancy outcome.25 The rate of spontaneous pregnancy loss in the first trimester is reported to be highest for those hematomas diagnosed before 8 weeks (19.6%) compared to those diagnosed after 8 weeks (3.6%; $P < .001$).25

A review and meta-analysis demonstrated that the identification of a subchorionic hematoma was associated with an increased risk for miscarriage, increasing from 8.9% to 17.6%, pooled OR 2.18, 95% CI 1.29, 3.68).26 A recent retrospective cohort study of 2446 patients with singletons presenting for ultrasound between 6 weeks and 13+6d weeks at a single center, demonstrated that subchorionic hematoma was associated with an increased risk of pregnancy loss before 20 weeks gestation (7.5% vs. 4.9%; $P = .026$) on univariate analysis, however, when adjusting for patient age and bleeding, this association was no longer significant.27 Similarly, these authors showed no increased risk of adverse outcome later in gestation.28 Given the possible increased risk for pregnancy loss, follow-up sonography can be considered in these cases.

**Chorionic Bump**

A chorionic bump is a focal convex protuberance that develops at the choriodecidual surface and protrudes into the gestational sac in the early first trimester, likely reflecting a hematoma or necrotic decidua (Figure 10). The finding has been associated with an increased risk of early pregnancy loss when identified before 11 weeks gestation. If a chorionic bump is identified and the pregnancy is otherwise normal in appearance with a normal heart rate, the live birth rate has been reported to be approximately 83%.29 In addition, there was no significant relationship between the volume of the chorionic bump or bleeding per vagina and the risk of pregnancy loss.29 In the latter part of the first trimester, the presence of a chorionic bump is not thought to be clinically relevant.30
Conclusions

Ultrasound is a powerful tool in the diagnosis and prediction of early pregnancy loss. Practitioners must be diligent to follow guidelines for diagnosing a pregnancy as non-viable in order to prevent an iatrogenic pregnancy termination. Although some patients will have sonographic findings that definitively allow the diagnosis of a failed pregnancy, many will have findings that are suggestive or inconclusive of miscarriage. A follow-up scan can be very helpful in these cases.

The timing of the sonographic evaluation is important in management, as too early an evaluation is likely to lead to an ultrasound report of a pregnancy of unknown location or an intrauterine pregnancy of uncertain viability. In a study of asymptomatic women attending an early pregnancy ultrasound unit, the diagnosis of a miscarriage could not be made on initial ultrasound examination until 35 days from LMP and most miscarriages were diagnosed when the first assessment was between 63 and 85 days after the LMP. These authors recommended that in order to reduce the number of inconclusive scans, asymptomatic women without a history of ectopic, delay an initial ultrasound until 49 days from LMP.

Healthcare providers taking care of women suspected of having or experiencing an early pregnancy loss should have training in how to compassionately and effectively communicate difficult news as the patient is at risk for posttraumatic stress, anxiety and depression.
In this video series, 3 OBGYNs share their real-world experience with an endometriosis pain treatment, from patient counseling to identifying suitable patients.

watch videos:
contemporaryobgyn.net/treat-endopain
Venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality. The estimated incidence of VTE during pregnancy and the postpartum period is 1 to 2 per 1,000 deliveries. The risk of VTE is particularly high during the postpartum period and especially following cesarean delivery.

There is considerable variation in the approach to VTE prophylaxis in pregnancy, including following cesarean delivery. Recent guidelines by various professional organizations provide conflicting recommendations based on low-grade evidence, mainly from observational data. At present, the available VTE risk stratification tools used to decide for or against pharmacological prophylaxis have not been validated in women undergoing cesarean delivery. Individualization of care is recommended for women at very high risk of VTE.

Q | What are the current guidelines for VTE prophylaxis following cesarean delivery?

Several guidelines define risk factors for VTE, including those summarized in Table 1 from the American College of Chest Physicians (ACCP), Royal College of Obstetricians and Gynaecologists (RCOG), and National Partnership for Maternal Safety (NPMS). The American College of Obstetricians and Gynaecologists (ACOG) recommends that all women undergoing a cesarean delivery receive mechanical prophylaxis with the use of pneumatic sequential compression devices started preoperatively and continued until the patient is ambulatory. The use of combined pharmacological and mechanical prophylaxis may also be supported based on individual risk assessment. ACOG does not endorse any specific risk stratification guideline. Hospitals are encouraged to evaluate women for VTE risk factors and to implement a prophylaxis protocol weighing benefits, harms, and cost-effectiveness. If VTE risk factors persist during the postpartum period, up to 6 weeks of pharmacological prophylaxis should be considered.

The ACCP suggests that the benefits of thromboprophylaxis outweigh potential harm when the absolute risk of VTE is 3% or higher. The presence of 1 major risk factor, 1 minor risk factor in the setting of an emergent cesarean delivery, or 2 or more minor risk factors suggests a VTE risk above 3%. For women undergoing cesarean delivery with no risk factors for VTE, ACCP recommends no prophylaxis other than early mobilization. In women at very high risk for VTE, combined pharmacological and mechanical prophylaxis is suggested. If VTE risk factors persist during the postpartum period, up to 6 weeks of prophylaxis is suggested.

The RCOG recommends thromboprophylaxis with low-molecular-weight heparin (LMWH) for 10 days after delivery should be considered for all women who have had caesarean sections and those having an elective caesarean section who have any additional risk factors. Prophylaxis with LMWH is recommended for 10
Vulvar lichen sclerosus (VLS) often goes untreated until advanced signs of skin damage occur. Treatment with potent topical steroids is aimed at relieving symptoms and preventing further damage. Fractional CO$_2$ lasers, meanwhile, have been shown histologically to improve vaginal tissue and to alleviate self-reported vulvar symptoms of itching and dyspareunia.

This interactive poster, narrated by Somi Javaid, MD, FACOG, details a study evaluating a series of fractional CO$_2$ laser treatments to improve clinical signs and architectural changes associated with VLS and, as an adjunctive therapy, to maintain symptomatic control of the disease.

Explore Interactive Poster: contemporaryobgyn.net/laser-vls
days following delivery in intermediate-risk women and for at least 6 weeks following delivery in high-risk women.

The NPMS recommends universal pneumatic compression devices for all women undergoing cesarean deliveries. The addition of pharmacological prophylaxis may be considered for women at high risk of VTE based on the use of either the RCOG guidelines or the modified Caprini scoring system. Hospitals may consider providing pharmacological VTE prophylaxis to all women undergoing a cesarean delivery because of the challenges in consistently identifying women with VTE risk factors.

**Table 1**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
<th>Risk Stratification</th>
</tr>
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<tbody>
<tr>
<td>American College of Obstetricians and Gynecologists</td>
<td>- Pneumatic compression devices for all women undergoing cesarean delivery.</td>
<td>A preferred risk scoring system is not endorsed; recommends each facility should carefully consider the risk assessment protocols available and implement one in a systematic way to reduce the incidence of VTE in pregnancy and the postpartum period.</td>
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<tr>
<td></td>
<td>- Women with additional risk factors for VTE may benefit from pharmacological prophylaxis.</td>
<td></td>
</tr>
<tr>
<td>American College of Chest Physicians</td>
<td>- Other than early mobilization, no prophylaxis is recommended in women without risk factors.</td>
<td>Major risk factors: Immobility for at least 1-week antepartum Postpartum hemorrhage with surgery Previous VTE Preeclampsia with fetal growth restriction Antithrombin deficiency Factor V Leiden or G20210A mutations Blood transfusion Postpartum infection Systemic lupus erythematosus Heart disease Sickle cell disease Minor risk factors: Obesity Multiple pregnancy Postpartum hemorrhage Smoking Fetal growth restriction Preeclampsia Protein C or S deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Menton and multiple risk factors are present or 1 minor risk factor is present in the setting of emergent cesarean delivery.</td>
</tr>
<tr>
<td>Royal College of Obstetricians and Gynaecologists</td>
<td>- High-risk women should receive LMWH for 6 weeks postpartum.</td>
<td>High-risk patients: Any previous VTE, any woman requiring antenatal LMWH, high-risk thrombophilia, low-risk thrombophilia with family history of thrombosis</td>
</tr>
<tr>
<td></td>
<td>- Intermediate-risk women should receive LMWH for at least 10 days after delivery.</td>
<td>Intermediate-risk patients: Any one of the following: Cesarean delivery during labor, BMI &gt; 40 kg/m², postdelivery readmission, surgical procedures during the puerperium, cancer, heart failure, active lupus, nephrotic syndrome, sickle cell disease, type 1 diabetes with nephropathy, inflammatory bowel disease, intravenous drug use or Two or more of the following: Age &gt; 35 years, parity &gt; 3, obesity, smoker, elective cesarean delivery, family history of VTE, low-risk thrombophilia, varicose veins, current systemic infection, preeclampsia, immobility, multiple pregnancy, preterm delivery, stillbirth, operative vaginal delivery, prolonged labor &gt; 24 hours, postpartum hemorrhage</td>
</tr>
<tr>
<td></td>
<td>- Low-risk women should be mobilized early and avoid dehydration.</td>
<td>Abbreviations: BMI, body mass index; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism</td>
</tr>
</tbody>
</table>
postpartum. Women with no previous personal history of VTE but who have tested positive for one of the high-risk inherited thrombophilias (antithrombin III deficiency, homozygous Factor V Leiden or G20210A, or heterozygous for both Factor V Leiden and G20210A) or who have a low-risk thrombophilia should also receive pharmacological VTE prophylaxis following cesarean delivery. Women with a previous diagnosis of antiphospholipid antibody syndrome should receive prophylactic or therapeutic doses of heparin (depending on previous history of VTE) during the puerperium irrespective of mode of delivery. The main discrepancy among current guidelines concerns pharmacological prophylaxis for women with no history of VTE and no inherited or acquired thrombophilia. Recommendations differ in part because they are based on observational studies and expert opinion due to a lack of clinical trial data. This presents a challenge for determining the true incidence of VTE and accurately assessing the risk-benefit ratio of pharmacological prophylaxis following cesarean delivery. The potential benefit of pharmacological prophylaxis needs to be weighed against the potential for adverse outcomes associated with the intervention. For instance, the use of pharmacological VTE prophylaxis following cesarean delivery has been associated with increased rates of wound separation and wound hematomas. In the absence of adequately powered clinical trials, accurate calculations of the number needed to treat (NNT) and number needed to harm (NNH) are limited. However, the available evidence suggests that the NNH may be lower than the NNT in most scenarios, particularly in the absence of risk factors or the presence of only a minor risk factor. Further, administrative and retrospective data obtained from analysis of large databases may overestimate the incidence of VTE, resulting in a similar overestimation of the benefit of any intervention aimed at preventing it.

Another consideration in making recommendations is that the use of risk assessment models (eg, Caprini and Padua) to predict VTE following cesarean delivery has not been adequately studied. The authors of a recent study questioning their utility during the peripartum period suggest the establishment of a maternal clinical registry and more extensive research to identify optimal models with which to predict VTE risk in the obstetrical population.²

At present, the available evidence to suggest that universal (or near universal) pharmacological VTE prophylaxis effectively reduces maternal mortality is limited.² The two most common agents used for VTE prophylaxis are LMWH and UFH. Current guidelines recommend LMWH (eg, enoxaparin) as the first-line pharmacological agent.²,³ Enoxaparin is not recommended in patients with significant renal dysfunction, defined as creatinine clearance less than 30 mL/min. Compared with UFH, enoxaparin has the advantage of better bioavailability, longer half-life, more predictable anticoagulation effect, less bleeding risks, and less risk of heparin-induced thrombocytopenia and osteopenia. For prophylaxis purposes, the recommended enoxaparin dosage is typically 40 mg subcutaneously once a day. Obese women may require higher doses; however, the optimal dose is unknown. Some evidence supports the use of intermediate doses of enoxaparin (40 mg subcutaneously every 12 hours) for obese women. UFH is a good choice in women with renal disease. Recommended prophylactic dosages range from 5000 to 10,000 units subcutaneously every 12 hours depending on gestational age (5000 units subcutaneously every 12 hours in the first trimester, 7500 units subcutaneously every 12 hours in the second trimester, and 10,000 units subcutaneously every 12 hours during the third trimester). In the postpartum period, doses of 5000 units subcutaneously every 8–12 hours are commonly utilized. There are insufficient data to recommend the use of new oral anticoagulants (eg, apixaban, rivaroxaban, dabigatran) during the postpartum period.
When is the optimal time to start thromboembolism prophylaxis after a cesarean delivery?

Current ACOG guidelines recommend starting VTE mechanical prophylaxis with sequential compression devices preoperatively in all women undergoing a cesarean delivery. The Society for Obstetric Anesthesia and Perinatology (SOAP) has addressed the optimal interval between neuraxial anesthesia and initiation of VTE pharmacological prophylaxis to prevent development of spinal or epidural hematomas. Prophylactic doses of enoxaparin (40 mg subcutaneously every day) may be started postoperatively as soon as 4 hours after catheter removal but not earlier than 12 hours after the block was performed. Intermediate doses of enoxaparin (40 mg subcutaneously every 12 hours) and therapeutic doses may also be started as soon as 4 hours after catheter removal but not earlier than 24 hours after the block was performed. Prophylactic doses of UFH may be started as early as 1 hour after removal of the neuraxial catheter.

In addition to concerns about spinal hematomas, timing to start VTE prophylaxis should also consider the risk of postoperative bleeding. With prophylactic doses of anticoagulation, bleeding complications are usually mild and rarely result in life-threatening hemorrhage, unlike bleeding risks with the use of full-dose anti-coagulation in the postoperative period. In cases with significant intraoperative bleeding complications, the decision of when to start pharmacological prophylaxis (if indicated) must be individualized, while recognizing that postpartum hemorrhage, blood transfusion, and prolonged surgery are risk factors for VTE. In these cases, initiation of UFH, which is reversible and has a shorter half-life, may be prudent.

Conclusion

VTE remains an important cause of maternal morbidity and mortality during pregnancy and the postpartum period. The use of mechanical prophylaxis sequential compression devices is an inexpensive, safe intervention and should be used in all women undergoing cesarean delivery until the woman is fully ambulatory. The decision to add pharmacological prophylaxis depends on the presence or absence of certain risk factors. Women with a previous personal history of deep venous thrombosis or pulmonary embolism and women with a personal history of an inherited thrombophilia should receive pharmacological prophylaxis following cesarean delivery. The use of universal or near-universal pharmacological prophylaxis for women undergoing cesarean delivery, other than those with a previous thrombosis or an inherited thrombophilia, cannot be recommended until further studies demonstrate that such a strategy is beneficial.

Summary of Recommendations

<table>
<thead>
<tr>
<th>Number</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>We recommend that all women who undergo cesarean delivery receive sequential compression devices starting prior to surgery and that they be continued until the patient is fully ambulatory.</td>
<td>1C</td>
</tr>
<tr>
<td>2</td>
<td>We suggest that women with a previous personal history of a deep venous thrombosis or pulmonary embolism who undergo cesarean delivery receive both mechanical (starting preoperatively and continuing until ambulatory) and pharmacological (for 6 weeks postoperatively) prophylaxis.</td>
<td>2C</td>
</tr>
<tr>
<td>3</td>
<td>We suggest that women with a personal history of an inherited thrombophilia (high risk and low risk) but no previous thrombosis who undergo cesarean delivery receive both mechanical (starting preoperatively and continuing until ambulatory) and pharmacological (for 6 weeks postoperatively) prophylaxis.</td>
<td>2C</td>
</tr>
<tr>
<td>4</td>
<td>We recommend the use of low-molecular-weight heparin as the preferred thromboprophylactic agent in pregnancy and the postpartum period.</td>
<td>1C</td>
</tr>
<tr>
<td>5</td>
<td>When pharmacologic thromboprophylaxis is needed in pregnant women with class III obesity, we suggest the use of intermediate doses of enoxaparin.</td>
<td>2C</td>
</tr>
<tr>
<td>6</td>
<td>We suggest that each institution develop a patient safety bundle with an institutional protocol for venous thromboembolism prophylaxis among women who undergo cesarean delivery.</td>
<td>Best Practice</td>
</tr>
</tbody>
</table>
A weekly contraceptive patch

THAT IS PURPOSEFULLY
designed for her

INTRODUCING TWIRLA®—the first novel
birth control patch approved in nearly 20 years

INDICATION AND USAGE
TWIRLA is indicated as a method of contraception for use in women of reproductive potential with a BMI <30 kg/m² for whom a combined hormonal contraceptive is appropriate.

Limitations of Use:
Consider the reduced effectiveness of TWIRLA in women with a BMI ≥25 to <30 kg/m² before prescribing TWIRLA. TWIRLA is contraindicated in women with a BMI ≥30 kg/m².

IMPORTANT SAFETY INFORMATION
WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS and CONTRAINDICATED IN WOMEN WITH A BMI ≥30 kg/m²
Cigarette Smoking and Serious Cardiovascular Events
Cigarette smoking increases the risk of serious cardiovascular events from combined 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, including TWIRLA, are contraindicated in women who are over 35 years of age and smoke.
Contraindicated in Women with a BMI ≥30 kg/m²
TWIRLA is contraindicated in women with a BMI ≥30 kg/m². Compared to women with a lower BMI, women with a BMI ≥30 kg/m² had reduced effectiveness and may have a higher risk for venous thromboembolic events (VTEs).

Please see additional Important Safety Information on next page and Brief Summary of full Prescribing Information.
WARNINGS AND PRECAUTIONS

TWIRLA; and use of hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir with or without dasabuvir.

headache; liver tumors, acute viral hepatitis, or severe (decompensated) cirrhosis, or liver disease; undiagnosed abnormal uterine bleeding;

Please see additional Important Safety Information on next page and Brief Summary of full Prescribing Information.

IMPORTANT SAFETY INFORMATION (con’t)

CONTRAINDICATIONS
TWIRLA is contraindicated and should not be used in women with a high risk of arterial or venous thrombotic disease, including women
with a BMI ≥30 kg/m^2; headaches with focal neurological symptoms, migraine with aura, women over 35 years of age with any migraine
headache; liver tumors, acute viral hepatitis, or severe (decompensated) cirrhosis, or liver disease; undiagnosed abnormal uterine bleeding;

— If a woman using TWIRLA develops new headaches that are recurrent, persistent, or severe, evaluate the cause and

— Discontinue TWIRLA during prolonged immobilization and, if feasible, stop TWIRLA at least 4 weeks before and through 2 weeks after

— Monitor blood pressure at routine visits and stop TWIRLA if blood pressure rises significantly. An increase in blood

— Studies suggest CHCs increase the risk of developing gallbladder disease and may also worsen existing
gallbladder disease.

— Monitor blood pressure at routine visits and stop TWIRLA if blood pressure rises significantly. An increase in blood

— Discontinue TWIRLA during prolonged immobilization and, if feasible, stop TWIRLA at least 4 weeks before and through 2 weeks after

— Start TWIRLA no earlier than 4 weeks after delivery in women who are not breast-feeding.

— Before starting TWIRLA, evaluate any past medical history or family history of thromboembolism or thromboembolic disorders and
consider whether history suggests inherited or acquired hypercoagulopathy.

Arterial Events — CHCs increase the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke,
particularly among older women (>35 years of age), smokers, and women with hypertension, dyslipidemia, diabetes, or obesity.

Please see additional Important Safety Information on next page and Brief Summary of full Prescribing Information.
IMPORTANT SAFETY INFORMATION (con’t)

WARNINGS AND PRECAUTIONS (con’t)

• Liver Disease – Discontinue TWIRLA if jaundice develops.
• Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment – Discontinue TWIRLA prior to starting therapy with the hepatitis C combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. TWIRLA can be restarted approximately 2 weeks following completion of treatment with that combination drug regimen.
• Hypertension – Monitor blood pressure at routine visits and stop TWIRLA if blood pressure rises significantly. An increase in blood pressure has been reported in women using CHCs, and this increase is more likely in older women with extended duration of use.
• Gallbladder Disease – Studies suggest CHCs increase the risk of developing gallbladder disease and may also worsen existing gallbladder disease.
• Adverse Carbohydrate and Lipid Metabolic Effects –
  • TWIRLA may decrease glucose tolerance. Carefully monitor prediabetic and diabetic women who are using TWIRLA.
  • Consider alternative contraception for women with uncontrolled dyslipidemia. TWIRLA may cause adverse lipid changes. Women with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using TWIRLA, which may increase the risk of pancreatitis.
• Headache – If a woman using TWIRLA develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue TWIRLA as indicated. Consider discontinuation of TWIRLA if there is any increased frequency or severity of migraines during CHC use (which may be prodromal of a cerebrovascular event).
• Bleeding Irregularities and Amenorrhea – Women using TWIRLA may experience unscheduled bleeding, especially during the first 3 months of use, or experience absence of scheduled bleeding. If bleeding persists or occurs after previously regular cycles on TWIRLA, or if scheduled bleeding does not occur, evaluate for causes such as pregnancy or, in the case of unscheduled bleeding, malignancy.
• Other Warnings and Precautions – Other warnings and precautions include depression, cervical cancer, increased serum concentrations of binding globulins, hereditary angioedema, and chloasma.

ADVERSE REACTIONS

The following serious adverse reactions occurred in <1% of women who received TWIRLA: cholelithiasis, cholecystitis, major depression, suicidal ideation, appendicitis, ectopic pregnancy, pneumonia, and gastroenteritis. A total of 4 VTEs in TWIRLA-treated patients were identified in the phase 3 clinical trial. The most common adverse reactions (≥2%) in clinical trials for TWIRLA are application site disorders, nausea, headache, dysmenorrhea, and increased weight.

Patients should be counseled that TWIRLA does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).

DRUG INTERACTIONS

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

This is not a comprehensive list of safety information related to TWIRLA.

Please see full Prescribing Information, including BOXED WARNING.

To report SUSPECTED ADVERSE REACTIONS, call 1-855-888-2467 or report via the FDA MedWatch Program at www.fda.gov/medwatch or 1-800-FDA-1088.

TWIRLA® (levonorgestrel and ethinyl estradiol) transdermal system

BRIEF SUMMARY (For full Prescribing Information, see package insert)

Women should be informed that this product does not protect against HIV infection (the virus that causes AIDS) or other sexually transmitted diseases.

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS and CONTRAINDED IN WOMEN WITH A BMI ≥30 kg/m²

See full prescribing information for complete boxed warning

• TWIRLA is contraindicated in women over 35 years old who smoke. Cigarette smoking increases the risk of serious cardiovascular events from combined hormonal contraceptive (HC) use.
• TWIRLA is contraindicated in women with a BMI ≥30 kg/m². Compared to women with a lower BMI, women with a BMI ≥30 kg/m² had reduced effectiveness and may have a higher risk for venous thromboembolic events.

INDICATION AND USAGE

TWIRLA is a combination of levonorgestrel, a progestin, and ethinyl estradiol, an estrogen, indicated as a method of contraception for use in women of reproductive potential with a BMI <30 kg/m² for whom a combined hormonal contraceptive is appropriate.

Limitations of Use

Consider TWIRLAs reduced effectiveness in women with a BMI ≥25 to <30 kg/m² before prescribing.

CONTRAINdications

TWIRLA should not be used in women with any of the following conditions:

• At high risk for arterial or venous thromboembolic events.
• Headaches with focal neurological symptoms, migraine headaches with aura.
• Women over 35 years of age with any migraine headache [see Warnings and Precautions]
• BMI ≥30 kg/m².
• Liver tumors (benign or malignant), acute viral hepatitis, or severe (decompensated) cirrhosis, or liver disease.
• Undiagnosed abnormal uterine bleeding.
• Pregnancy, given there is no reason to use CHCs during pregnancy.
• Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past.
• Hypersensitivity to any components of TWIRLA.

Observe reactions include itching and irritation at the TDS application site.

Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for alanine aminotransferase (ALT) elevations >20 times the ULN, were significantly more frequent in women using ritonavir, with or without dasabuvir, than women not using ritonavir, with or without dasabuvir.

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders and Other Vascular Conditions

Stop TWIRLA if an arterial or venous thromboembolic event occurs.

Stop TWIRLA if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

Discontinue TWIRLA during prolonged immobilization and resume treatment based on clinical judgment. If feasible, stop TWIRLA at least 4 weeks before and 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start TWIRLA no earlier than four weeks after delivery in women who are not breast-feeding.

The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the likelihood of ovulation increases after the third postpartum week.

Before starting TWIRLA, evaluate any past medical history or family history of thromboembolism or thromboembolic disorders. Consider whether the history suggests an inherited or acquired hypercoagulopathy.

Liver Disease

Elevated Liver Enzymes

Discontinue TWIRLA if jaundice develops. Acute liver test abnormalities may necessitate the discontinuation of CHC use until the liver tests return to normal and CHC causation has been excluded.

Liver Tumors

CHCs increase the risk of hepatic adenomas. Rupture of hepatic adenomas may cause death from abdominal hemorrage. Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>6 years) CHC users.

Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

In clinical trials with Hepatitis C combination drug regimens containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations >5 times the upper limit of normal (ULN), including some cases >20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as CHCs. Discontinue TWIRLA prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. TWIRLA can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

Hypertension

For all women, including those with well-controlled hypertension, monitor blood pressure at routine visits and stop TWIRLA if blood pressure rises significantly. An increase in blood pressure has been reported in women using CHCs, and this increase is more likely in older women with extended duration of use.

Age-Related Considerations

The risk for cardiovascular disease and prevalence of risk factors for cardiovascular disease increases with age. Consider the presence of underlying risk factors that may increase the risk of cardiovascular disease or VTE, particularly before initiating a CHC for women over 35 years, such as: hypertension, diabetes, dyslipidemia, obesity.

Gallbladder Disease

Studies suggest an increased risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease. A past history of CHC-related cholecystitis predicts an increased risk with subsequent CHC use. Women with a history of pregnancy-related cholecystitis may be at an increased risk for CHC-related cholecystitis.

Adverse Carbohydrate and Lipid Metabolic Effects

Dyslipidemia

Careful monitoring of lipid abnormalities should be done in the event TDS change is missed.

Hyperglycemia

TWIRLA may decrease glucose tolerance. Carefully monitor prediabetic and diabetic women who are using TWIRLA.

Hypercoagulopathy

Consider alternative contraception for women with uncontrolled dyslipidemia. TWIRLA may cause adverse lipid changes. Women with hyperglycemia or, a family history thereof, may have an increase in serum triglyceride concentrations when using TWIRLA, which may increase the risk of pancreatitis.

Headache

If a woman using TWIRLA develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue TWIRLA if indicated. Consider discontinuation of TWIRLA if there is any increase in frequency or severity of migraines during use (which may be prodrug of a cerebrovascular event).

Bleeding Irregularities and Amenorrhea

Unscheduled and Scheduled Bleeding and Spotting

Women using TWIRLA may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first three months of use. Bleeding irregularities may resolve over time or by changing to a different contraceptive product. If bleeding persists or occurs after previously regular cycles on TWIRLA, evaluate for causes such as pregnancy or malignancy.

Amenorrhea and Oligomenorrhea

Women who use TWIRLA may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant. If scheduled bleeding does not occur, consider the possibility of pregnancy. If the woman has not adhered to the prescribed dosing schedule, consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures. If the woman has adhered to the prescribed dosing schedule and misses two consecutive periods, rule out pregnancy.

Alternate continuation of TWIRLA, amenorrhea or oligomenorrhea may occur, especially if these conditions were pre-existent.

Depression

Carefully observe women with a history of depression and discontinue TWIRLA if depression recurs to a serious degree. Data on the association of CHCs with onset of depression or exacerbation of existing depression are limited.

Cervical Cancer

Some studies suggest that CHCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. There is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

Effect on Binding Globulins

The estrogen component of TWIRLA may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin.

Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

Chloasma

Chloasma may occur with TWIRLA use, especially in women with a history of chloasma gravidarum. Advise women with a history of chloasma to avoid exposure to the sun or ultraviolet radiation while using TWIRLA.

ADVERSE REACTIONS

CLINICAL TRIAL EXPERIENCE

The safety of TWIRLA was evaluated in a 12-month, multicenter, open-label, single-arm clinical trial conducted in the United States. Women applied TWIRLA (120 mcg LNG/30 mcg EE) for 13 28-day treatment cycles. One treatment cycle is defined as three consecutive weeks that one TDS is applied followed by one week that TWIRLA is not applied. The most common adverse reactions that occurred in ≥2% of the 2,031 women that used TWIRLA TDS is applied for seven-day wear followed by one week that TWIRLA is not applied. TWIRLA TDS is applied for seven-day wear followed by one week that one TDS is applied.

A total of four VTEs (including pulmonary embolism and deep vein thrombosis) in TWIRLA-treated women were identified in the clinical trial. Of these, all were in women with a BMI ≥30 kg/m².

Other Serious Adverse Reactions

The following serious adverse reactions occurred in <1% of women who received TWIRLA: cholelithiasis, cholecystitis, major depression, suicidal ideation, appendicitis, ectopic pregnancy, pneumonia, and gastroenteritis.
DRUG INTERACTIONS
Effects of Other Drugs on Combined Hormonal Contraceptives
CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase systemic exposure of the estrogen and/or progestin component of CHCs. Concomitant use of CHCs with metabolic enzyme inducers may decrease the plasma concentrations of the estrogen and/or progestin component of CHCs, potentially diminishing effectiveness. Counsel women to use a backup or alternative method of contraception when enzyme inducers are used with TWIRLA.

Significant increases and/or decreases in systemic exposure of the estrogen and/or progestin have been noted when CHCs are co-administered with some HIV protease inhibitors, HDV protease inhibitors, and some non-nucleoside reverse transcriptase inhibitors.

Effects of Combined Hormonal Contraceptives on Other Drugs
Concomitant use of CHCs with lamotrigine, acetaminophen, morphine, salicylic acid, and temazepam may decrease systemic exposure of these drugs. Concomitant use of CHCs with thyroid hormone replacement therapy or corticosteroid replacement therapy may increase systemic exposure of thyroid-binding and cortisol-binding globulin. Concomitant of other drugs (e.g., cyclosporine, prednisolone, theophylline, tiotidine, and voriconazole), may increase systemic exposure of these drugs.

USE IN SPECIFIC POPULATIONS
Pregnancy
Discontinue TWIRLA if pregnancy occurs. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects following exposure to CHCs before conception or during early pregnancy.

Lactation
Contraceptive hormones and/or metabolites are present in human milk. CHCs can reduce milk production in breastfeeding women. This reduction can occur at any time but is less likely to occur once breastfeeding is well established. Advise the nursing woman to use another method of contraception until she discontinues breastfeeding. No studies have been conducted on the use of TWIRLA in breastfeeding women.

OVERDOSAGE
There have been no reports of serious adverse outcomes from overdose of CHCs, including ingestion by children. Overdose may cause uterine bleeding in women and nausea. In case of suspected overdose, the TWIRLA TDS should be removed and symptomatic treatment given.

PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Patient Information and Instructions for Use).

• Advise the woman that cigarette smoking increases the risk of serious cardiovascular events from CHC use. Women who are over 35 years old and smoke should not use TWIRLA.
• Advise the woman that an increased risk of VTE compared to non-users of CHCs is greatest after initially starting a CHC or restarting (following a 4-week or greater interruption in intake) the same or a different CHC.
• TWIRLA is not to be used during pregnancy. Instruct the woman to stop TWIRLA if pregnancy is confirmed during treatment.
• Advise the woman that TWIRLA does not protect against HIV infection and other sexually transmitted infections.
• Apply one TDS weekly for 3 weeks followed by one TDS free week. Instruct women what to do in the event TDS change is missed.
• Postpartum women who have not yet had a period when they start TWIRLA need to use an additional method of contraception until they have used the TDS for one week.
• A back-up or alternative method of contraception is needed when enzyme inducers are used with TWIRLA.
• TWIRLA may reduce breast milk production. This is less likely to occur if breast-feeding is well established. When possible, nursing women should use other methods of contraception until they have discontinued breast-feeding.
• Amenorrhea may occur. Advise the woman to contact a health care provider in the event of amenorrhea in two or more consecutive cycles or in case of symptoms of pregnancy such as morning sickness or unusual breast tenderness.
• Resumption of fertility after discontinuing TWIRLA is expected.
• Advise women to avoid frequent or prolonged water exposure and to avoid use of large amounts of body lotions or oils. Advise women to check the TDS for partial or complete TDS detachment daily and after frequent or prolonged water exposure.

Manufactured by:
Corium International, Inc.
4558 50th Street, SE.
Grand Rapids, MI 49512

Manufactured for:
Agile Therapeutics, Inc.
101 Poor Farm Rd.
Princeton, NJ 08540
Was this a failure to diagnose ovarian failure?

The outcome in this case underscores the need for solid documentation, especially when one of the defendants has passed.

**Factual Summary**

On March 24, 2014, a 26-year-old female patient began treatment with the defendants’ practice, when she was examined and evaluated by Defendant A. The patient completed a questionnaire, in which she documented the reason for the appointment as “irregular period/other symptoms having to do with that.” She did not specify any other symptoms. The patient reported her last menstrual period (LMP) as occurring on Nov. 29 to Dec. 8, 2013, and again on Feb. 3, 2014. She had no past obstetrical history. Her gynecologic history was negative for sexually transmitted diseases (STD) and pelvic inflammatory disease. Her medical history was pertinent for anxiety, but she was no longer on fluoxetine. Her mother had ovarian cancer but both parents were alive and well. The patient smoked ½ packs of cigarettes per day. She had no known drug allergies. Defendant A referred her for lab work including a complete metabolic panel, complete blood count (CBC), and hormone levels. Bloodwork was performed on April 10, 2014 and reported to Defendant A on April 16. The triiodothyronine (T3) uptake was high at 36. The luteinizing hormone (LH) was 1.8 with follicle-stimulating hormone (FSH) at 8.0. The prolactin was 12, dehydroepiandrosterone 235, and testosterone 17. The lab report contains the following reference ranges: follicular phase (2.5-10.2 mIU/mL); mid-cycle peak (3.1-17.7 mIU/mL); luteal phase (1.5-9.1 mIU/mL); and postmenopausal (23-116.3 mIU/mL). Prolactin levels were reported as 12.0 ng/mL, with reference ranges as follows: Follicular phase (.0-1.1 ng/mL), mid-follicular (0.0 – 1.0 ng/mL), mid-cycle (.5-1.7 ng/mL), luteal phase (1.0-21 ng/mL), mid-luteal (6.0-24 ng/mL), post-menopausal (0.0-1.0 ng/mL), oral contraceptives (.3-9 ng/mL).

On Sept. 6, the patient presented to her primary care physician (PCP) with complaints of a pelvic infection that had been diagnosed by a walk-in clinic the day earlier. Her PCP advised her to follow up with her gynecologist and follow the antibiotics recommendations of the walk-in clinic. There was no discussion of amenorrhea documented in the records at this visit.

Approximately six weeks later, on Oct. 27, the patient returned to the defendants’ practice, and was evaluated by Defendant A. The exam and findings were generally negative. Cultures were taken for gonorrhea and chlamydia, as well as urine culture and sensitivity tests. Defendant A diagnosed a yeast infection and prescribed fluconazole. The cultures for gonorrhea, chlamydia and a urine
On Dec. 15, the patient presented to her PCP with complaints of missed periods, requesting a pregnancy test. Her PCP did a pregnancy test, which was negative. He recommended follow up with her ob/gyn. On Feb. 3, 2015, she again returned to her PCP with complaints of not feeling well, including headache and anxiety. She was evaluated and the working plan included follow up with her ob/gyn, diet, exercise, water intake, and to go to the ER if her symptoms persisted.

On May 11, she presented again to her PCP’s office for “routine gynecological treatment.” She reported she was “feeling well and with no complaints.” Her last menstrual period was documented as April 27. The plan was for blood work including CBC, a metabolic panel, STD screenings, thyroid levels, and to return to the office for routine care as needed.

On May 18, nearly six months after her PCP first advised her to return to her ob/gyn for follow-up care, the patient returned to Defendant A’s office, this time for a possible yeast infection with itchy discharge. Fluconazole 150 mg by mouth once a day was prescribed. On June 1, the patient returned with concerns of a possible lost tampon. Defendant A performed an internal exam, found no lost tampon, and prescribed metronidazole 0.75 vaginally at bedtime for five days for bacterial vaginosis.

On Aug. 21, the patient returned to her ob/gyn’s office. Her last menstrual period had been 3 months earlier. The plan was to repeat labs in

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was to check labs and birth control pills were prescribed. On Dec. 14, she went for blood work, which came back abnormal. The FSH was in the menopausal range at 25.1 IU/L.

On Dec. 21, the patient called the defendants’ clinic, stating that she had a repeat bacterial infection. A prescription for metronidazole was called to her pharmacy. This was the last contact that the plaintiff had with the defendants’ office.

On Feb. 1, 2016, the patient presented for the first time to the offices of non-party ob/gyn. She reported her last menstrual period started on Jan. 18, 2016. She reported frequent bacterial infections and amenorrhea. She was diagnosed with bacterial vaginosis, and prescribed clindamycin. No further work up was performed at this time, despite the report of amenorrhea during this visit.

Six months later, on Aug. 11, she returned to non-party ob/gyn's office for further evaluation and treatment of a yeast infection. At this visit, she was sent for further blood work. FSH was reported as 70.9 mIU/mL. The lab report contained the following reference ranges: follicular phase (3.5-12.5 mIU/mL); mid-cycle peak (4.7 – 21.5 mIU/mL); luteal phase (1.7-7.7 mIU/mL); and postmenopausal (25.8-134.8 mIU/mL).

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**Allegations**

The plaintiff alleged that from March 2014 through December 2015, the defendants failed to timeline and properly consider lab and sonogram results, failed to order further studies, failed to refer the plaintiff to a fertility specialist, and failed to consider her complaints and concerns. As a result, she claimed she was put into early ovarian failure and rendered infertile.
Discovery

The plaintiff testified that prior to her treatment with Defendant B she had some “weird body issues” including body aches, joint pains as well as headaches, fatigue, and anxiety. The symptoms began to snowball into one another; and she reported that hot flashes and dizziness started around July of 2016. She reported that from about 2010 to 2013 her periods were regular on a 28-31 day cycle lasting 4-6 days, and she would have some typical symptoms of PMS such as cramping, but no other complaints of abnormal periods. In 2014, she started noticing abnormal periods. This is when she started treatment with the defendants. She defined abnormal as “not as frequent and not on a schedule.” She also started suffering from frequent bacterial infections. She also testified that during one visit Defendant A stated that she should “consider yourself lucky. No girl wants her period. Come back and see me when you want kids.” She recalled a discussion over being put on birth control, but she did not want to go on it because of past experiences. She was told by subsequent physicians that she had the FSH level of a “menopausal woman.” She also testified that had she known earlier she could have used fertility preserving treatment such as freezing her eggs. The fertility specialist advised her that it was too late for egg retrieval; however, she was a good candidate for in vitro fertilization. Unfortunately, Defendant A passed away before he could testify in response to the patient’s assertion that he downplayed her complaints and test results to her detriment. Absent an opportunity to produce a witness to rebut those assertions, and given the reasonable opportunity to produce a witness to rebut those assertions, and given the reasonable evidence that the patient did continue to have periods. For example, when a sonogram was done on April 14, the LMP was listed as April 5, 2014, and there was a June 1, 2015, visit for a possible lost tampon. Additionally, after the patient left the defendants’ care in December 2015, there was an LMP listed of Jan. 18, 2016, at her subsequent doctor’s office. Once the initial labs came back within normal limits and once the sonogram on April 14 showed normal ovaries with a left-side ovary that was ovulating, there was no reason to suspect the patient was going into ovarian failure. He felt the patient should have been advised of her elevated FSH in August 2015, but that at that point the die was cast and it would not have altered outcome.

Result

After all depositions were concluded we moved for summary judgment dismissal of the case. While the motion was pending, but prior to opposing, the patient’s attorney contacted our office seeking a reasonable settlement as to the estate of Defendant A. Ultimately the case settled for $25,000.

Analysis

Putting aside the opportunity to resolve this case for less than the cost of trying it, the matter settled primarily for two reasons. The first reason was the absence of any documentation by the defendants of awareness or follow-up with the patient for the elevated FSH in November 2015. Whether or not the die was cast, as it were, documenting acknowledgment of the abnormal results and discussion with the patient still was required. This became even more necessary here, where Defendant A passed before he could testify in response to the patient’s assertion that he downplayed her complaints and test results to her detriment. Absent an opportunity to produce a witness to rebut those assertions, and given the reasonable demand, the decision was made to resolve the matter rather than risk a sympathetic verdict, despite the defensibility of the care.

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