CONTRACEPTION

Immediate Postpartum LARC

Examining what’s available and barriers to utilization

Tania Basu Serna, MD, MPH, and Chloe Bass, MD

ContemporaryOBGYN.net
The only one for almost everyone

Only Paragard® (intrauterine copper contraceptive) IUS, with 1 hormone-free active ingredient (copper), delivers the strongest combination of benefits for the widest range of women2-4.

The Paragard Promise:
• Proven >99% efficacy
• 100% hormone free
• Pregnancy prevention for up to 10 years
• Immediately reversible whenever she decides

Satisfy more patients with Paragard—the only highly effective, reversible birth control that is completely hormone free. Learn more at hcp.paragard.com or call 1-877-PARAGARD.

Indication
Paragard is a copper-containing IUS (intrauterine system) indicated for the prevention of pregnancy for up to 10 years.

Important Safety Information
• Paragard must not be used by women who had a post-pregnancy or post-abortion uterine infection in the past 3 months; have cancer of the uterus or cervix; acute pelvic inflammatory disease (PID); an infection of the cervix; an allergy to any component (including copper); or Wilson's disease.
• If a woman misses her period, she must be promptly evaluated for ectopic pregnancy.
• Possible serious complications that have been associated with IUSs are PID, embedment, perforation of the uterus, and expulsion.
• Paragard must not be used by pregnant women as this can be life-threatening and may result in loss of pregnancy or infertility.
• Menstrual cycles may become heavier and longer with intermenstrual spotting. Bleeding may be heavier than usual at first.
• Paragard does not protect against HIV or STIs.

See next page for Brief Summary of Full Prescribing Information.


*According to the Centers for Disease Control and Prevention (CDC), Paragard is one of the least restrictive birth control options across all patient types compared to other IUSs.
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text continues...

- Pregnancy prevention for up to 10 years
- 100% hormone free
- Proven >99% efficacy
- Paragard must not be used by pregnant women as this can be life threatening and Paragard is a copper-containing IUS (intrauterine system) indicated for the prevention of pregnancy for up to 10 years.

- Hypersensitivity to any component of Paragard including copper or any of the trace elements present in the copper component of Paragard

- Pelvic Inflammatory Disease and Endometritis
- Pregnancy prevention with Paragard is essential in order to minimize serious infection such as tubal damage, and premature delivery. Prenatal care should include counseling about these risks and that she should report immediately any flu-like symptoms, fever, chills, cramping, pain, bleeding, discharge or leakage of fluid, or any other symptom that suggests complications of the pregnancy.

- Sepsis

- Pelvic Inflammatory Disease and Endometritis

- Insertion of Paragard is contraindicated for use in pregnant females because there is no need for pregnancy prevention in a female who is already pregnant and Paragard may cause adverse pregnancy outcomes. If a female becomes pregnant with Paragard in place, there is an increased risk of miscarriage, sepsis, premature labor, and premature delivery. Advise the female of the potential risks if pregnancy occurs with Paragard.

- Lactation

- Pediatric Use

- Geriatric Use

- Paragard has not been studied in women over 65 years of age and is not indicated in this age group.

- Breeding Pattern Alterations

- Drug Interactions

- Pregnancy

- Risk Summary
CHAIRMAN’S LETTER

Welcoming 2020

In the United States, most pregnancies in the first year postpartum are unintended, highlighting the need for improved communication about immediate postpartum contraception. One of the most effective methods to reduce short interval pregnancy is long-acting reversible contraception (LARC), one of our focuses this month.

In the January cover article, Drs. Tania Basu Serna and Chloé Bass discuss why ob/gyns should counsel their patients about postpartum LARC. They examine the pros and cons of five LARC methods available in the United States and also delve into techniques for device placement.

We’re also tackling the issue of whether ob/gyns should provide MIS hysterectomy. In a debate-style article, Dr. R. Wendel Naumann writes about why moving away from the procedure is an overreaction, while Dr. Amanda Nickles Fader explains why safety concerns stemming from the LACC trial results should dissuade ob/gyns from using the procedure. If you’d like to weigh in on the issue, be sure to contact us at COGEditorial@mmhgroup.com or bschwartz@mmhgroup.com.

Finally, we are reminded that goodbyes are never easy. In this month’s editorial, our Editor-in-Chief for the past 20 years, Dr. Charles Lockwood, announces that he has stepped down. Looking back on his time with the magazine, Dr. Lockwood reflects on his relationships with contributors to the magazine, reminisces about some of his favorite editorials, and thanks the readers, who were his inspiration. If you have any parting words for Dr. Lockwood you’d like to share, please send them to COGEditorial@mmhgroup.com.

We are looking forward to a busy 2020 and are excited to see what’s in store for Contemporary OB/GYN.

Mike Hennessy, Sr.
Chairman and Founder, MJH Life Sciences
A Fond Farewell

In late 1999, I was asked by Contemporary OB/GYN’s founding Editor-in-Chief, Dr. John Queenan, to join its Editorial Board. It was an unexpected honor and just a bit intimidating given that the Board was a veritable “who’s who” of ob/gyn greats. I quickly realized that the twin pillars of the magazine’s success were John’s inspirational leadership and the quality, sagacity, and editorial independence of that board. For 25 years, Dr. Queenan had been a master at picking the COG board members who, in turn, identified key topics, emerging trends and outstanding authors. John led their deliberations, added his own prescient ideas and, of course, crafted truly memorable editorials.

The next year, I was stunned when John asked me to become COG’s second Editor-in-Chief. I have enjoyed my time in this post immensely. Fortunately, I strictly followed John’s “recipe” by assembling a great board, a number of whom have been with me since the start, including Drs. Joe Leigh Simpson, Paula Adams Hillard, and Sharon Phelan. I was blessed to be able to add other leaders in the field including my old friends Joshua Copel from Yale, one of the true greats in obstetrical ultrasound, and Sarah Kilpatrick, Chair of Obstetrics and Gynecology at Cedars-Sinai in Los Angeles and an expert in medical complications of pregnancy. Newer friends included Drs. John Delancey, a pioneer and leader in urogynecology; Ilana Cass, a brilliant gynecologic oncologist and now Chair of the Department of Obstetrics & Gynecology at Dartmouth; Chris Pettker, a leader in the patient safety movement from Yale; and Steve Ory, a master clinician and reproductive endocrinologist from Florida International University in Miami. I was also lucky enough to recruit Dr. Jon Einarsson, an international authority in minimally invasive gynecological surgery from Harvard, as Deputy Editor. What great success the magazine has enjoyed over the past two decades is largely due to these wonderful folks as well as their predecessors, including giants like Drs. Leon Speroff and Ed Wallach.

Perhaps the most daunting task over the past two decades has been coming up with ideas for editorial. Some concepts were obvious, like telling the story of 9/11 from the perspective of my patients at NYU and Bellevue Hospital. Others were inspired by the recurrent professional liability crisis, onerous new government regulations, political threats to women’s reproductive health, rapidly changing healthcare financing, physician burnout, and the challenges of residency training. However, most reflected bread and butter clinical topics including the safety of vaginal breech deliveries and trials of labor after prior cesareans, the causes of maternal mortality and preterm birth, the appropriate use of antenatal corticosteroids, misoprostol and low molecular weight heparin, and screening for thrombophilias, genetic disorders, Group B streptococcus and gestational diabetes. Gyn topics included postmenopausal hormone therapy, new contraceptives, screening for cervical cancer, and the need to encourage human papillomavirus vaccination. While I have not shied away from controversial topics, I have also tried to tell stories from the perspective of busy clinicians.

And I have been honored to receive a number of national publishing awards for these editorials, including three prestigious Jesse H. Neal Awards from the American Society of Business Publications Editors, as well as two Gold Awards for Editorials and an Award in the Editorial/Editor’s Letter category from the American Society of Healthcare Publication Editors. My approach to writing has been simple: find a topic I was interested in or passionate about, critically review all relevant literature, and then sit down and write. I do hope my editorials have helped shape ob/gyn practice in positive ways. I have certainly enjoyed hearing from readers, who have not been shy about providing feedback in person, by phone, by e-mails, through formal letters to the editor, and more recently, via social media.

It is hard to imagine it’s been 20 years. I have truly enjoyed every minute. But this seems like a propitious time to pass the Editor-in-Chief “baton” to someone from the next generation of ob/gyn leaders who can provide a different perspective and their own passion. Over the next few months, the magazine will select a new leader and I am sure they can...
OVER A YEAR OF PATIENT EXPERIENCE

ORILISSA® (elagolix) is indicated for the management of moderate to severe pain associated with endometriosis.

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 ORLISSA FOR MORE THAN 30,000 patients

ORLISSA 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 ORLISSA, 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 ORLISSA

These data reflect the number of HCPs who have prescribed and the number of women prescribed since ORLISSA 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 ORLISSA.
- 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 ORLISSA, estrogen-containing contraceptives are expected to reduce the efficacy of ORLISSA. The effect of progestin-only contraceptives on the efficacy of ORLISSA is unknown.
- Advise women to use non-hormonal contraceptives during treatment and for one week after discontinuing ORLISSA.

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 ORLISSA. Safety and effectiveness of ORLISSA in patients less than 18 years of age have not been established.

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


Please see Brief Summary of full Prescribing Information on the following page of this advertisement.
Reduction in Menstrual Bleeding

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

Suicidal ideation, suicidal behavior and exacerbation of mood disorders have been reported with use of ORILISSA. ORILISSA is contraindicated in women with known depression, bipolar disorder, or a history of suicide attempts or suicide.

Changes in Lipid Profiles

Lipid increases occurred within 1 to 2 months after the start of ORILISSA treatment. ORILISSA may increase total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (apo B). Limit concomitant use of drugs that are substrates of P-gp (e.g., rosuvastatin).

Evaluation of Bone and Other Tissues

In clinical trials, ORILISSA treatment resulted in reductions in BMD at the lumbar spine, hip, and other peripheral sites compared to placebo. The effect of ORILISSA on BMD was assessed by dual-energy X-ray absorptiometry (DEXA) and the percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 2% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily. In Study EM-2, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was 1.7% (95% CI -1.8, -0.8) with ORILISSA 150 mg once daily and -3.0% (95% CI -3.5, -2.6) with ORILISSA 200 mg twice daily (Table 3). The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was <1% with ORILISSA 150 mg once daily, 6% with ORILISSA 200 mg twice daily and 0% with placebo. In the blinded extension study EM-4, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 2% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline to Month 6</th>
<th>N</th>
<th>Treatment Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORILISSA 150 mg</td>
<td>0.4 (-1.0, 1.8)</td>
<td>184</td>
<td>0.6 (-0.3, 1.5)</td>
</tr>
<tr>
<td>ORILISSA 200 mg</td>
<td>-2.6 (-3.8, -1.3)</td>
<td>183</td>
<td>0.6 (-0.3, 1.5)</td>
</tr>
<tr>
<td>Placebo</td>
<td>-1.9 (-3.2, -0.6)</td>
<td>182</td>
<td></td>
</tr>
</tbody>
</table>

Note: For ORILISSA 150 mg and ORILISSA 200 mg, N=476 in total. In Study EM-1, n=67 in 150 mg once daily group and n=63 in 200 mg twice daily group due to follow-up DEXA data unavailable. In Study EM-2, n=66 in 150 mg once daily group and n=62 in 200 mg twice daily group due to follow-up DEXA data unavailable. In Study EM-4, n=184 in ORILISSA 150 mg once daily group and n=183 in ORILISSA 200 mg twice daily group due to follow-up DEXA data unavailable. Placebo data are from Study EM-2 (placebo n=182).
Suicidal ideation, Suicidal Behavior and/or Completion of Suicide

In the placebo-controlled clinical trials (Studies EM-1 and EM-2), suicidal ideation, suicide attempts, or depression were not noted.

Among the 2092 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 EM-3 (150 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 continued the clinical trial treatment.

Hematologic Transaminase Elevations

In the placebo-controlled clinical trials (Studies EM-1 and EM-2), serum transaminase elevations were noted during ORILISSA treatment in EM-1 and EM-2. In EM-1, 12% of subjects with mildly elevated LFTs (L-UC ≥ 1.5, <3 x upper limit) at baseline had an increase in LFTs of ≥ 3 times the upper limit of the reference range. Most increases involved alanine aminotransferase (ALT) and were noted within 4-7 months after initiation of ORILISSA and placebo, respectively. The highest measured serum transaminase concentration during treatment was < 3 times the upper limit of the reference range.

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

<table>
<thead>
<tr>
<th>Lipid Class</th>
<th>Treatment</th>
<th>Mean Change from Baseline (mg/dL)</th>
<th>Maximum Increase from Baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>ORILISSA 150 mg Once Daily</td>
<td>-6%</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>ORILISSA 200 mg Twice Daily</td>
<td>-7%</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>-6%</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>Range of Subjects:</td>
<td>5-12 months</td>
<td>51-122</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Maximum Increase from Baseline</td>
<td>3%</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Range of Subjects:</td>
<td>2-4 months</td>
<td>41-45</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Maximum Increase from Baseline</td>
<td>1%</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Range of Subjects:</td>
<td>1-3 months</td>
<td>41-45</td>
</tr>
</tbody>
</table>

Lipid changes occurred within 1 to 2 months after the start of ORILISSA and remained stable thereafter over 12 months.

Hyperprolactinemia Reactions

In Studies EM-1 and EM-2, no hyperprolactinemia reactions including rash occurred in 9.8% of ORILISSA-treated subjects and 6.1% of placebo-treated subjects. Two events leading to drug discontinuation in 0.4% of ORILISSA-treated subjects and 0.3% of placebo-treated subjects.

Endometrial Effects

Endometrial biopsies were performed in subjects in Study EM-1 and its extension at Month 6 and Month 12. These biopsies showed a dose-dependent decrease in proliferative and secretory biopsy patterns and an increase in quiescent/premalignant stimulated biopsy patterns. There were no abnormal biopsy findings on treatment, such as endometrial hyperplasia or cancer.

Effect on menstrual bleeding patterns

The effects of ORILISSA on menstrual bleeding were evaluated for up to 12 cycles in the endometriosis clinical trials during which subjects classified their flow of menstrual bleeding (if present) in the last 24 hours as spotting, light, normal, heavy, or very heavy. There was a dose-related reduction in mean number of bleeding and spotting days and bleeding intensity in those subjects without postmenopausal bleeding.

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

<table>
<thead>
<tr>
<th>Bleeding/Spotting Days or Mean Intensity Scores</th>
<th>ORILISSA 150 mg Once Daily</th>
<th>ORILISSA 200 mg Twice Daily</th>
<th>Placebo</th>
<th>Baseline Range of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration of Bleeding/Spotting Days (in days)</td>
<td>5.3</td>
<td>5.8</td>
<td>6.4</td>
<td>3-12</td>
</tr>
<tr>
<td>Mean Intensity</td>
<td>2.6</td>
<td>2.2</td>
<td>2.6</td>
<td>2-3</td>
</tr>
</tbody>
</table>

Intensity for subjects who reported at least 1 day of bleeding or spotting during the 7 days was summarized as ranges from 1-4, 1-3, 2-3, 2-4, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, >12 days.

ORILISSA also demonstrated a dose-dependent increase in the percentage of women with any degree of bleeding or spotting in a 36-day interval over the treatment period. The incidence of amenorrhea during the first six months of treatment was 47% for ORILISSA 150 mg once daily, 12.6-52% for ORILISSA 200 mg twice daily and less than 1% for placebo. During the second six months of the trial, the incidence of amenorrhea ranged from 11-15% for ORILISSA 150 mg once daily and 46-57% for ORILISSA 200 mg twice daily.

By 6 months of therapy with ORILISSA 150 mg once daily, resumption of menses after stopping treatment was reported by 59%, 87% and 95% of women within 1-2, 2-4, and 4-6 months, respectively. By 6 months of therapy with ORILISSA 200 mg twice daily, resumption of menses after stopping treatment was reported by 60%, 89%, and 96% of women within 1, 2, and 6 months, respectively.

After 12 months of therapy with ORILISSA 150 mg once daily resumption of menses after stopping treatment was reported by 77%, 95% and 98% of women within 1, 2, and 6 months, respectively. After 12 months of therapy with ORILISSA 200 mg twice daily resumption of menses after stopping treatment was reported by 50%, 91% and 96% of women within 1, 2, and 6 months, respectively.

DRUG INTERACTIONS

Potential for ORILISSA to Affect Other Drugs

Elagolix is a weak to moderate inducer of cytochrome P450 (CYP) 3A. Co-administration with ORILISSA may decrease plasma concentrations of drugs that are substrates of CYP3A (e.g., azapropazone). Elagolix is an inhibitor of transfer proteins (P-gp). Co-administration with ORILISSA may increase plasma concentrations of drugs that are substrates of P-gp (e.g., trimethoprim).

Potential for Other Drugs to Affect ORILISSA

Elagolix is a substrate of OATP1B1 and OATP1B3. Concomitant use of ORILISSA 200 mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and strong CYP3A inhibitors to 6 months. Co-administration of ORILISSA with drugs that induce CYP3A may decrease elagolix plasma concentrations.

The use of concomitant use of P-gp inhibitors or inducers on the pharmacokinetics of ORILISSA is not recommended. Co-administration of ORILISSA with drugs that inhibit OATP1B1 may increase elagolix plasma concentrations. Co-administration use of strong CYP3A inhibitors (e.g., cyclosporine and gefitinib) is contraindicated.

Drug Interactions - Examples and Clinical Management

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

Table 7. Established Drug Interactions Based on Drug Interaction Trials

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Effect on ORILISSA</th>
<th>Concomitant Effect on Established Drug</th>
<th>Clinical Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive</td>
<td>Amlodipine</td>
<td>No dose adjustment is needed for amlodipine</td>
<td>Maximal elagolix concentration achieved (Cmax) in patients co-administered with amlodipine</td>
<td>Consider elagolix concentration during treatment with Amlodipine</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Warfarin</td>
<td>No dose adjustment is needed for warfarin</td>
<td>Maximal elagolix concentration (Cmax) in patients co-administered with warfarin</td>
<td>Consider elagolix concentration during treatment with Warfarin</td>
</tr>
</tbody>
</table>

The direction of the arrow indicates the direction of the change in the area under the curve (AUC) (↑ increase, ↓ decrease).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Pregnancy Exposure Registry

There is no pregnancy monitoring of ORILISSA in pregnant women. ORILISSA is contraindicated in women who become pregnant while treated with ORILISSA. Patients should be encouraged to enroll in the pregnancy registry (1-800-732-7241).

**Risk Summary**

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

The limited human data from the use of ORILISSA in pregnant women is insufficient to determine whether there is a risk for major birth defects or miscarriage. Although two cases of congenital malformations were reported in clinical trials with ORILISSA, the percent identified and miscarriages were reported at a similar incidence across treatment groups (see Table 7).

When pregnant rats and rabbits were treated with elagolix during the period of organogenesis, postimplantation loss was observed in pregnant rat of doses 20 times the MRHD and in rabbits of doses 10 times the MRHD. There were no structural abnormalities in the fetuses in mice at up to 50 times the MRHD and no abnormalities were observed at doses up to 10 times the MRHD. There were no apparent decreases in birth weights associated with ORILISSA in these species.

There is a pregnancy registry that monitors outcomes in women who are treated with ORILISSA. Women who are pregnant or planning to become pregnant should be advised of the potential risk to the fetus.

**CONTRAINDICATIONS**

- Use of ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) (see Contraindications).

- Use of ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) (see Contraindications).

In case of overdose, the physician should not administer any specific antidote or administer a specific therapeutic treatment, except supportive care.

**NONCLINICAL TOXICOLOGY**

Carcinogenicity, Mutagenicity, Impairment of Fertility

In 2-year oncogenicity studies conducted in mice (90, 150, or 300 mg/kg/day) and rats (150, 500, or 1000 mg/kg/day) that administered ORILISSA at doses of 10 times the MRHD or greater than placebo, there were no increases in the incidence of tumors. The background incidence for major birth defects and miscarriage in clinically recognized pregnancies was 2-4% and 15-20% respectively.
male and female (and liver tumors in male and female) and liver (males only) tumors at the high dose (12 to 13-fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans. Elagolix was not genotoxic or mutagenic in a battery of tests, including the in vitro bacterial reverse mutation assay, the in vitro mammalian cell forward mutation assay at the thymidine kinase (TK+) locus in L5178Y mouse lymphoma cells, and the in vivo mouse micronucleus assay. In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/day in female rats is approximately 5-fold. However, because elagolix has low affinity for the GnRH receptor in the rat (see Use in Specific Populations), and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

**PATIENT COUNSELING INFORMATION**

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

- Advise patients on contraceptive options, not to get pregnant while using ORILISSA, to be mindful that menstrual changes could reflect pregnancy and to discontinue ORILISSA if pregnancy occurs (see Contraindications and Warnings and Precautions).
- There is a pregnancy registry that monitors outcomes in women who become pregnant while treated with ORILISSA. Inform patients they can enroll by calling 1-833-782-7241 (see Use in Specific Populations).
- Inform patients that estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA.
- Inform patients about the risk of bone loss. Advise adequate intake of calcium and vitamin D (see Warnings and Precautions).
- Advise patients to seek immediate medical attention if suicidal ideation and behavior, new onset or worsening depression, anxiety, or other mood changes occur (see Warnings and Precautions).
- Advise 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 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 follow FDA instructions for disposing of medication in the household trash, www.fda.gov/drugdisposal, and not to flush down the toilet.

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THE EDITORS ARE PLEASED TO ANNOUNCE the availability of our parent company’s continuing education activities. We’ve picked this one especially for our readers - http://bit.ly/BreastCancerCME

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Induction of labor and risk of stillbirth

by JUDITH M. ORVOS, ELS

A nationwide study by Swedish researchers suggests that inducing labor at no later than 41 weeks could be one of the few interventions that reduce stillbirths. While urging caution in interpretation of their results, the authors say the findings could be particularly important for management of nulliparas.

Findings from the study—which was stopped early because of a significantly higher rate of perinatal mortality in the expectant management group—were published in BMJ. SWEPIS (SWedish Post-term Induction Study) was a multicenter, open-label, randomized superiority trial conducted at 14 hospitals in Sweden from 2016 to 2018.

Methods
Of the 2760 women enrolled, all of whom had low-risk, uncomplicated pregnancies, 1381 were randomized to induction at 41 weeks and 1379 to expectant management with induction at 42 weeks. In many centers in the UK and Scandinavia, induction is common no later than 42 weeks. Recent studies have shown a significantly increased risk of perinatal mortality and morbidity at 41 weeks, and of stillbirth beginning at 39 weeks.

In the induction group, there were fewer admissions to a [NICU], lower incidence of neonatal jaundice...and fewer infants with macrosomia.

The primary outcome of SWEPIS was a composite of perinatal outcome including one or more of stillbirth, neonatal mortality, Apgar < 7 at 5 minutes, pH < 7.00 or metabolic acidosis in the umbilical artery, hypoxic ischemic encephalopathy, intracranial hemorrhage, convulsions, meconium aspiration syndrome, mechanical ventilation within 72 hours, or obstetric brachial injury. The secondary outcome was perinatal mortality. The primary analysis was intent to treat.

Findings
No perinatal deaths occurred in the group induced at 41 weeks but six occurred in the expectant management group (5 stillbirths, 1 early neonatal death; \( P = 0.03 \)). No differences were seen between the groups in the composite primary perinatal outcome (2.4% [33/1381] induction group; 2.2% [31/1379] expectant management; RR 1.06, 95% CI 0.6 to 1.73; \( P = 0.90 \)). The proportion of cesarean deliveries, instrumental vaginal deliveries, or major maternal morbidities also did not differ between the groups.

The authors also found that in the induction group, there were fewer admissions to a neonatal intensive care unit, lower incidence of neonatal jaundice requiring therapy, and fewer infants with macrosomia. The rate of cesarean delivery did not differ significantly between the two groups.

Of note, the researchers said, all perinatal deaths occurred in the nulliparous women. “If this finding can be replicated in future studies,” they indicated, “it could mean that nulliparous women may require particular attention, and interventions such as labor induction might be even more important in this group.” The number needed to treat with induction of labor at 41 weeks to prevent one perinatal death was 230, which the authors said was lower than previous estimates.

Judith M. Orvos, ELS, is an editorial consultant for Contemporary OB/GYN.

SOURCE
Plasma transfusion for persistent PPH: Does timing matter?

by Judith M. Orvos, ELS

Dutch investigators theorized that outcomes in new mothers would be better with initiation of plasma transfusion within 60 minutes of persistent postpartum hemorrhage (PPH). Findings from their new study, however, tell a different story.

Methods
Published in JAMA Network Open, the results are from a multicenter cohort study conducted in the Netherlands. The authors identified women in the transfusion strategies in women during major obstetric hemorrhage (TeMPOH-1) study, which retrospectively assessed transfusion strategies used in women during major obstetric hemorrhage. The cohort in the new analysis had persistent PPH, defined as PPH with at least 1000 mL of blood loss refractory to first-line interventions to control bleeding.

In the Netherlands, in women with PPH who are hemodynamically stable enough, uterine or internal iliac artery embolization is used before resorting to hysterectomy. If embolization is not available in an institution, it is common practice to transfer the patient to a nearby hospital with embolization facilities.

The current study included 1216 women (mean age 31.6 years) with PPH, of whom 932 (76.6%) delivered vaginally and 780 (64.1%) had PPH caused by uterine atony. The authors used time-dependent propensity score matching to select women who received plasma during the first 60 minutes of persistent PPH. Each woman was matched with a woman who had PPH of the same severity and received the same treatment but who had not received plasma at the moment of matching. Transfusions were not guided by coagulation tests.

The main outcomes were incidence of adverse maternal outcomes, defined as a composite of death, hysterectomy, or arterial embolization. Seven of the women (0.6%) died of PPH, 62 (5.1%) underwent hysterectomy, and 159 (13.1%) had uterine artery embolization.

Findings
Among women who received plasma during the first 60 minutes of persistent PPH, 114 could be matched with a comparable woman who had not received plasma at the moment of matching. Incidence of adverse maternal outcomes was similar between the women, with adverse outcomes recorded in 24 women (21.2%) who received early plasma transfusion and 23 women (19.9%) who did not receive early plasma transfusion (odds ratio 1.09; 95% CI 0.57-2.09). Results of sensitivity analyses were comparable to the primary results.

Conclusions
While the results do not support the authors’ original hypothesis, they said they should not be taken to indicate that plasma transfusion has no place in treatment of women with severe PPH. “Rather,” they said, “our study underlines the importance of developing tools to diagnose coagulopathy during persistent PPH. These tools may enable individualization of treatment of women with persistent PPH by identifying women who develop coagulopathy during persistent PPH.”

Judith M. Orvos, ELS is a freelance writer for Contemporary OB/GYN.

FOR REFERENCES VISIT contemporaryobgyn.net/PlasmaTransfusion

Fond farewell
CONTINUED FROM PAGE 3

maintain COG’s extraordinary success over the past 45 years if they also follow John Queenan’s tried and true formula.

In closing, I want to thank our dedicated, brilliant, and very witty past and present editorial board members. I am also incredibly grateful to my terrific managing editors, including Judy Orvos, Paul Cerrato, Susan Olmstead, and Linda Wetzel, whose professionalism and sage counsel have been invaluable. Finally, I want to thank our wonder-ful readers, who were my inspiration.

Dr. Lockwood, former editor-in-chief, is Senior Vice President, USF Health, and Dean, Morsani College of Medicine, University of South Florida.
Immediate postpartum LARC

Besides routinely offering postpartum LARC to their patients, ob/gyns must advocate for policies that support these devices.

by TANIA BASU Serna, MD, MPH, AND CHLOE BASS, MD

In the first year postpartum, 70% of pregnancies are unintended.5 Unintended and short-interval pregnancies are associated with increased rates of preterm birth and adverse maternal and neonatal outcomes.6 The World Health Organization recommends spacing pregnancies at least 18 months apart and in the United States, the Office of Disease Prevention and Health Promotion continues to aim to reduce the proportion of pregnancies conceived within 18 months of a previous birth, per their Healthy People 2020 objectives.7

Why LARC?

Intrauterine devices (IUDs) and contraceptive implants, also known as long-acting reversible contraceptives (LARC), are the most effective reversible contraceptives and can be safely initiated immediately postpartum. LARCs have the highest continuation rates among reversible methods with effectiveness greater than 99% (Figure 1). The major advantages of LARCs are that they are not user-dependent and return to fertility is rapid after discontinuation. Placement in the postpartum period is associated with higher continuation rates compared with interval placement. ACOG supports immediate postpartum LARC insertion as a best practice.4,10

LARC methods available in the United States

Currently there are five IUDs and one contraceptive implant available in the United States.

COPPER INTRAUTERINE DEVICE

Paragard is the copper T380A IUD commercially available in the United States. It is US Food and Drug Administration-approved for use up to 10 years but has been shown to be effective up to...
CONTRACEPTION

12 years. The T-shaped device is a base of polyethylene wrapped with copper wire around the stem and arms. Mechanisms of action (MOAs) include inhibition of sperm migration and viability and damage to or destruction of the ovum. Postfertilization events may occur, but the copper IUD does not disrupt a pregnancy after implantation. It has a reported 1-year failure rate of 0.8 per 100 women. The most-reported adverse events (AE) are abnormal uterine bleeding and pain.

LEVONOGESTREL INTRAUTERINE SYSTEMS

There are four levonorgestrel intrauterine systems (LNG-IUS) currently available in the United States (Mirena, Liletta, Kyleena, Skyla) (Table 1). All are T-shaped and include a polydimethylsiloxane sleeve containing levonorgestrel in the stem. All LNG-IUS have a similar primary MOA: prevention of fertilization by increasing the amount and viscosity of cervical mucus. Most women who use an LNG-IUS ovulate but experience diminished menstrual bleeding due to the local effect of the levonorgestrel on the endometrium. LNG-IUS are not abortifacients and do not disrupt pregnancy.

CONTRACEPTIVE IMPLANT

The etonogestrel contraceptive implant is placed subdermally and consists of an ethylene vinyl acetate copolymer core containing 68 mg of etonogestrel. The single-rod implant is 4 cm in length and 2 mm in diameter and is preloaded in a disposable sterile applicator. The 2001 version of the implant has been updated and was introduced to the United States in 2011. The newer implant is radiopaque with a new inserter designed to prevent deep placement. Its primary MOA is ovulation suppression, but it also thickens cervical mucus and has endometrial effects. After implant insertion, changes in menstrual patterns are common and include amenorrhea, or frequent, infrequent, or prolonged bleeding. Complications related to implant insertion and removal are rare.

Postpartum LARC safety

ACOG states that immediate postpartum IUD insertion (within 10 minutes after placental delivery in vaginal and cesarean births), should be offered routinely as a safe and effective option for postpartum contraception. The Centers for Disease Control and Prevention US Medical Eligibility Criteria (US CDC MEC) classifies immediate postpartum copper IUD insertion as Category 1 (Table 2). Immediate postpartum insertion of LNG-IUS and the contraceptive implant is MEC Category 1 or 2, depending on breastfeeding status (Table 2). Immediate postpartum IUD insertion is contraindicated for women in whom uterine infection, puerperal sepsis, or ongoing postpartum hemorrhage are diagnosed. Immediate postpartum initiation of the contraceptive implant either before hospital discharge or after a hospital stay for birth should be offered routinely as a safe and effective options regardless of breastfeeding status. The US CDC MEC classifies placement of an implant in non-breastfeeding women less than 21 days postpartum as Category 1 and classifies placement for breastfeeding women as Category 2, given theoretical concerns regarding milk production; after 30 days postpartum,
it is classified as US MEC Category 1 in breastfeeding women.20

**POSTPLACENTAL IUD PERFORATION AND EXPULSION**

Uterine perforation at time of postplacental IUD placement is rare. In a prospective study of 8343 women receiving the Copper T380A at different postpartum timings, only one perforation occurred out of 460 postplacental insertions (0.2%).21 This risk is not greater than with interval IUD insertion.

The rate of postplacental IUD expulsion, on the other hand, is higher than after interval insertion. Reported expulsion rates range from 2% to 27% after vaginal delivery and 0% to 20% after cesarean delivery.22,23 In a large randomized controlled trial (RCT) of postplacental IUD insertion, Chen et al. randomized 102 women to postplacental insertion of the 52-mg LNG-IUS or interval insertion 6 to 8 weeks later. Expulsion was higher with postplacental insertion than with interval insertion. However, 10 of 12 women who experienced expulsion after immediate postpartum placement had a new LNG-IUS inserted and both groups had similar rates of IUS use at 6 months (84% vs. 77%, P = 0.32).24

Another study randomized women to immediate IUD placement at cesarean delivery versus interval placement at 6 weeks postpartum and found that significantly more women in the immediate placement group continued the IUD at 6 months (83% vs. 64%, RR 1.3, CI 1.02-1.66).25 In the interval group, 39% did not obtain the IUD, 25% did not return for the postpartum visit, and 14% either declined the IUD or had an unsuccessful insertion.25 When looking at expulsion rates after postplacental IUD insertion versus after insertions at other postpartum intervals (> 10 min to 48 or 72 hours), data are conflicting. Despite the higher expulsion rate for immediate postpartum IUD placement, evidence from clinical trials and cost-benefit analyses strongly suggest superiority of immediate placement, especially for women at greatest risk of not having recommended postpartum follow-up. Patients should be counseled about the increased expulsion risk, as well as signs and symptoms of expulsion. Given that many women experience barriers to interval LARC placement, advantages of immediate postpartum placement may outweigh disadvantages.

**BLEEDING**

Postplacental IUD insertion does not appear to cause increased vaginal bleeding. A Cochrane review of RCTs comparing immediate postpartum versus delayed insertion of the contraceptive implant found that women who received an immediate postpartum implant had a higher mean number of days of abnormal vaginal bleeding and side effects within 6 weeks postpartum but that did not lead to differences in continuation rates at 6 months.26 There appeared to be little or no difference between the groups in heavy irregular vaginal bleeding or associated severe cramping within 12 months.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>LARC methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name</strong></td>
<td><strong>Medication and device type</strong> (dose)</td>
</tr>
<tr>
<td>Kyleena</td>
<td>LNG-IUS (19.5 mg)</td>
</tr>
<tr>
<td>Liletta</td>
<td>LNG-IUS (52 mg)</td>
</tr>
<tr>
<td>Mirena</td>
<td>LNG-IUS (52 mg)</td>
</tr>
<tr>
<td>Skyla</td>
<td>LNG-IUS (13.5 mg)</td>
</tr>
<tr>
<td>Paragard</td>
<td>Copper T 380A IUD (380 mm²)</td>
</tr>
<tr>
<td>Nexplanon/ Implanon</td>
<td>Etonogestrel single-rod implant (68 mg)</td>
</tr>
</tbody>
</table>

Adapted from ACOG Practice Bulletin on Long Acting Reversible Contraception
Abbreviations: FDA, US Food and Drug Administration; LARC, long-acting reversible contraception; LNG-IUS, levonorgestrel intrauterine system; IUD, intrauterine device.
**EFFECT ON BREASTFEEDING**

Given that progesterone withdrawal after delivery of the placenta is thought to trigger lactogenesis, there are theoretical concerns about progestin IUDs and implants preventing onset of milk production. Observational studies suggest they have no effect on lactogenesis, successful initiation and continuation of breastfeeding, or on infant growth and development. The Copper-T lacks hormones and thus is classified MEC Category 1 for immediate postpartum use by breastfeeding women. Data on the immediate postpartum use of LNG-IUS are limited to a secondary analysis of a small RCT of immediate versus delayed postpartum placement, which showed no difference in patient-reported breastfeeding at 6 to 8 weeks and 3 months. However, more women in the delayed placement group reported breastfeeding at 6 months. Small numbers limit the ability to draw definitive conclusions from this study.

**Given current available evidence, women should be counseled about theoretical risks of reduced duration of breastfeeding with immediate LNG-IUS placement but the majority of evidence has not shown a negative effect on breastfeeding outcomes.** For this reason, immediate postpartum insertion of an LNG-IUS in breastfeeding women is classified as MEC Category 2. Placement of the contraceptive implant in non-breastfeeding women less than 21 days postpartum is Category 1 and placement for breastfeeding women is Category 2; after 30 days postpartum, it is Category 1 in breastfeeding women.

**VTE RISK**

One of the main considerations for postpartum contraception is risk of venous thromboembolism (VTE), given the already increased risk in this period. The Copper-T, LNG-IUS, and implant do not increase risk of VTE and are good options for women with medical problems for which estrogen is contraindicated.

**Techniques for postplacental IUD placement**

After vaginal delivery, IUD insertion can be performed manually or with a ring forceps. The IUD is removed from the inserter and strings are trimmed to 10 cm. Typically, the strings of the Copper T do not need to be trimmed. The arms of the IUD are gently grasped with the forceps and placed at a slight angle to facilitate placement. The IUD is passed through the cervix to the fundus with the other hand applying downward fundal pressure. Ultrasound guidance can be used to ensure appropriate positioning. At time of cesarean delivery, after delivery of the placenta and uterine tone is achieved, the IUD is placed at the fundus with the inserter, manually or with the ring forceps, and the strings are directed through the cervix. The hysterotomy is then closed in the usual fashion. Formalized training is advisable prior to provision of an immediate postpartum IUD; ACOG instructional videos are available.

Currently there is insufficient evidence to support routine use of ultrasound for postplacental placement of IUDs, so it is reasonable not to use the technology this setting. If there is a concern about fundal placement of the IUD, an ultrasound can be used to ensure proper positioning. Lack of ultrasound availability should not prohibit provision of postplacental IUD at time of vaginal delivery.

**Follow-up**

ACOG now recommends that, ideally, all women have some contact with an obstetrical provider within the first 3 weeks postpartum; the timing of a comprehensive postpartum visit should be individualized and patient centered. Assessment of how a patient is doing

---

**TABLE 2**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Implant</th>
<th>LNG-IUS</th>
<th>Cu-IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 10 minutes after delivery of placenta</td>
<td>-</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10 minutes after delivery of placenta to less than 4 weeks after delivery</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>More than 4 weeks after delivery</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Less than 1 month postpartum</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>More than 1 month postpartum</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Abbreviations:** Cu, copper; IUD = intrauterine device; LARC, long-acting reversible contraception; LNG-IUS, levonorgestrel intrauterine system.

**Data from the U.S. Medical Eligibility Criteria for Contraceptive Use 2010.**

**Categories:** 1 = a condition for which there is no restriction for use of the contraceptive method; 2 = a condition for which the advantages of using the method generally outweigh the theoretic or proven risks; 3 = a condition for which the theoretic or proven risks usually outweigh the advantages of using the method; 4 = a condition that represents an unacceptable health risk of the contraceptive method is used.
with her immediate postpartum LARC should be performed. For patients who have had postplacental IUD placement, a speculum exam can be performed to visualize the IUD strings. The strings can be trimmed as they often lengthen. Routine ultrasound surveillance is not recommended.

If incidental displacement of the IUD is diagnosed, removal is not mandated but can be considered after appropriate patient counseling, if desired. Patients who receive a postpartum implant should be examined like any other patients with an implant, with verification that the device can be palpated and inspection of the insertion site.

**MANAGEMENT OF LOST IUD STRINGS**

Inability to visualize IUD strings after postplacental placement ranges from 5% for LNG-IUS placement after vaginal delivery to 44% to 79% for IUD placement during cesarean delivery. If the IUD strings are not visualized or palpated at the external os, it may be necessary to use ultrasound to confirm the intrauterine location. Women who undergo postplacental IUD placement should be counseled that confirmation of the IUD may require ultrasound examination.

**POSTPARTUM LARC COST-EFFECTIVENESS**

Several studies have shown that postpartum insertion of LARC typically is more expensive upfront but is cost-saving overall because of reductions in future unintended pregnancies. A 2015 cost-effectiveness analysis calculated postpartum IUD placement had an estimated cost savings of approximately $282,540 per 1,000 women over a 2-year period. Higher cost was incurred at time of postplacental IUD placement due to more devices used (in part due to expulsion and replacement), but that was offset by prevention of an additional 88 unintended pregnancies over 2 years per 1,000 women. Another model found that immediate insertion of contraceptive implants was associated with a higher cost at insertion ($1,091 per patient for immediate placement vs. $650 per patient for delayed placement, likely due to more implants placed in the immediate group) but was more effective in preventing pregnancies, saving $1,263 per patient. This prevented 191 unintended pregnancies per 1,000 women with a total savings of $1,263,000 compared with delayed insertion. One caveat is that savings may depend on payer; a 2009 cost-benefit analysis estimated that a postpartum IUD program for patients with Emergency Medicaid would be costly to individual hospitals with a loss of 70 cents per $1 spent. Conversely, the same program funded by the state government would save an estimated $2.94 for every $1 spent. This difference was attributed to the likelihood that the state would cover all costs of future unintended pregnancies but hospitals would not see future profits from same-hospital deliveries.

**Challenges and barriers to postpartum LARC utilization**

In a 2018 ACOG survey, only 26.9% of Fellows and Junior Fellows were offering postpartum LARC. Implementing an immediate postpartum LARC program within an individual institution has similar barriers; Hofler et al. in 2017 interviewed personnel from 10 Georgia hospitals working to establish these programs and found that lack of knowledge, financial concerns, and competing clinical and administrative priorities were roadblocks to program success. These programs also require collaboration and buy-in at multiple levels by clinicians, patient care team members, pharmacists, administrators, and billing and electronic health record staff, which can be challenging to coordinate. ACOG recognizes these challenges and provides resources through the Postpartum Contraceptive Access Initiative to assist providers who want to implement a postpartum LARC program at their institution.
Both natural and surgical premature menopause before age 40 are associated with a small but statistically significant increased risk for subsequent cardiovascular disease (CVD) compared to that in postmenopausal women without premature menopause, according to a cohort study in JAMA.

The composite outcome included coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease and venous thromboembolism.

The authors noted that although recent guidelines embrace using history of menopause before age 40 to refine atherosclerotic cardiovascular disease (ASCVD) risk assessments in middle-aged women, “robust data on cardiovascular disease risk in this population is lacking.”

Methods
The cohort of 144,260 eligible women was from the large-scale, long-term observational UK Biobank study, comprising adult residents of the United Kingdom recruited between 2006 and 2010. All included women were 40 to 69 years old (mean age 59.9) and postmenopausal at study enrollment, with median follow-up of 7 years through August 2016. Natural premature menopause was defined as menopause before age 40 without oophorectomy, while surgical premature menopause was bilateral oophorectomy before age 40.

Findings
Overall, 3.4% (n = 4,903) of women had natural premature menopause and 0.4% (n = 644) had surgical premature menopause. The primary outcome of incidence of composite CVD was 3.9% (n = 5,415) in women with no premature menopause (5.7/1,000 woman-years) and 6.0% (n = 292) in women with natural premature menopause (8.7/1,000 woman-years), representing a difference vs. no premature menopause of +3.08/1,000 woman-years (95% confidence interval [CI]: 2.06 to 4.10; \( P < 0.001 \)).

Among the 7.6% of women (n = 49) with surgical premature menopause (11.27/1,000 woman-years), the difference vs. no premature menopause was +5.57/1,000 woman-years (95% CI: 2.41 to 8.73; \( P < 0.001 \)). Overall, natural and surgical premature menopause had hazard ratios of 1.36 (95% CI: 1.19 to 1.56; \( P < 0.001 \)) and 1.87 (95% CI: 1.36 to 2.58; \( P < 0.001 \)), respectively, after accounting for conventional CVD risk factors and menopausal hormone therapy.

The Framingham Heart Study found that a higher premenopausal Framingham risk factor was linked to earlier age at menopause. The current study, though, concluded that premature menopause may not be limited to co-morbid with conventional CVD risk factors, but may separately increase odds of developing these risk factors. In addition, the study found that the CVD risk connected to premature menopause extended beyond ASCVD.

Conclusions
“Postmenopausal state is associated with increase in cytokines and oxidative stress, which may contribute to osteogenesis of valvular interstitial cells,” wrote the authors, noting that it is unknown if this mechanism links premature menopause to aortic stenosis.

Lastly, the form of menopause may be connected to differential cardiovascular risk. Although significant differences in risk between natural and surgical premature menopause were not evident in fully adjusted models, risk differences may arise from differential development of conventional cardiovascular risk facts. There is also the possibility the study had reduced statistical power.

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

SOURCE
NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

- NEXPLANON should not be used in women who have known or suspected pregnancy; current or past history of thrombosis or thromboembolic disorders; liver tumors, benign or malignant, or active liver disease; undiagnosed abnormal genital bleeding; known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past; and/or allergic reaction to any of the components of NEXPLANON.

Complications of insertion and removal

- NEXPLANON should be inserted subdermally and be palpable after insertion. Palpate immediately after insertion to ensure proper placement. Undetected failure to insert the implant may lead to unintended pregnancy. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

- Insertion and removal-related complications may include pain, paresthesias, bleeding, hematoma, scarring, or infection. If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. Implant removal may be difficult or impossible if the implant is not inserted correctly, inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. If at any time the implant cannot be palpated, it should be localized and removal is recommended.

- There have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Endovascular or surgical procedures may be needed for removal.

NEXPLANON and pregnancy

- Be alert to the possibility of an ectopic pregnancy in women using NEXPLANON who become pregnant or complain of lower abdominal pain.

- Rule out pregnancy before inserting NEXPLANON.

Educate her about the risk of serious vascular events

- The use of combination hormonal contraceptives increases the risk of vascular events, including arterial events [stroke and myocardial infarction (MI)] or deep venous thromboembolic events (venous thromboembolism, deep venous thrombosis (DVT), retinal vein thrombosis, and pulmonary embolism). Women with risk factors known to increase the risk of these events should be carefully assessed. Postmarketing reports in women using etonogestrel implants have included pulmonary embol (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.
SELECTED SAFETY INFORMATION (continued)

- Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum.
- Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Consider removing the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

Counsel her about changes in bleeding patterns

- Women are likely to have changes in their menstrual bleeding pattern with NEXPLANON, including changes in frequency, intensity, or duration. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy. In clinical studies of the non-radiopaque etonogestrel implant, changes in bleeding pattern were the most common reason reported for stopping treatment (11.1%). Counsel women regarding potential changes they may experience.

Be aware of other serious complications, adverse reactions, and drug interactions

- Remove NEXPLANON if jaundice occurs.
- Remove NEXPLANON if blood pressure rises significantly and becomes uncontrolled.
- Prediabetic and diabetic women using NEXPLANON should be carefully monitored.
- Carefully observe women with a history of depressed mood. Consider removing NEXPLANON in patients who become significantly depressed.
- The most common adverse reactions (≥10%) reported in clinical trials were headache (24.9%), vaginitis (14.5%), weight increase (13.7%), acne (13.5%), breast pain (12.8%), abdominal pain (10.9%), and pharyngitis (10.5%).
- Drugs or herbal products that induce enzymes, including CYP3A4, may decrease the effectiveness of NEXPLANON or increase breakthrough bleeding.
- The efficacy of NEXPLANON in women weighing more than 130% of their ideal body weight has not been studied. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. Therefore, NEXPLANON may be less effective in overweight women.
- Counsel women to contact their health care provider immediately if, at any time, they are unable to palpate the implant.
- NEXPLANON does not protect against HIV or other STDs.

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

Nexplanon®
(etonogestrel implant) 68mg

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.

INDICATIONS AND USAGE
NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION
The use of NEXPLANON does not depend on daily, weekly or monthly administration. All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON.

A NEXPLANON implant is inserted subdermally just under the skin on the inner side of the non-dominant upper arm. The insertion site is overlying the triceps muscle about 8 1/2 cm (3 3/4 inches) from the medial epicondyle of the humerus and 3 1/2 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult or impossible. Complications of Insertion and Removal

NEXPLANON should be inserted subdermally so that it will be palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert NEXPLANON properly may go unnoticed unless it is palpated immediately after insertion. Undetected failure to insert the implant may lead to subdermal insertion. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, or scarring, may occur.

If NEXPLANON is inserted deeply (intramuscular or in the fascial, neural or vascular muscle may occur. To help avoid the risk of intramuscular or neural or vascular injury, NEXPLANON should be inserted subdermally just under the skin on the inner side of the non-dominant upper arm over the triceps muscle about 8 1/2 cm (3 3/4 inches) from the medial epicondyle of the humerus and 3 1/2 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. Deep insertions of NEXPLANON have been associated with dislocations of the implant (subscapular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start appropriate treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, incised in fascious tissue, or has been removed. There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion. There also have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to disinsertions or intravascular insertion. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be necessary for removal. If at any time the implant cannot be palpated, it should be localized and removal is recommended.

Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged. Removal of NEXPLANON implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the management of complications located in the chest. Healthcare providers familiar with the chest should be consulted. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a previously resolved adverse event.

Changes in Menstrual Bleeding Patterns
After starting NEXPLANON, women are likely to have a change from their normal menstrual bleeding pattern. These may include changes in bleeding frequency (less, more, frequent or continuous), intensity (reduced or increased) or duration. In clinical trials of the non-radiopaque etonogestrel implant (IMPLANON), bleeding patterns ranged from amenorrhea (1 in 5 women) to frequent and prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of NEXPLANON use is broadly predictive of the future bleeding pattern for many women. Women should be counseled regarding the bleeding pattern they may experience so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy.

In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding pattern were the most common reason for stopping treatment (11%). Irregular bleeding (10.6%) was the single most common reason for stopping treatment, while amenorrhea (0.3%) was cited less frequently.

In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentage of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of days that bleeding patterns are observed, are summarized in Table 2.

Table 1: Percentages of Patients With 0, 1-7, 8-21, or >21 Days of Spotting or Bleeding Over a 90-Day Interval While Using the Non-Radiopaque Etonogestrel Implant (IMPLANON)

<table>
<thead>
<tr>
<th>Total Days of Spotted or Bleeding</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Days</td>
<td>19%</td>
</tr>
<tr>
<td>1-7 Days</td>
<td>24%</td>
</tr>
<tr>
<td>8-21 Days</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;21 Days</td>
<td>33%</td>
</tr>
</tbody>
</table>

Table 2: Bleeding Patterns Using the Non-Radiopaque Etonogestrel Implant (IMPLANON) During the First 2 Years of Use

<table>
<thead>
<tr>
<th>Bleeding Patterns</th>
<th>Definitions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrequent</td>
<td>Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)</td>
<td>33.6</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>No bleeding and/or spotting in 90 days</td>
<td>22.2</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Any bleeding and/or spotting episode lasting more than 14 days in 90 days</td>
<td>17.7</td>
</tr>
<tr>
<td>Frequent</td>
<td>More than 5 bleeding and/or spotting episodes in 90 days</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Based on 3,315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion

<table>
<thead>
<tr>
<th>% - Percentage of 90-day intervals with this pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>in case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.</td>
</tr>
</tbody>
</table>

ECTOPIC PREGNANCIES
As well as progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON who become pregnant or complain of lower abdominal pain. Although ectopic pregnancies are uncommon among women using NEXPLANON, a pregnancy that occurs in a woman using NEXPLANON may be more likely to be ectopic than a pregnancy occurring in a woman using no contraception.

Thrombotic and Other Vascular Events
The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (venous thromboembolism, deep vein thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of vascular events be counseled regarding the bleeding pattern changes they may experience so that they know what to expect. There have been postmarketing reports of serious arterial and venous thrombotic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using etonogestrel implants. NEXPLANON should be removed in the event of a thrombosis.

Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum. Women with a history of the thromboembolic disorders should be made aware of the possibility of a recurrence. Evaluate for retinal vein thrombosis immediately if there is unexplained loss of vision, photopsia, diplopia, papilledema, or retinal vascular changes. Consider removal of the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

Ovarian Cysts
If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. On rare occasion, surgery may be required.

Carcinoma of the Breast and Reproductive Organs
Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer may be hormonally sensitive (see Contraindications). Some studies suggest that the use of combination hormonal contraceptives might increase the incidence of breast cancer; however, other studies have not confirmed such findings. Some studies suggest that the use of combination hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors. Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

Liver Disease
Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove NEXPLANON if jaundice develops. Hepatic adenomas and adenocarcinomas have been associated with combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only products (IMPLANON). The risk of hepatocellular carcinoma is very low and may be metabolized in women with liver impairment. Use of NEXPLANON in women with active liver disease or liver cancer is contraindicated (see Contraindications).

Weight Gain
In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the use of hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. Therefore, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors. Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

Elevated Blood Pressure
Women with a history of hypertension-related diseases or renal disease should be discouraged from using hormonal contraception. For women with well-controlled hypertension, use of NEXPLANON can be considered. Women with hypertension using NEXPLANON should be closely monitored. If sustained hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not respond adequately to antihypertensive therapy, NEXPLANON should be removed.

Gallbladder Disease
Studies suggest a small increased relative risk of developing gallbladder disease among continuation hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only products (IMPLANON).

Carbohydrate and Lipid Metabolic Effects
Use of NEXPLANON may induce mild insulin resistance and small changes in glucose concentrations of unknown clinical significance. Carefully monitor prediabetic and diabetic women using NEXPLANON. Women who are being treated for hypothyroidism should be followed closely if they elect to use NEXPLANON. Some progestins may elevate LDL levels and may render the control of hyperlipidemia more difficult.

Depressed Mood
Women with a history of depressed mood should be carefully observed. Consideration should be given to removing NEXPLANON in patients who become significantly depressed.

Return to Ovulation
In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the estradiol levels in blood remained below sensitivity of the assay three weeks after removal of the implant. Menstrual bleeding was observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.
Fluid Retention

Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

Contact Lens

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

In Silo Broken or Bent Implant

There have been reports of broken or bent implants while in the patient’s arm. Based on in vitro data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety (see Dosage and Administration).

Monitoring

A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

Drug–Laboratory Test Interactions

Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thymine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

AdVERSE REACTIONS

In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPALON® [etonogestrel implant]) (11% of women). Adverse reactions that resulted in a rate of discontinuation of >1% are shown in Table 3.

Table 3: Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPALON®)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding irregularity1</td>
<td>11.1%</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>2.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.3%</td>
</tr>
<tr>
<td>Acne</td>
<td>1.3%</td>
</tr>
<tr>
<td>Depression</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

1 Includes “frequent”, “heavy”, “prolonged”, “spotting”, and other patterns of bleeding irregularity.

Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-radiopaque etonogestrel implant clinical trials are listed in Table 4.

Table 4: Common Adverse Reactions Reported by ≥5% of Subjects in Clinical Trials With the Non-Radiopaque Etonogestrel Implant (IMPALON®)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>24.9%</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>14.5%</td>
</tr>
<tr>
<td>Weight increase</td>
<td>13.7%</td>
</tr>
<tr>
<td>Acne</td>
<td>13.5%</td>
</tr>
<tr>
<td>Breast pain</td>
<td>12.8%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10.9%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10.5%</td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>9.6%</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>7.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.2%</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>7.2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.8%</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>6.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.4%</td>
</tr>
<tr>
<td>Pain</td>
<td>5.6%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>5.6%</td>
</tr>
<tr>
<td>Depression</td>
<td>5.5%</td>
</tr>
<tr>
<td>Hiper Reactivity</td>
<td>5.4%</td>
</tr>
<tr>
<td>Insertion site pain</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematomas (0.7%), bruising (2.3%), pain (1.0%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives

Substances increasing the plasma concentrations of HCs: Co-administration of certain HCs and other drugs may increase the concentration of CYP3A4 inhibitors such as etonogestrel, verapamil, fluoxetine, pharmacologically active metabolites of rifampin, and ritonavir may increase the serum concentrations of progestins, including etonogestrel.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are substrates for CYP3A4. Etonogestrel may slightly increase the plasma concentrations of protegins when administered with the HIV protease inhibitors (e.g., nelfinavir, ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir, and/or indinavir and atazanavir/ritonavir) or increase (e.g., indinavir and atazanavir/ritonavir) HIV protease inhibitors (e.g., beceprevir and telaprevir) or with non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz) or increase (e.g., etravirine). These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral and anti-retroviral concomitant medications to identify potential interactions.

Effects of Hormonal Contraceptives on Other Drugs

Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (e.g., cyclosporine) or decrease (e.g., lamotrigine).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant (see Contraindications). Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogesrer during organogenesis at doses of 351 or >711 times the anticipated human dose (60 μg/day). NEXPLANON should be removed if maintaining a pregnancy.

Lactation

Risk Summary

Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. However, in nursing women, etonogestrel may be secreted in human milk. This may reduce milk production with certainty, but the clinical significance is unknown. In nursing women, it is not known whether etonogestrel could impair the development and function of the breastfed infant.

Pediatric Use

Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

Geriatric Use

This product has not been studied in women over 65 years of age and is not indicated in this population.

Hepatic Impairment

No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated (see Contraindications).

Overweight Women

The effectiveness of the etonogestrel implant in women who weighed more than 100% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with increasing weight after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE

Overdose may result if more than one implant is inserted. In case of suspected overdose, the implant should be removed.

NONCLINICAL TOXICOLOGY

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON, no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the in vitro Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the in vivo mouse micronucleus test. Fertility in rats returned after withdrawal from treatment.

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

• Counsel women about the insertion and removal procedure of the NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have the record of the location of the implant.

• Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.

• Counsel women that NEXPLANON does not protect against HIV infection (AIDS) or other STIs.

• Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889, USA.

For more detailed information, please read the Prescribing Information.

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Parental use and adolescent misuse of marijuana

by JUDITH M. ORVOS, ELS

In the United States, marijuana use by adults has increased in recent years. Adolescents whose parents use the drug may be at higher risk of substance abuse, according to results of a new nationwide study.

The findings, published in JAMA Network Open, are from a cross-sectional study based on survey data from the 2015 to 2018 National Survey on Drug Use and Health (NSDUH). Conducted by the Substance Abuse and Mental Health Services Administration (SAMSHA), NSDUH was designed to be nationally representative of substance use among the US civilian, noninstitutionalized population aged 12 years and older.

Methods

Participants surveyed were adolescents aged 12 to 17 who lived with a sampled parent born between 1955 and 1984 and young adults aged 18 to 30 living with a samples parent born between 1955 and 1980. A maximum of two people were selected for the survey from any one dwelling unit, meaning that a child and both parents living in the same home were never all included.

During the interviews, which lasted approximately 1 hour, the researchers collected information on lifetime use and past-year use of tobacco, alcohol, and illicit drugs (i.e. marijuana, cocaine, heroin, hallucinogens, inhalants, and methamphetamine) and misuse of prescription opioids, stimulants, sedatives, and tranquilizers. Parental use of marijuana was assessed at four levels: never use, lifetime use, less than 52 days of past-year use, and 52 days or more of past-year use.

Findings

A total of 24,900 mother-offspring or father-offspring dyads were surveyed. Of the mothers living with adolescent offspring, 8.2% (95% CI, 7.3% to 9.2%) had used marijuana in the past year while 7.6% (95% CI, 6.2% to 9.2%) of mothers living with young adult offspring, compared with 9.6% and 9.0% of fathers, respectively. Past-year marijuana use was higher in adolescents whose mothers had lifetime marijuana use than in those whose mothers never used the drug (ARR 1.3; 95% CI, 1.1 to 1.6; P = .007), less than 52 days of past-year marijuana use (ARR 1.7; 95% CI, 1.1 to 2.7; P = .02), or 52 days or more of past-year marijuana use (ARR 1.5; 95% CI, 1.1 to 2.2; P = .02). Similar trends were seen among young adults (P = .001, P = .049 and P = .002, respectively).

Comparing with their peers whose parents had no past marijuana use and after adjusting for covariates, adolescents whose mothers had lifetime marijuana use had a higher adjusted risks of past-year tobacco use, past-year marijuana use, or 52 days or more of past-year marijuana use (ARR 1.3; 95% CI, 1.0 to 1.6; P = .03, ARR 1.5; 95% CI, 1.0 to 2.1; P = .04, and ARR 1.6; 95% CI, 1.1 to 2.3; P = .03, respectively). The adjusted risk was also higher for young adults whose mothers had lifetime marijuana use (ARR 1.2; 95% CI, 1.0 to 1.5; P = .04).

Compared with their peers whose parents had no past marijuana use and after adjusting for covariates, risk of past-year alcohol use was higher among adolescents whose mothers had lifetime marijuana use (ARR 12; 95% CI, 1.1 to 1.4; P = .004) less than 52 days of past-year marijuana use (ARR 1.5; 95% CI, 1.2 to 1.9; P = .002) or 52 days or more of past-year marijuana use (ARR 1.3; 95% CI, 1.0 to 1.7; P = .04). After adjusting for covariates, parental marijuana use was not associated with opioid misuse by offspring.

Judith M. Orvos, ELS is a freelance writer for Contemporary OB/GYN.

FOR REFERENCES VISIT contemporaryobgyn.net/MarijuanaUse
Is it still reasonable to offer MIS hysterectomy?
Two ob/gyns provide arguments for and against offering the procedure.

Yes. Moving away from the procedure is an overreaction

by R. WENDEL NAUMANN, MD

Radical hysterectomy is the preferred method of treatment for early cervical cancer, especially in younger women. Surgery for cervical cancer often eliminates the need for radiation, which is associated with premature ovarian failure, chronic bowel and bladder toxicity, and poor sexual function. With improvements in surgical equipment and techniques, radical hysterectomy can now be performed either by laparoscopy or robotic-assisted minimally invasive techniques. Minimally invasive surgery (MIS) allows faster recovery, shorter hospital stays, decreased peri-operative morbidity including less blood loss, lower wound infection rates, less fever, lower rates of sepsis, lower risk of deep venous embolism, and less risk of post-operative ileus. It is likely that MIS can also avoid the known morbidity of open surgery, such as ventral hernia formation and the 10-fold increase in bowel obstruction due to adhesions associated with open hysterectomy.

While MIS has many benefits, the recently reported LACC trial has created controversy with respect to oncologic safety of the minimally invasive approach to radical hysterectomy in cervical cancer. The primary endpoint

CONTINUED ON PAGE 24

No. LACC results raise serious safety concerns

by AMANDA NICKLES FADER, MD

Cervical cancer is among the most frequently diagnosed malignancies and the fourth leading cause of cancer-related death in women, with 570,000 new cases and 311,000 deaths anticipated worldwide in 2019. Despite decades of Pap smear screening, human papillomavirus (HPV) co-testing, and the recent availability of the HPV vaccine, cervical cancer and its precursor, cervical dysplasia, remain a significant public health threat for women worldwide.

In women with early-stage cervical cancer, surgery is indisputably the treatment with the most positive impact on long-term survival. Standard radical hysterectomy and pelvic lymphadenectomy, which are performed through either a transverse or vertical abdominal incision, are associated with the potential for procedural morbidity and patient recovery time. More than a decade ago, however, a new approach to gynecologic cancer surgery was welcomed by surgeons with the Phase III Gynecologic Oncology Group LAP2 trial, a study which demonstrated significant perioperative benefits and almost identical survival outcomes for laparoscopic compared with open hysterectomy in patients with early-stage

CONTINUED ON PAGE 26
Yes. Moving away from the procedure is an overreaction

CONTINUED FROM PAGE 23

of this international, randomized controlled trial (RCT) was a 7.2% non-inferiority disease-free survival (DFS) boundary at 4.5 years. The design of this trial with this boundary comes a priori with the expectation that we are willing to accept up to a 7.2% difference in DFS in return for the advantages of MIS. The LACC trial was inconclusive with respect to the primary endpoint as the DFS confidence interval in the trial crossed the non-inferiority boundary. However, in the LACC trial, there was a decrease in DFS, with an increase in local recurrence risk and overall cervical cancer mortality associated with MIS. Despite the fact that this trial was inconclusive for the primary endpoint, many of the narratives, and even the abstract of the article itself, do not make this obvious. Instead, the adverse secondary endpoints have been highlighted and some institutions have declared a moratorium on minimally invasive radical hysterectomy as a result.

While randomized RCTs should be the highest level of evidence for treatment of our patients, we must be careful in interpreting these data. All clinical trials, including RCTs, have pitfalls and can be prone to over-interpretation. Because we set the risk of a Type I error at 0.05, we accept that 1:20 RCTs will demonstrate false-positive results. More importantly, we often erroneously hold secondary endpoints to the same degree of certainty that we hold the primary outcome of a trial, forgetting that these secondary endpoints should be hypothesis-generating. This is certainly true for the LACC trial about which significant concern has been expressed over secondary endpoints that were not prespecified in the original statistical plan. In this trial, the confidence intervals for DFS, local recurrence, and recurrence due to cervical cancer did not cross parity. However, because these endpoints were not prespecified or corrected for multiple comparisons, they were not assigned a P value when the LACC trial was reported.

With the published results of the LACC trial, we must consider that there is a possibility that minimally invasive radical hysterectomy does have an inferior oncologic outcome when compared to open hysterectomy and that should be discussed with our patients as part of the consent process. However, one needs to examine the data carefully before completely condemning this procedure for all patients, especially when MIS is associated with significant advantages. One must ask, are any issues with the conduct of the trial that are problematic? Do the results make sense? Are there problems with the design of the clinical trial that cast doubts on the outcomes? Are the inclusion criteria for the trial so broad or one subgroup over-represented so that the results may not apply to everyone included in the trial? Are these international results applicable to practice in the United States?

Given the relative rarity of cervical cancer and the high demand for MIS in the United States, the LACC trial was conducted internationally and many of the patients were enrolled in countries where medical resources are more limited than they are in the United States. Surgical trials are difficult to conduct as there is significant variability between surgeons, international differences in practice patterns with respect to patient selection for surgery, preoperative imaging, and postoperative therapy. Because no standard preoperative imaging was mandated in this trial, we cannot be assured that there was adequate stratification of risk factors between the groups in the LACC trial even though pathologic factors appeared to be balanced. In this trial there was no central pathology review and data on basic variables such as tumor size were missing in 15% of patients. Further, no specific recommendations for postoperative therapy were mandated by the protocol. This is critical as pelvic radiation has been shown to reduce risk of recurrence by approximately 50% in patients with high-risk tumors and is associated with improved overall survival. While adjuvant therapy in the form of chemotherapy and radiation were used at similar rates in both the open and laparoscopic arms, we do not know how this correlates with risk factors for recurrence in the two groups or exactly what kind of postoperative therapy was prescribed. The preoperative evaluation and postoperative therapy are clearly important when one considers that 27% of recurrences reported in the LACC trial were within 1 year of the surgery, a phenomenon that should be relatively rare after radical hysterectomy for early cervical cancer with negative margins and adequate adjuvant therapy.
One of the most important aspects of a RTC is stratification for risk factors that can influence the outcome of the trial. One concerning aspect of the LACC data is that there was an imbalance in the number of non-cancer-related deaths in the laparoscopic arm unrelated to the surgery, with five deaths in the minimally invasive arm due to causes not related to the cancer or to the surgery, and one additional death due to complications with a second unrelated cancer that prevented adequate adjuvant therapy. This is compared to only one death unrelated to cervical cancer in the open group. This death was not otherwise described and we do not know if it was surgically related. Due to the study design, these deaths are included in the DFS and overall survival (OS) calculation. While the differences between the arms with respect to disease recurrence or death from cervical cancer remained after these cases were excluded, this would still suggest that there is some imbalance between the two arms not accounted for in the randomization stratification.

Another striking observation is that the laparoscopic arm actually performed better than any other reported large series of radical hysterectomies. Thus, the differences between the two groups were not a result of poor performance of the laparoscopic arm, but an over-performance of the open arm. The 3-year disease-specific survival in the MIS arm was 95.6%. However, the 3-year disease specific survival in the open arm was 99.6% in a population where almost half the patients had tumors > 2 cm, half had > 50% cervical invasion, and 13% of patients had positive nodes. The DFS and OS in the open arm are also abnormally high when compared to every other series of abdominal radical hysterectomy. Because no previous study has demonstrated similar results, one has to consider whether these numbers simply represent a statistical anomaly or are the result of under-reporting of recurrences or deaths due to the challenging logistics of an international trial, casting further doubts on the results of this trial.

Local recurrence risk is a concern with MIS and that was the most significant finding between arms of the LACC trial. Local failure can occur due to inadequate surgical margins or possibly due to tumor contamination of the peritoneal cavity by use of uterine manipulators commonly used during laparoscopic surgery. In the LACC trial, the rate of positive surgical margins between the two arms was comparable. Sub-analysis of the data suggests that patients with larger tumors are clearly at the highest risk of local recurrence, suggesting that there may be a contamination issue with larger tumors. The LACC trial showed a significantly higher risk of local recurrence in patients treated with laparoscopic surgery when their tumors were > 2 cm. In both the open and the laparoscopic groups, the local recurrence risk was less than 5%, except in the laparoscopic group with tumors > 2 cm, for whom the rate of local recurrence was almost 15%.

While the results of the LACC trial are concerning, it is not a definitive trial to end the practice of minimally invasive radical hysterectomy in all patients. The DFS and OS differences seen in the LACC trial were secondary endpoints and should be considered exploratory. Just as the US Food and Drug Administration requires two RCTs with a clearly defined primary endpoint for drug approval, we should hold surgical trials to similar standards, thus the LACC trial should prompt a call for another trial to be conducted in the United States or other countries with similar practice patterns with careful attention to oncologic principles and standardized postoperative therapy. Prior to the LACC trial, patient preference for MIS precluded adequate accrual, but the LACC data should rekindle an interest and make such a trial feasible.

Moving completely away from minimally invasive radical hysterectomy without a definitive trial is an over-reaction to the available data. The current situation with MIS in cervical cancer is very similar to that in rectal cancer where two non-inferiority trials have been reported with inconclusive results. One of these trials was similar to the LACC trial in that the confidence interval for the primary endpoint did not include parity. However, as previously stated about this trial, “Failure to show non-inferiority cannot be used to imply inferiority.” It seems to be an over-reaction to use data from a single inconclusive trial as a basis for abandoning a procedure that has clear benefits. An unintended consequence of a move away from...
MIS is that it may decrease the availability of surgery for young patients with cervical cancer. Despite the advantages of surgery, only 9% of women with cervical cancer in the National Inpatient Sample Database from 2008 through 2015 were treated with radical hysterectomy. This likely reflects careful selection of patients for this surgery and suggests that the selection criteria for radical hysterectomy in the United States are particularly stringent, thus the patients treated with surgery here may not be similar to those in the LACC trial. In addition, it has been reported that patients having MIS have a higher body mass index and minimally invasive radical hysterectomy might be offered to patients who might not be candidates for an open radical hysterectomy due to technical challenges of open surgery in women who weigh > 100 Kg.

The LACC trial should be a call for caution and careful patient selection along with informed consent. This is a reasonable approach until we have more information. While we should inform our patients about the results of this trial when discussing surgery for cervical cancer, it is still reasonable to offer minimally invasive radical hysterectomy, especially to patients with tumors < 2 cm or who have tumors that can be removed prior to surgery.

No. LACC results raise serious safety concerns

Continued from Page 23

uterine cancer. Because of outcomes in this and other trials, gynecologic oncologists endeavored to expand the indications for minimally invasive surgery (MIS), including in cervical cancer. Based on subsequent retrospective data touting superior perioperative results and similar oncologic outcomes compared with open approaches, minimally invasive radical hysterectomy was embraced by gynecologic oncology surgeons worldwide for treatment of stage IA2-IB1 cervical cancer.

However, recently, Ramirez and colleagues reported the results of the Laparoscopic Approach in Cervical Cancer (“LACC”) study in the New England Journal of Medicine, the first—and only—Phase III trial addressing the relationship between surgical approach and survival outcomes in early-stage cervical cancer. A total of 631 patients with early-stage squamous cell tumors or adenocarcinomas were randomized to undergo either an open or minimally invasive radical hysterectomy. Midway through this non-inferiority trial, the Data Safety and Monitoring Committee identified a disproportionate number of deaths in the minimally invasive cohort, triggering study closure after an interim analysis revealed inferior disease-free survival at 4.5 years, as well as significantly higher death rates, in the minimally invasive compared to the open hysterectomy cohort. These striking and surprising results were paradigm shifting and raised serious concerns regarding the safety of performing minimally invasive radical hysterectomy.

Critics question the results and ask “why?” and “how?”

Many have questioned how the unexpected results of the LACC trial could be so incongruous with prior published data. In journal editorials and at national society meetings, minimally invasive enthusiasts and thoughtful gynecologic oncology critics have voiced concerns over perceived trial weaknesses that may limit conclusions. As a surgeon who has studied minimally invasive innovations and performed countless robotic and laparoscopic cancer staging procedures in my career, I was astonished with the LACC trial results, and my voice was among the chorus of critics focused on the trial limitations and urging others that it was premature to sound the death knell for MIS in cervical cancer. I wondered:

- **“How can MIS be so dangerous for women with early-stage cervical cancer when we have not observed similar trends in those with early-stage endometrial cancer?”**
- **“There is no definitive explana-**
FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

IMVEXXY (estradiol vaginal inserts) is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

IMPORTANT SAFETY INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

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

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

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

WARNINGS AND PRECAUTIONS
- IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY.
- The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.
- The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.
- Other warnings include: gallbladder disease; severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice.
- Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
- Women on thyroid replacement therapy should have their thyroid function monitored.

ADVERSE REACTIONS
- The most common adverse reaction with IMVEXXY (incidence ≥3 percent) and greater than placebo was headache.

Please see Brief Summary of the Full Prescribing Information, including BOXED WARNING, on the following page.


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INDICATIONS AND USAGE

IMVEXXY® is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

DOSEAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin [see Warnings and Precautions (5.5, 5.15) in full prescribing information].

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see Warnings and Precautions (5.8) in full prescribing information].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information].

The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (0.625 mg)-alone, relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

The WHI Memory Study (WHMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke, and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg) relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

The WHMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions (5.3, 5.2), and Clinical Studies (14.2) in full prescribing information].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if estrogen therapy is needed.

CONTRAINDICATIONS

Undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease (e.g., stroke and myocardial infarction (MI) or a history of these conditions; known anaphylactic reaction or angioedema with IMVEXXY® known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

WARNING AND PRECAUTIONS

Risks from Systemic Absorption

IMVEXXY® is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY® (Pharmacokinetics [12.3] in full prescribing information). The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account.

Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment years and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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

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

Breast Cancer

In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.86] [see Clinical Studies (14.2) in full prescribing information].

Estrogen plus progestin therapy has demonstrated an increased risk of invasive breast cancer. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The use of estrogen-alone and estrogen plus progestin therapy has been associated with reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations (8.4), and Clinical Studies (14.3) in full prescribing information].

Other Warnings and Precautions include:

Galbladder disease; severe hypercalcemia; visual abnormalities; elevated blood pressure; hypertigryceridemia; hepatic impairment and/or past history of cholestati jaundice; hypothyroidism (women on thyroid replacement therapy may require higher doses of thyroid hormone); fluid retention; hypercalcemia; exacerbation of endometriosis; hereditary angioedema; exacerbation of other conditions (asthma, diabetes mellitus, epilepsy, migrane, porphyria, systemic lupus erythematosus, and hepatic hemangiomata).

ADVERSE REACTIONS

Clinical Trials Experience: In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reaction with IMVEXXY® (incidence ≥ 3 percent) and greater than placebo was headache.

Post-Marketing Experience: The following adverse reactions have been identified during post-approval use of IMVEXXY® 4 and 10 mg. Genitourinary System: vaginal discharge.

DRUG INTERACTIONS

Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration.

USE IN SPECIFIC POPULATIONS

IMVEXXY® is not indicated for use in pregnancy, in females of reproductive potential, or in children.

Geriatric Use

An increased risk of probable dementia in women over 65 years of age was reported in the Women’s Health Initiative Memory ancillary studies of the Women’s Health Initiative.
tion to account for these findings, so what do we make of them?”

- “Why are the LACC trial results seemingly so different than other retrospective studies?”
- “Are the study surgeons using irresponsible techniques or is lack of experience an issue?”

However, after conducting a comprehensive trial analysis and reviewing the many studies that have emerged since the LACC trial publication, my early view on this matter has shifted considerably to one of sober appreciation of these data and an understanding that we could not continue as we had before in our surgical approach to cervical cancer. Herein, I will discuss dilemmas with conducting surgical trials, critically appraise the LACC trial strengths and limitations, review the existing literature on early-stage cervical cancer survival outcomes by surgical approach, and present an argument on why it may be time for the “old” radical hysterectomy technique to become relevant again.

The problem with surgical innovation and trials

Surgical innovation is important, and as technology expands, there is increasing pressure on surgeons to incorporate the latest surgical procedures and tools into their practices. However, with that incorporation must come rigorous evaluation. The cervical cancer story shows us that evidence from retrospective case series alone may no longer be acceptable as the only evaluation of a surgical approach, and that procedures—especially those used to treat life-threatening conditions like cancer—must be evaluated robustly in randomized controlled trials (RCTs). The Phase III study is the gold standard in this regard, and the power of this study type is its rigorous design which minimizes risk of random or systematic bias/error, and thus, the risk of making an incorrect conclusion about the efficacy of a treatment. Despite this, surgical trials are notoriously difficult to conduct and pose particular practical and methodological challenges. The RCT has been widely accepted for evaluating the efficacy of medical treatments but less so for surgical procedures. Critics cite methodologic issues related to surgery as the reason, including concerns related to standardization of the surgical procedure, challenges of or inability to performing blinding of subjects and investigators, variability of surgeon experience with a given procedure, patient differences, and patient and surgeon acceptance of surgical trials.

The LACC trial is not immune to these concerns and several limitations have been cited, including:

1. a lack of central pathology review and standardization of adjuvant therapies after radical hysterectomy;
2. a concern for variability in surgeon experience with open and minimally invasive radical hysterectomy and that most of the recurrences came from a select number of study sites;
3. the fact that cervical cancer surgery is technically complex, and patient, surgeon and procedural variables may all impact trial outcomes;
4. missing patient data; and
5. subjective patient evaluations without standardized preoperative imaging.

These trial biases are legitimate and will be discussed below; however, what critics fail to mention is that the same study flaws are augmented even further in the smaller, retrospective published studies that preceded the LACC trial.

With regards to the study recurrences, which were largely grouped at 14 of the 33 participating cancer centers, this can be explained, in part, by the fact that several of these particular centers enrolled more patients and became study sites earlier than other centers without recurrences. Whether unique patient or surgeon factors contributed to the institutional pattern of recurrence is unknown. However, the trial was enriched with gynecologic oncology surgeons who were laparoscopic/robotic experts, and were vetted based on their expertise in minimally invasive—not open—radical hysterectomy skills. On the subject of missing data, the authors report that only 8% of trial data were missing at the final analysis, which is within the industry standard range for missing data in RCTs. And while postoperative treatment was not standardized, use of adjuvant radiation and chemotherapy was well balanced between the surgical cohorts.

Perhaps one of the most provocative LACC trial results was that the minimally invasive cohort did not necessarily experience poorer disease-free survival (DFS) than predicted (86%) based on a prespecified DFS of 90% at 4.5 years and a 7.2% equivalence margin. Instead, the open hysterectomy cohort had higher-than-expected DFS (96.5%).

Some argue that while MIS appears inferior to open radical hysterectomy in the LACC trial, the treatment effect estimated from the historical experience with the control arm was ultimately erroneous and the constancy assumption of the trial (the assessment of
The likelihood that the current control arm effect is similar to the past effect) was not upheld. In other words, the observed non-inferiority boundary is only meaningful if the constancy assumption is sustained; therefore, if the open cohort results are indeed anomalous in terms of what was predicted, then the study conclusions are undermined. However, this argument does not stand for several reasons. While the open hysterectomy cohort had higher-than-expected DFS results compared to older clinical trials, some of these prior studies contained patients at a much higher baseline risk of recurrence. In addition, several more contemporary, retrospective analyses (several discussed in this editorial) show similar survival trends as the LACC trial. Most importantly, the trial’s Data Safety and Monitoring Committee recommended early closure due to significantly worse mortality noted in the MIS cohort on interim analysis. This mortality signal was so strong that it would have been unethical to keep the trial open in an effort to assess if the prespecified non-inferiority margin was ultimately met. Therefore, the mortality data cannot be dismissed and trumps any minor statistical technicalities.

### Table 1: Summary of national gynecologic cancer society recommendations on radical hysterectomy in early stage cervical cancer

<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Society of Gynecologic Oncology</td>
<td>“The Society of Gynecologic Oncology of Canada (GOC) recommends withholding the routine use of MIS for radical hysterectomy in patients with cancer of the cervix.”</td>
</tr>
<tr>
<td>British Gynecologic Cancer Society</td>
<td>“Clinicians and patients should exercise caution when considering undergoing minimal access radical hysterectomy for the management of early-stage cervical cancer.”</td>
</tr>
<tr>
<td>U.S. National Comprehensive Cancer Network</td>
<td>“The standard and historical approach for radical hysterectomy is with an open abdominal approach. Several key contemporary reports have questioned the presumed therapeutic equivalency of open versus MIS approaches.”</td>
</tr>
<tr>
<td>European Society of Gynecologic Oncology</td>
<td>“The prior statement, ‘Minimally invasive approach is favored for radical hysterectomy in cervical cancer’ is no longer valid and should be removed and replaced by ‘The open approach is the gold standard.’”</td>
</tr>
<tr>
<td>Society of Gynecologic Oncology</td>
<td>“Gynecologic oncologists are encouraged to consider all available data as they counsel individual patients to determine the most appropriate surgical approach. We anticipate additional data to emerge on this topic.”</td>
</tr>
<tr>
<td>Korean Society of Gynecologic Oncology</td>
<td>“The results of the LACC trial, as well as institutional data, should be discussed with the patient before choosing MIS radical hysterectomy.”</td>
</tr>
</tbody>
</table>

### Discrepancy in the pre- vs post-LACC trial data

While surgical trials are difficult to conduct, comparisons of prior randomized and non-randomized studies have shown that results can diverge, both in direction and magnitude. There are countless examples of “effective” surgical treatments being discredited in randomized trial settings. However, findings from alternative (non-randomized) study designs cannot be given the same vote of confidence, due to the substantial risk of bias. And while many surgeons accept the need in principle for randomized studies, they struggle to reconcile their surgical experience and personal beliefs with the actual data. Never has this been more apparent than with the LACC trial. But why did these trial results diverge so much from the data found in previously published literature?

My informal Pubmed review of English language studies with the search terms “cervical cancer” “laparoscopy,” “robotics,” “minimally invasive surgery,” “laparoscopic radical hysterectomy” and “robotic radical hysterectomy” revealed hundreds of studies, which was expected. What I did not anticipate was that the vast majority (~99%) were focused on surgical outcomes only and omitted data on recurrence and survival outcomes. Specifically, most of the data were retrospective, most studies were small and included fewer than 100 patients, and fewer than 0.5% reported on survival (and of these, not a single study was powered for survival outcomes).

In contrast, the literature that has
arisen peri- or post-LACC trial has been illuminating. A companion analysis by Melamed and colleagues suggests that the survival outcomes observed in the LACC trial have validity. Using an innovative study design to analyze patients with Stage IA2-IB1 cervical cancer in two population-based, retrospective data sets, the authors determined that overall survival rates dropped significantly and systematically each year after robotic surgery adoption in the United States. These data may, in part, reflect the steep surgeon learning curve for minimally invasive radical hysterectomy and it will be interesting to follow those trends out beyond the initial 4 years presented in this study. In addition, several subsequent international cancer registry and multi-institutional studies have been published recently showing almost identical survival trends/outcomes as the LACC trial. These studies are presented in a table available online at contemporaryobgyn.net/MISHysterectomyNO, and include analyses conducted in the United States, Canada, the United Kingdom, and Korea, among others. Furthermore, given the totality of the emerging data on this issue, the national gynecologic cancer societies/agencies that define standards of care in each of these respective countries have recently issued updated position statements regarding concerns with the minimally invasive radical hysterectomy approach for early stage cervical cancer. Excerpts of these statements are found in Table 1.

Unknowns
What remains unknown is why women with apparent early-stage cervical cancer who undergo MIS radical hysterectomy experience worse survival outcomes than those who undergo open radical hysterectomy. Is the worse mortality observed in the minimally invasive cohorts of the LACC trial, the Melamed et al analysis, and other recent population-based analyses purely a function of surgical modality, or are surgeon technique and learning curve, patient factors, flawed study methodology, or the intersection of all of the above at play? Some suggest that uterine manipulators are the biggest culprit while others implicate CO2 abdominal insufflation or exposure of the cervical tumor to the peritoneal cavity. Surgeon experience and procedural radicality may also impact outcomes, although the surgeons who participated in the LACC trial were vetted for their expertise (apparently by video assessment) with minimally invasive radical procedures. The use of manipulators, surgical extraction techniques and procedural radicality were not reported in the LACC trial, and discerning their impact would potentially be high yield. CO2 gas is not likely the problem, as the patterns of recurrence in the LACC trial are not consistent with aerosolization of tumor cells in the abdomen. In addition, it’s not clear from the LACC trial and other studies whether women with Stage IA2 tumors may safely undergo minimally invasive radical hysterectomy, as these cohorts are underpowered in all of the contemporary analyses. Further studies may help elucidate these questions and identify subgroups of women who will most benefit from minimally invasive approaches.

Conclusions
Every published surgical trial ever performed has limitations, and the LACC trial has its share of flaws. But this is not a reason to avoid conducting randomized procedure-based studies nor to completely dismiss study findings when they are performed—especially when they are the best available data and the results are unexpected and not aligned with our prior beliefs. When considering the collective body of contemporary data on surgical approach in early-stage cervical cancer, minimally invasive radical hysterectomy can no longer be considered the standard surgical procedure for treating Stage IA2 and IB1 cervical cancer. In select cases, this approach may be appropriate. However, the retrospective and population-based data that have emerged since the LACC trial strongly support the Phase III study findings. Until further data are available, caution should be heeded by clinicians considering minimally invasive surgery in women with early-stage cervical cancer, with rigorous counseling regarding LACC trial results and shared decision-making between the patient and her surgeon with respect to her individual risks and benefits for such a procedure.

Disclosures
The authors report no potential conflicts of interest with regard to this article.
Endometriosis: Predicting laparoscopic treatment complications

by BOB KRONEMYER

Postoperative complications from laparoscopic treatment for suspected endometriosis could not be predicted by preoperative patient characteristics or surgical findings of advanced endometriosis, according to a retrospective cohort study.

However, the study in *Acta Obstetricia et Gynecologica Scandinavica* did find that adhesiolysis, ureterolysis and an increased number of total procedures were predictive of perioperative complications.

“Laparoscopic treatment of endometriosis is highly variable, depending on the goals of the patient, the extent of disease and the skills of the surgeon,” said principal investigator Nisse Clark, MD, MPH, a minimally invasive gynecologic surgeon at Massachusetts General Hospital in Boston. “For instance, a simple procedure may only require a laparoscopic survey and a peritoneal biopsy, whereas a more complex procedure may entail a radical excision of all deep-infiltrating lesions, paralleling an oncologic debulk.”

**Methods**
The cohort of 397 women underwent laparoscopic treatment of suspected endometriosis at Brigham and Women’s Hospital in Boston between 2009 and 2016. Predictors of major perioperative complications were assessed by comparing the characteristics of women who had any major intraoperative or postoperative complications to women with no complications.

The procedures were excision of superficial endometriosis (55.4% of women), excision of deep-infiltrating endometriosis (24.9%), fulguration of endometriosis (38.3%), hysterectomy (23.2%), ovarian cystectomy (33.5%), salpingectomy (18.6%), oophorectomy (15.1%) and bowel resection (1.0%). The women, many of whom had multiple procedures, were followed for 60 days following each surgery, during which time 4.5% (n = 18) developed a major perioperative complication.

**Findings**
Women with advanced endometriosis (defined as stage III or IV endometriosis, rectovaginal endometriosis or deep-infiltrating endometriosis) were more likely to have a complication, though not a statistical significant difference. In total, 77.8% of women with a complication versus 56.7% of women without a complication had advanced endometriosis ($P = 0.077$).

On the other hand, women with a complication were significantly more likely to have undergone adhesiolysis or ureterolysis: 88.9% with a complication versus 52.5% without a complication for adhesiolysis ($P = 0.002$) and 61.1% of women with a complication versus 28.8% without a complication for ureterolysis ($P = 0.003$). The total number of procedures was also greater for women who had a complication: 4.3 vs. 3.2 ($P = 0.003$). All other procedure characteristics were comparable between women with and without complications.

**Conclusions**
“We were surprised to find that advanced endometriosis did not increase the risk of a complication with statistical significance,” Dr. Clark said. “Instead, we found that certain intraoperative procedures, such as ureterolysis and adhesiolysis, and the total number of procedures performed increased the risk of a complication.”

These procedural factors are surrogates for surgical complexity that more reliably predict complications than disease classification, according to the study. “Our study suggests that intraoperative events are the main driver of postoperative surgical outcomes,” Dr. Clark said. “One could conclude, therefore, that patients who undergo extensive laparoscopic dissection are most at risk of a complication, and thus surgeons should have heightened awareness for potential complications during or after surgery in these women.”

Future improvements in radiologic imaging, like assessment for deep-infiltrating disease with pelvic ultrasound, “will hopefully improve our ability to identify patients at risk of requiring significant dissection and its associated risks,” she said.

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

**SOURCE**
For today’s fertility specialist, challenges abound. If an increasing percentage of women present with retained products of conception or irregularities in the uterine lining, what diagnostic tools can an ob/gyn count on for accurate detection as well as optimized fertility treatment that follows?

In this Contemporary OB/GYN™ podcast, Aaron Styer, MD, discusses the role of hysteroscopy in his practice. Dr. Styer explains his comprehensive approach and considers advantages of hysteroscopy for evaluation, and the removal of retained products of conception.

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Vulvovaginal candidiasis (VVC) is relatively common, and research from Sexually Transmitted Diseases indicates a woman’s risk could be increased by certain personal behaviors as well as the composition of her vaginal microbiota. Candida albicans is the most common etiology for VCC and this study looked at what factors are associated with its molecular detection.

The objective of the study was to better understand epidemiologic factors associated with molecular C. albicans detection and to evaluate how the vaginal microbiota and relative abundance of individual bacterial taxa differ between women with and without C. albicans detected using molecular methods.

Methods
For the cross-sectional study, vaginal swabs were self-collected by 394 non-pregnant, reproductive-age women. The participants submitted two swabs; one was used to characterize the composition and structure of the vaginal microbiota and the other was used the prepare a smear for Nugent Gram stain scoring.

The authors were able to detect C. albicans using polymerase chain reaction targeting C. albicans ITS1/2 region. Vaginal microbiota was characterized using 16S rRNA gene amplification sequencing of the V3 to V4 hypervariable regions and then clustered into community state types (CSTs).

Five primary CSTs were identified in this study; four dominated by Lactobacillus species (L. iners, L. crispatus, L. gasseri, L. jensenii), plus one lacking significant numbers of Lactobacilli and characterized by higher proportions of strict and facultative anaerobic bacteria (termed CST IV). The authors used multiple logistic regression to identify risk factors associated with C. albicans detection.

Findings
The authors detected C. albicans in 21% of vaginal samples (83 of 394). Women in whom C. albicans was detected were more likely to report use of tampons, engage in receptive oral sex, and use of over-the-counter (OTC) antifungals to self-treat for vaginal infections before seeing a doctor for examination.

Neither self-reported diagnosis of VVC nor bacterial vaginosis in the prior 60 days were associated with C. albicans detection. Furthermore, detection was not associated with vaginal pH, reporting any type of vaginal symptom in the past 60 days, age, history of pregnancy, use of hormonal contraception in the past 60 days, number of recent sexual partners, or other forms of sexual activity in the past 60 days.

In multivariable modeling, women with a L.crispatus-dominated CST had increased, but not statistically significant, odds of C. albicans detection compared with a low-Lactobacillus CST IV after cofactor adjustment of receptive oral sex and a history of self-treatment with OTC antifungals (adjusted odds ratio, 2.05%; 95% CI 0.97-4.37, n=323). However, using the same model, antifungal use and receptive oral sex were significantly associated with C. albicans detection, with a dose-response trend for increasing frequency of oral sex and escalating odds of C. albicans detection.

When assessing individual bacteria to determine if there were taxa that were most likely to be associated with C. albicans detection, the authors identified L. crispatus, Lactobacillus coleohominis, Prevotella oris, and Prevotella verorali-sas being in higher relative abundance in women in whom C. albicans was detected. In women without C. albicans, the authors more abundant Mobiluncus, Moryella, and Fusobacterium.

Conclusions
The authors believe their findings indicate that L. crispatus-dominated vaginal microbiota may be associated with increased C. albicans detection. They also point to receptive oral sex as a risk factor for C. albicans colonization.

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

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Disrupted delivery plan leaves OB in difficult situation

Did this community physician act accordingly after the patient was diagnosed with MAP?

**Facts**

A 32-year-old G5P4004 with four prior cesarean deliveries underwent an ultrasound at 12 weeks’ gestation, which revealed a pregnancy in the lower uterine segment with a probable placenta previa. An ultrasound at 20 weeks’ gestation revealed a definite placenta previa, with lacunae and hypervascularity suggestive of a morbidly adherent placenta (MAP, now called placenta accreta spectrum). Magnetic resonance imaging (MRI) confirmed the ultrasound findings.

Although the mother was a long-term patient of the obstetrician, she was transferred from a community setting to a regional perinatal center 40 miles away. Her care continued at the perinatal center with a plan for cesarean hysterectomy at 34 to 35 weeks’ gestation. The patient was instructed to call the perinatal center immediately if she experienced any bleeding or significant contractions prior to the planned delivery date.

At 32 weeks’ gestation, the patient awoke in the night with severe pain and bleeding. She called 911 and was brought by ambulance to the local community hospital at 11:00 pm, where, fortuitously, the original referring physician was on call. Although the physician had not cared for the patient for several months, regular communication had been from the perinatal center. The physician was aware of the plan for cesarean hysterectomy. Although the patient’s vital signs and fetal heart monitor readings were stable, the degree of pain and bleeding necessitated urgent delivery at the community hospital. Anesthesia was consulted, multiple sites of intravenous (IV) access were established, and the blood bank was prepared for possible massive hemorrhage. The patient underwent a low transverse cesarean under general anesthesia and delivered a viable male infant who weighed 1845 g and had Apgar scores of 5 and 7 at 1 and 5 minutes, respectively. The baby did well. The placenta separated “normally,” but significant bleeding was noted at delivery and the estimated blood loss was not documented. Although bleeding initially was brisk, the uterus was deemed “dry” following primary closure.

Over the next 6 hours, the patient had multiple episodes of hypotension and bleeding. She did not leave the operating room (OR), nor could she be extubated. She received multiple uterotonics, 12 units of packed red blood cells and 10 units of fresh frozen plasma. The community obstetrician consulted with the regional perinatal center, as well as intensivists and hematologists at the community hospital. Subsequently, the patient developed disseminated intravascular coagulation (DIC). She was ultimately transported by helicopter to the regional perinatal center, where she was moribund on arrival and died upon admission to the hospital. Autopsy concluded that death was due to the obstetrical hemorrhage and DIC from a placenta accreta.

Dr. Shwayder is extremely grateful to Steven Warsaf, MD, who shared this case from his files. The case also appears in a book they coauthored, Legal Concepts and Best Practices in Obstetrics: The Nuts and Bolts Guide to Mitigating Risk.
Sex last night?

A negative fFN result is valid.

Even if a patient has had sex in the prior 24 hours:

- A negative result is valid
- A positive result may not be valid & should be confirmed > 24 hours

The majority of patients will test negative, even if they’ve had sex in the prior 24 hours.