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# OBG MANAGEMENT

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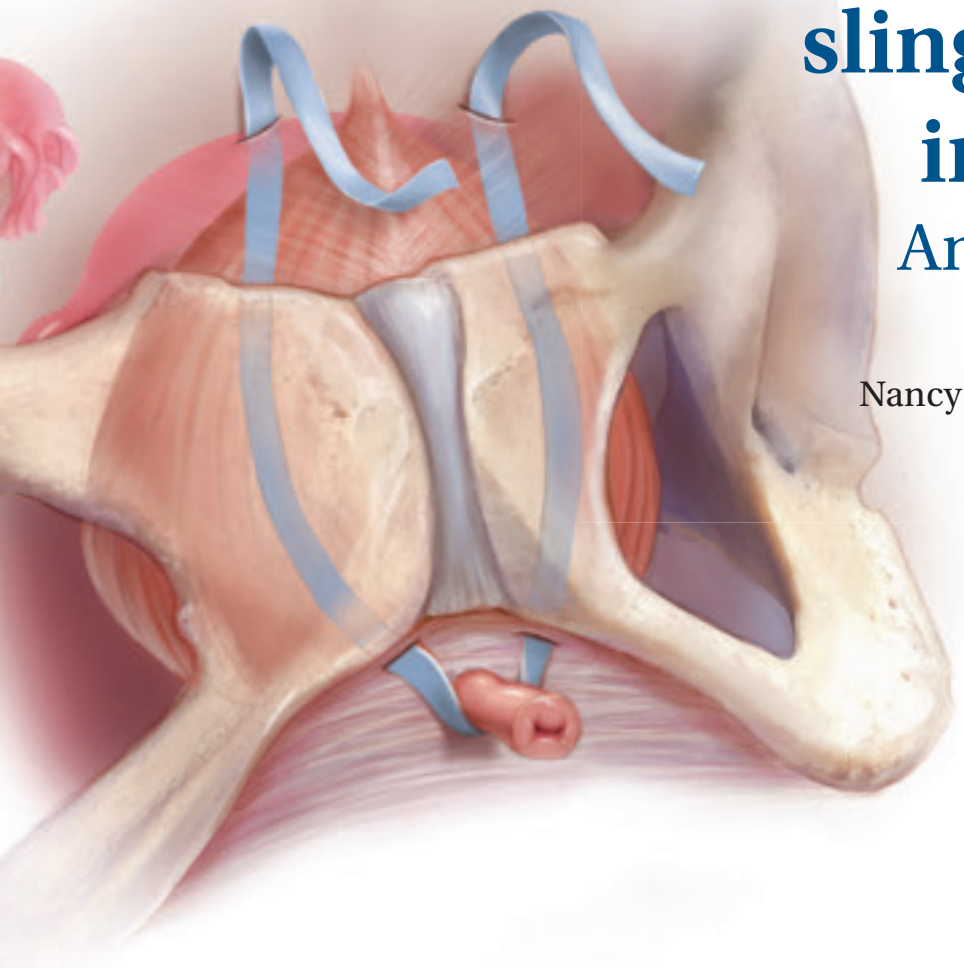
Roundtable
**The EMR's role in ObGyn burnout and patient care**

**Discerning optimal long-term osteoporosis tx**
Michael R. McClung, MD



# When to use which sling for urinary incontinence

## An evidence-based approach

Nancy Ringel, MD; Lee A. Richter, MD

**Contraception for women with migraine with aura**
Allison L. Gilbert, MD, MPH; Robert L. Barbieri, MD

**To AROM or not to AROM?**

**Persistent vulvar itch: What is the diagnosis?**
Only at mdedge.com/obgyn

**Contraception updates**
p. 16


*Statistical significance for dyspareunia was not achieved with the 150 mg QD dose of ORILISSA.

## 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 (due to risk of bone loss), 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.

## WITH DOSE-DEPENDENT EFFICACY, CHOOSE THE DOSAGE BASED ON HER NEEDS[1]

**The dose-dependent efficacy and safety results of ORILISSA help you choose the most appropriate dosage for your patients based on symptom severity and treatment objectives.[1]**

**Proven relief of moderate to severe pain associated with endometriosis**

Dysmenorrhea
Non-menstrual Pelvic Pain

**150 mg QD**

Dysmenorrhea
Non-menstrual Pelvic Pain
Dyspareunia

**200 mg BID**

Tablets and packages pictured are not actual size.

### Hepatic Transaminase Elevations

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

### Reduced Efficacy with Estrogen-Containing Contraceptives

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

### ADVERSE REACTIONS

- The most common adverse reactions (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions, and mood changes.

**Consider the proven efficacy of ORILISSA as a next step for her.[1]**
**Explore more at ORILISSA.com/hcp**

These are not all the possible side effects of ORILISSA.

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

**Reference: 1.** Orilissa [package insert]. North Chicago, IL: AbbVie Inc; 2018.

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

Orilissa®
elagolix tablets 150 mg 200 mg

# ORILISSA™ (elagolix) tablets, for oral use

**PROFESSIONAL BRIEF SUMMARY**
**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

## INDICATIONS AND USAGE

ORILISSA is indicated for the management of moderate to severe pain associated with endometriosis.

## DOSAGE AND ADMINISTRATION

### Important Dosing Information

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

**Table 1. Recommended Dosage and Duration of Use**

| Dosing Regimen | Maximum Treatment Duration | Coexisting Condition |
|---|---|---|
| Initiate treatment with ORILISSA 150 mg once daily | 24 months | None |
| Consider initiating treatment with ORILISSA 200 mg twice daily | 6 months | Dyspareunia |
| Initiate treatment with ORILISSA 150 mg once daily. Use of 200 mg twice daily is not recommended. | 6 months | Moderate hepatic impairment (Child-Pugh Class B) |

### Hepatic Impairment

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

Compared to women with normal liver function, those with moderate hepatic impairment had approximately 3-fold higher elagolix exposures and those with severe hepatic impairment had approximately 7-fold higher elagolix exposures. Because of these increased exposures and risk for bone loss:

- ORILISSA 150 mg once daily is recommended for women with moderate hepatic impairment (Child-Pugh B) with the duration of treatment limited to 6 months. Use of ORILISSA 200 mg twice daily is not recommended for women with moderate hepatic impairment *[see Use in Specific Populations]*.
- ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) *[see Contraindications and Use in Specific Populations]*.

### Missed Dose

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

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

## CONTRAINDICATIONS

ORILISSA is contraindicated in women:

- Who are pregnant *[see Use in Specific Populations]*. Exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss.
- With known osteoporosis because of the risk of further bone loss *[see Warnings and Precautions]*
- With severe hepatic impairment because of the risk of bone loss *[see Use in Specific Populations]*
- With concomitant use of strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil) *[see Drug Interactions]*

## WARNINGS AND PRECAUTIONS

### Bone Loss

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

Although the effect of supplementation with calcium and vitamin D was not studied, such 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 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 subjects had a higher incidence of depression and mood changes compared to placebo, and ORILISSA subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history *[see Adverse Reactions]*. Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits *[see Adverse Reactions]*. Patients with new or worsening depression, anxiety or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORILISSA if such events occur.

### Hepatic Transaminase Elevations

In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3-times the upper limit of the reference range occurred with ORILISSA. Use the lowest effective dose of ORILISSA 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 *[see Adverse Reactions]*.

### Reduced Efficacy with Estrogen-Containing Contraceptives

Based on the mechanism of action of ORILISSA, estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA. The effect of progestin-only contraceptives on the efficacy of ORILISSA is unknown. Advise women to use non-hormonal contraceptives during treatment with ORILISSA and for one week after discontinuing ORILISSA *[see Use in Specific Populations, Drug Interactions]*.

## ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Bone loss *[see Warnings and Precautions]*
- Change in menstrual bleeding pattern and reduced ability to recognize pregnancy *[see Warnings and Precautions]*
- Suicidal ideation, suicidal behavior, and exacerbation of mood disorders *[see Warnings and Precautions]*
- Hepatic transaminase elevations *[see Warnings and Precautions]*

### Clinical Trials Experience

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

The safety of ORILISSA was evaluated in two six-month, randomized, double-blind, placebo-controlled clinical trials [EM-1 (NCT01620528) and EM-2 (NCT01931670)] in which a total of 952 adult women with moderate to severe pain associated with endometriosis were treated with ORILISSA (475 with 150 mg once daily and 477 with 200 mg twice daily) and 734 were treated with placebo. The population age range was 18-49 years old. Women who completed six months of treatment and met eligibility criteria continued treatment in two uncontrolled, blinded six-month extension trials [EM-3 (NCT01760954) and EM-4 (NCT02143713)], for a total treatment duration of up to 12 months.

Serious Adverse Events

Overall, the most common serious adverse events reported for subjects treated with ORILISSA in the two placebo-controlled clinical trials (Studies EM-1 and EM-2) included appendicitis (0.3%), abdominal pain (0.2%), and back pain (0.2%). In these trials, 0.2% of subjects treated with ORILISSA 150 mg once daily and 0.2% of subjects treated with ORILISSA 200 mg twice daily discontinued therapy due to serious adverse reactions compared to 0.5% of those given placebo.

Adverse Reactions Leading to Study Discontinuation

In the two placebo-controlled clinical trials (Studies EM-1 and EM-2), 5.5% of subjects treated with ORILISSA 150 mg once daily and 9.6% of subjects treated with ORILISSA 200 mg twice daily discontinued therapy due to adverse reactions compared to 6.0% of those given placebo. Discontinuations were most commonly due to hot flushes or night sweats (1.1% with 150 mg once daily and 2.5% with 200 mg twice daily) and nausea (0.8% with 150 mg once daily and 1.5% with 200 mg twice daily) and were dose-related. The majority of discontinuations due to hot flushes or night sweats (10 of 17, 59%) and nausea (7 of 11, 64%) occurred within the first 2 months of therapy.

In the two extension trials (Studies EM-3 and EM-4), discontinuations were most commonly due to decreased BMD and were dose-related. In these trials, 0.3% of subjects treated with ORILISSA 150 mg once daily and 3.6% of subjects treated with ORILISSA 200 mg twice daily discontinued therapy due to decreased BMD.

Common Adverse Reactions:

Adverse reactions reported in ≥ 5% of women in the two placebo-controlled trials in either ORILISSA dose group and at a greater frequency than placebo are noted in the following table.

**Table 2. Percentage of Subjects in Studies EM-1 and EM-2 with Treatment-Emergent Adverse Reactions Occurring in at Least 5% of Subjects (either ORILISSA Dose Group) and at a Greater Incidence than with Placebo**

| | ORILISSA 150 mg Once Daily N=475 | ORILISSA 200 mg Twice Daily N=477 | Placebo N=734 |
|---|---|---|---|
| | % | % | % |
| Hot Flush or Night Sweats | 24 | 46 | 9 |
| Headache | 17 | 20 | 12 |
| Nausea | 11 | 16 | 13 |
| Insomnia | 6 | 9 | 3 |
| Mood altered, mood swings | 6 | 5 | 3 |
| Amenorrhea | 4 | 7 | <1 |
| Depressed mood, depression, depressive symptoms and/or tearfulness | 3 | 6 | 2 |
| Anxiety | 3 | 5 | 3 |
| Arthralgia | 3 | 5 | 3 |

Less Common Adverse Reactions:

In Study EM-1 and Study EM-2, adverse reactions reported in ≥ 3% and < 5% in either ORILISSA dose group and greater than placebo included: decreased libido, diarrhea, abdominal pain, weight gain, dizziness, constipation and irritability.

The most commonly reported adverse reactions in the extension trials (EM-3 and EM-4) were similar to those in the placebo-controlled trials.

Bone Loss

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

In Studies EM-1 and EM-2, there was a dose-dependent decrease in BMD in ORILISSA-treated subjects compared to an increase in placebo-treated subjects.

In Study EM-1, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was -0.9% (95% CI: -1.3, -0.4) with ORILISSA 150 mg once daily and -3.1% (95% CI: -3.6, -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 2% with ORILISSA 150 mg once daily, 7% with ORILISSA 200 mg twice daily and < 1% with placebo. In the blinded extension Study EM-3, 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 8% 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 -1.3% (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**

| | ORILISSA 150 mg Once Daily | ORILISSA 200 mg Twice Daily | Placebo |
|---|---|---|---|
| **EM-1** | | | |
| N | 183 | 180 | 277 |
| Percent Change from Baseline, % | -0.3 | -2.6 | 0.5 |
| Treatment Difference, % (95% CI) | -0.9 (-1.3, -0.4) | -3.1 (-3.6, -2.6) | |
| **EM-2** | | | |
| N | 174 | 183 | 271 |
| Percent Change from Baseline, % | -0.7 | -2.5 | 0.6 |
| Treatment Difference, % (95% CI) | -1.3 (-1.8, -0.8) | -3.0 (-3.5, -2.6) | |

To assess for recovery, the change in lumbar spine BMD over time was analyzed for subjects who received continuous treatment with ORILISSA 150 mg once daily or ORILISSA 200 mg twice daily for up to 12 months and who were then followed after cessation of therapy for an additional 6 months. Partial recovery of BMD was seen in these subjects (Figure 1).

In Study EM-3, if a subject had BMD loss of more than 1.5% at the lumbar spine or more than 2.5% at the total hip at the end of treatment, follow-up DXA was required after 6 months off-treatment. In Study EM-4, all subjects were required to have a follow-up DXA 6 months off treatment regardless of change in BMD and if a subject had BMD loss of more than 1.5% at the lumbar spine or more than 2.5% at the total hip after 6 months off treatment, follow-up DXA was required after 12 months off-treatment. Figure 2 shows the change in lumbar spine BMD for the subjects in Study EM-2/EM-4 who completed 12 months of treatment with ORILISSA and who had a follow-up DXA 12-months off treatment.

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

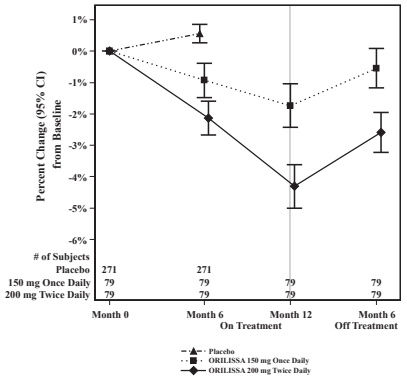
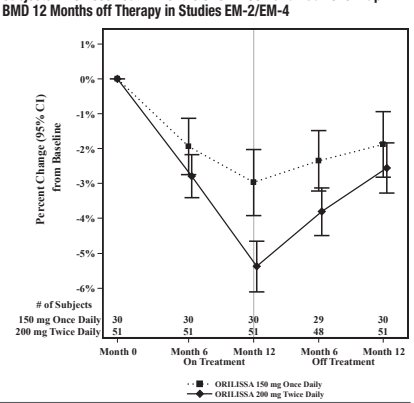



**Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4**



Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

In the placebo-controlled trials (Studies EM-1 and EM-2), ORILISSA was associated with adverse mood changes (see Table 2 and Table 4), particularly in those with a history of depression.

**Table 4. Suicidal Ideation and Suicidal Behavior in Studies EM-1 and EM-2**

| Adverse Reactions | ORILISSA 150 mg Once Daily (N=475) n (%) | ORILISSA 200 mg Twice Daily (N=477) n (%) | Placebo (N=734) n (%) |
|---|---|---|---|
| Completed suicide | 1 (0.2) | 0 | 0 |
| Suicidal ideation | 1 (0.2) | 1 (0.2) | 0 |

A 44-year-old woman received 31 days of ORILISSA 150 mg once daily then completed suicide 2 days after ORILISSA discontinuation. She had no relevant past medical history; life stressors were noted.

Among the 2090 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 4, there were two additional reports of suicidal ideation: one subject in EM-3 (150 mg once daily) and one in a Phase 2 study (75 mg once daily, an unapproved dose). Three of these subjects had a history of depression. Two subjects discontinued ORILISSA and two completed the clinical trial treatment periods.

Hepatic Transaminase Elevations

In the placebo-controlled clinical trials (Studies EM-1 and EM-2), dose-dependent asymptomatic elevations of serum ALT to at least 3-times the upper limit of the reference range occurred during treatment with ORILISSA (150 mg once daily – 1/450, 0.2%; 200 mg twice daily – 5/443, 1.1%; placebo – 1/696, 0.1%). Similar increases were seen in the extension trials (Studies EM-3 and EM-4).

Changes in Lipid Parameters

Dose-dependent increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and serum triglycerides were noted during ORILISSA treatment in EM-1 and EM-2. In EM-1 and EM-2, 12% and 1% of subjects with mildly elevated LDL-C (130-159 mg/dL) at baseline had an increase in LDL-C concentrations to 190 mg/dL or higher during treatment with ORILISSA and placebo, respectively. In EM-1 and EM-2, 4% and 1% of subjects with mildly elevated serum triglycerides (150-300 mg/dL) at baseline had an increase in serum triglycerides to at least 500 mg/dL during treatment with ORILISSA and placebo, respectively. The highest measured serum triglyceride concentration during treatment with ORILISSA was 982 mg/dL.

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

| | ORILISSA 150 mg Once Daily N=475 | ORILISSA 200 mg Twice Daily N=477 | Placebo N=734 |
|---|---|---|---|
| **LDL-C (mg/dL)** | | | |
| Mean change at Month 6 | 5 | 13 | -3 |
| Maximum increase during Treatment Period | 137 | 107 | 122 |
| **HDL-C (mg/dL)** | | | |
| Mean change at Month 6 | 2 | 4 | 1 |
| Maximum increase during Treatment Period | 43 | 52 | 45 |
| **Triglycerides (mg/dL)** | | | |
| Mean change at Month 6 | <1 | 11 | -3 |
| Maximum increase during Treatment Period | 624 | 484 | 440 |

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

Hypersensitivity Reactions

In Studies EM-1 and EM-2, non-serious hypersensitivity reactions including rash occurred in 5.8% of ORILISSA treated-subjects and 6.1% of placebo-treated subjects. These events led to study drug discontinuation in 0.4% of ORILISSA-treated subjects and 0.5% 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/minimally stimulated biopsy patterns. There were no abnormal biopsy findings on treatment, such as endometrial hyperplasia or cancer.

Based on transvaginal ultrasound, during the course of a 3-menstrual cycle study in healthy women, ORILISSA 150 mg once daily and 200 mg twice daily resulted in a dose-dependent decrease from baseline in mean endometrial thickness.

Effects on menstrual bleeding patterns

The effects of ORILISSA on menstrual bleeding were evaluated for up to 12 months using an electronic daily diary where subjects classified their flow of menstrual bleeding (if present in the last 24 hours) as spotting, light, medium, or heavy. ORILISSA led to a dose-dependent reduction in mean number of bleeding and spotting days and bleeding intensity in those subjects who reported menstrual bleeding.

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

| | ORILISSA 150mg Once Daily | | ORILISSA 200mg Twice Daily | | Placebo | |
|---|---|---|---|---|---|---|
| | Baseline | Month 3 | Baseline | Month 3 | Baseline | Month 3 |
| Mean bleeding/ spotting days in prior 28 days | 5.3 | 2.8 | 5.7 | 0.8 | 5.4 | 4.6 |
| Mean Intensity score[a] | 2.6 | 2.2 | 2.5 | 2.0 | 2.6 | 2.4 |

[a]Intensity for subjects who reported at least 1 day of bleeding or spotting during 28 day interval. Scale ranges from 1 to 4, 1 = spotting, 2 = light, 3 = medium, 4 = heavy

ORILISSA also demonstrated a dose-dependent increase in the percentage of women with amenorrhea (defined as no bleeding or spotting in a 56-day interval) over the treatment period. The incidence of amenorrhea during the first six months of treatment ranged from 6-17% for ORILISSA 150 mg once daily, 13-52% for ORILISSA 200 mg twice daily and less than 1% for placebo. During the second 6 months of treatment, the incidence of amenorrhea ranged from 11-15% for ORILISSA 150 mg once daily and 46-57% for ORILISSA 200 mg twice daily.

After 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, and 6 months, respectively. After 6 months of therapy with ORILISSA 200 mg twice daily, resumption of menses after stopping treatment was reported by 60%, 88%, and 97% 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 55%, 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.

Elagolix is an inhibitor of efflux transporter P-glycoprotein (P-gp). Co-administration with ORILISSA may increase plasma concentrations of drugs that are substrates of P-gp (e.g., digoxin).

**Potential for Other Drugs to Affect ORILISSA**

Elagolix is a substrate of CYP3A, P-gp, and OATP1B1.

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 effect of concomitant use of P-gp inhibitors or inducers on the pharmacokinetics of ORILISSA is unknown. Co-administration of ORILISSA with drugs that inhibit OATP1B1 may increase elagolix plasma concentrations. Concomitant use of ORILISSA and strong OATP1B1 inhibitors (e.g., cyclosporine and gemfibrozil) is contraindicated.

**Drug Interactions - Examples and Clinical Management**

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

**Table 7. Established Drug Interactions Based on Drug Interaction Trials**

| Concomitant Drug Class: Drug Name | Effect on Plasma Exposure of Elagolix or Concomitant Drug | Clinical Recommendations |
|---|---|---|
| Antiarrhythmics digoxin | ↑ digoxin | Clinical monitoring is recommended for digoxin when co-administered with ORILISSA. |
| Antimycobacteria rifampin | ↑ elagolix | Concomitant use of ORILISSA 200 mg twice daily and rifampin is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and rifampin to 6 months. |
| Benzodiazepines oral midazolam | ↓ midazolam | Consider increasing the dose of midazolam and individualize therapy based on the patient's response. |
| Statins rosuvastatin | ↓ rosuvastatin | Consider increasing the dose of rosuvastatin. |

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**

Risk Summary

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

The limited human data with the use of ORILISSA in pregnant women are 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, no pattern was identified and miscarriages were reported at a similar incidence across treatment groups *(see Data).*

When pregnant rats and rabbits were orally dosed with elagolix during the period of organogenesis, postimplantation loss was observed in pregnant rats at doses 20 times the maximum recommended human dose (MRHD). Spontaneous abortion and total litter loss was observed in rabbits at doses 7 and 12 times the MRHD. There were no structural abnormalities in the fetuses at exposures up to 40 and 12 times the MRHD for the rat and rabbit, respectively *(see Data).*

The background risk for major birth defects and miscarriage in the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

*Human Data*

There were 49 pregnancies reported in clinical trials of more than 3,500 women (of whom more than 2,000 had endometriosis) treated with ORILISSA for up to 12 months. These pregnancies occurred while the women were receiving ORILISSA or within 30 days after stopping ORILISSA. Among these 49 pregnancies, two major congenital malformations were reported. In one case of infant cleft palate, the mother was treated with ORILISSA 150 mg daily and the estimated fetal exposure to ORILISSA occurred during the first 30 days of pregnancy. In one case of infant tracheoesophageal fistula, the mother was treated with ORILISSA 150 mg daily and the estimated fetal exposure to ORILISSA occurred during the first 15 days of pregnancy.

Among these 49 pregnancies, there were five cases of spontaneous abortion (miscarriage) compared to five cases among the 20 pregnancies that occurred in more than 1100 women treated with placebo. Although the duration of fetal exposure was limited in ORILISSA clinical trials, there were no apparent decreases in birth weights associated with ORILISSA in comparison to placebo.

*Animal Data*

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

In rats, maternal toxicity was present at all doses and included six deaths and decreases in body weight gain and food consumption. Increased postimplantation losses were present in the mid dose group, which was 20 times the MRHD based on AUC. In rabbits, three spontaneous abortions and a single total litter loss were observed at the highest, maternally toxic dose, which was 12 times the MRHD based on AUC. A single total litter loss occurred at a lower non-maternally toxic dose of 150 mg/kg/day, which was 7 times the MRHD.

No fetal malformations were present at any dose level tested in either species even in the presence of maternal toxicity. At the highest doses tested, the exposure margins were 40 and 12 times the MRHD for the rat and rabbit, respectively. However, because elagolix binds poorly to the rat gonadotropin-releasing hormone (GnRH) receptor (~1000 fold less than to the human GnRH receptor), the rat study is unlikely to identify pharmacologically mediated effects of elagolix on embryofetal development. The rat study is still expected to provide information on potential non-target-related effects of elagolix.

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

Maternal plasma concentrations in rats on lactation day 21 at 100 and 300 mg/kg/day (47 and 125 ng/mL) were 0.06-fold and 0.16-fold the maximal elagolix concentration ($C_{max}$) in humans at the MRHD. Because the exposures achieved in rats were much lower than the human MRHD, this study is not predictive of potentially higher lactational exposure in humans.

**Lactation**

Risk Summary

There is no information on the presence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. There are no adequate animal data on the excretion of ORILISSA in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORILISSA and any potential adverse effects on the breastfed child from ORILISSA.

Data

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

**Females and Males of Reproductive Potential**

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

Pregnancy Testing

Exclude pregnancy before initiating treatment with ORILISSA. Perform pregnancy testing if pregnancy is suspected during treatment with ORILISSA *[see Warnings and Precautions].*

Contraception

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

**Pediatric Use**

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

**Renal Impairment**

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

**Hepatic Impairment**

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

ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) *[see Contraindications].*

## OVERDOSAGE

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

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) that administered elagolix by the dietary route revealed no increase in tumors in mice at up to 19-fold the MRHD based on AUC. In the rat, there was an increase in thyroid (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]*.
- Inform patients that estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA.
- Inform patients about the risk of bone loss. Advise adequate intake of calcium and vitamin D *[see Warnings and Precautions]*.
- Advise patients to seek immediate medical attention for suicidal ideation and behavior. Instruct patients with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention *[see Warnings and Precautions]*.
- Counsel patients on signs and symptoms of liver injury *[see Warnings and Precautions]*.
- Instruct patients who miss a dose of ORILISSA to take the missed dose on the same day as soon as she remembers and then resume the regular dosing schedule:
  - 150 mg once daily: no more than 1 tablet each day should be taken.
  - 200 mg twice daily: no more than 2 tablets each day should be taken.
- Instruct patients to dispose of unused medication via a take-back option if available or to otherwise follow FDA instructions for disposing of medication in the household trash, www.fda.gov/drugdisposal, and not to flush down the toilet.

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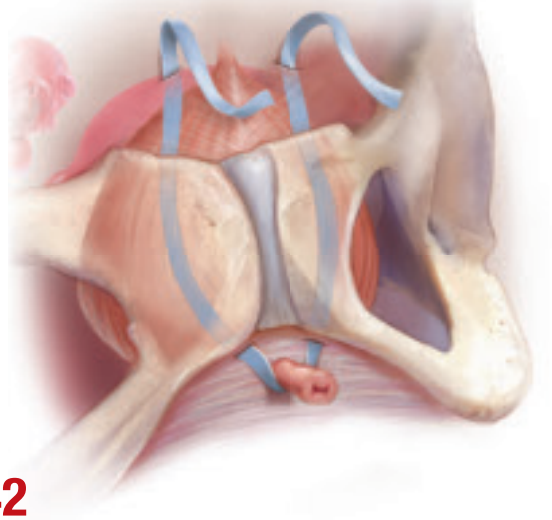







Migraine with aura **10**

EMR and burnout **30**

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†Cologuard specificity: 87% overall specificity, excluding CRC and advanced adenomas, and including all nonadvanced adenomas, nonneoplastic findings, and negative results on colonoscopy. 90% specificity in participants with no lesions biopsied on colonoscopy.[3]

‡Negative predictive value (NPV) is defined as the probability that disease is absent in those with a negative result; it is highly dependent on the prevalence of the disease. NPV was derived from the patient population evaluated in the Imperiale et al publication.[3]

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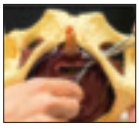

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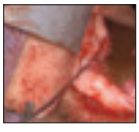

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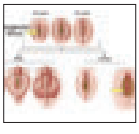

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EDITORIAL

# When providing contraceptive counseling to women with migraine headaches, how do you identify migraine with aura?

The diagnosis of aura is not well understood by primary care clinicians. The Visual Aura Rating Scale (VARS) helps non-neurologists identify those with migraine with aura.

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Most physicians know that migraine with aura is a risk factor for ischemic stroke and that the use of an estrogen-containing contraceptive further increases this risk.[1-3] Additional important and prevalent risk factors for ischemic stroke include cigarette smoking, hypertension, diabetes, and ischemic heart disease.[1] The American College of Obstetricians and Gynecologists (ACOG)[2] and the Centers for Disease Control and Prevention (CDC)[3] recommend against the use of estrogen-containing contraceptives for women with migraine with aura because of the increased risk of ischemic stroke (Medical Eligibility Criteria [MEC] category 4—unacceptable health risk, method not to be used).

However, those who have migraine with aura can use nonhormonal and progestin-only forms of contraception, including copper- and levonorgestrel-intrauterine devices, the etonogestrel subdermal implant, depot medroxyprogesterone acetate, and progestin-only pills (MEC category 1—no restriction).[2,3] ACOG and the CDC advise that estrogen-containing contraceptives can be used for those with migraine without aura who have no other risk factors for stroke (MEC category 2—advantages generally outweigh theoretical or proven risks).[2,3] Given the high prevalence of migraine in reproductive-age women, accurate diagnosis of aura is of paramount importance in order to provide appropriate contraceptive counseling.

*The authors report no financial relationships relevant to this article.*

PHOTO: BLUESTONE/SCIENCE SOURCE

## When is migraine with aura the right diagnosis?

In clinical practice, there is a high level of confusion about the migraine symptoms that warrant a diagnosis of migraine with aura. One approach to improving the accuracy of such a diagnosis is to refer every woman seeking contraceptive counseling who has migraine headaches to a neurologist for expert adjudication of the presence or absence of aura. But in the clinical context of contraceptive counseling, neurology consultation is not always readily available, and requiring consultation increases barriers to care. However, there are tools—such as the Visual Aura Rating Scale (VARS), which is discussed below—that may help nonneurologists identify migraine with aura.[4] First, let us review the data that links migraine with aura with increased risk of ischemic stroke.

### Migraine with aura is a risk factor for stroke

Multiple case-control studies report that migraine with aura is a risk factor for ischemic stroke.[1,5,6] Studies also report that women with migraine with aura who use estrogen-containing contraceptives have an even greater risk of ischemic stroke. For example, one recent case-control study used a commercial claims database of 1,884 cases of ischemic stroke among individuals who identify as women 15 to 49 years of age matched to 7,536 controls without ischemic stroke.[1] In this study, the risk of ischemic stroke was increased more than 2.5-fold by cigarette smoking (adjusted odds ratio [aOR], 2.59), hypertension (aOR, 2.73), diabetes (aOR, 2.78), migraine with aura (aOR, 2.89), and ischemic heart disease (aOR, 5.49). For those with migraine with aura who also used an estrogen-containing contraceptive, the aOR for ischemic stroke was 6.08. By contrast, the risk for stroke among those with migraine with aura who were not using an estrogen-containing contraceptive was 2.65. Furthermore, among those with migraine without aura, the risk of ischemic stroke was only 1.77 with the use of an estrogen-containing contraceptive.

Although women with migraine with and without aura are at increased risk for stroke, the absolute risk is still very low. For example, one review reported that the incidence of ischemic stroke per 100,000 person-years among women 20 to 44 years of age was 2.5 for those without migraine not taking estrogen-containing contraceptives, 5.9 for those with migraine with aura not taking estrogen-containing contraceptives, and 14.5 among those with migraine with aura and taking estrogen-containing contraceptives.[6] Another important observation is that the incidence of thrombotic stroke dramatically increases from adolescence (3.4 per 100,000 person-years) to 45-49 years of age (64.4 per 100,000 person-years).[7] Therefore, older women with migraine are at greater risk for stroke than adolescents.

**TABLE 1** International Headache Society Diagnostic criteria for migraine without aura[8]

A. At least five lifetime attacks fulfilling criteria B through D
B. Headache attacks lasting 4 to 72 hours (untreated or successfully treated)
C. Headache has at least two of the following four characteristics:
   a. Unilateral location
   b. Pulsating quality
   c. Moderate or severe pain intensity
   d. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following:
   a. Nausea or vomiting or both
   b. Photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

## Diagnostic criteria for migraine with and without aura

In contraceptive counseling, if an estrogen-containing contraceptive is being considered, it is important to identify women with migraine headache, determine migraine subtype, assess the frequency of migraines and identify other cardiovascular risk factors, such as hypertension and cigarette smoking. The International Headache Society has evolved the diagnostic criteria for migraine with and without aura, and now endorses the criteria published in the 3rd edition of the International Classification of Headache Disorders (ICHD-3; **TABLES 1** and **2**).[8] For nonneurologists, these criteria may be difficult to remember and impractical to utilize in daily contraceptive counseling. Two simplified tools, the ID Migraine Questionnaire[9] and the Visual Aura Rating Scale (**TABLE 3**)[4] may help identify women who have migraine headaches and assess for the presence of aura.

### The ID Migraine Questionnaire

In a study of 563 people seeking primary care who had headaches in the past 3 months, 3 questions were

**TABLE 2 International Headache Society diagnostic criteria for migraine with aura**[8]

A. At least TWO attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   a. Visual
   b. Sensory
   c. Speech and/or language
   d. Motor
   e. Brainstem
   f. Retinal
C. At least three of the following six characteristics:
   a. At least one aura symptom spreads gradually over ≥ 5 minutes
   b. Two or more aura symptoms occur in succession
   c. Each individual aura symptom lasts 5 to 60 minutes
   d. At least one aura symptom is unilateral
   e. At least one aura symptom is positive (ie, scintillations or pins and needles)
   f. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis (including but not limited to transient ischemic attack, stroke, or seizure)

identified as being helpful in identifying women with migraine. This 3-question screening tool had reasonable sensitivity (81%), specificity (75%), and positive predictive value (93%) compared with expert diagnosis using the ICHD-3.[9] The 3 questions in this screening tool, which are answered "Yes" or "No," are:

During the last 3 months did you have the following symptoms with your headaches:

1. Feel nauseated or sick to your stomach?
2. Light bothered you?
3. Your headaches limited your ability to work, study or do what you needed to do for at least 1 day?

If two questions are answered "Yes" the patient may have migraine headaches.

### Visual Aura Rating Scale for the diagnosis of migraine with aura

More than 90% of women with migraine with aura have visual auras, leaving only a minority with non–visual aura, such as tingling or numbness in a limb, speech or language problems, or muscle weakness. Hence for non-neurologists, it is reasonable to **focus on the accurate diagnosis of visual aura to identify those with migraine with aura.**

In the clinical context of contraceptive counseling, the Visual Aura Rating Scale (VARS) is especially useful because it has good sensitivity and specificity, and it is easy to use in practice (**TABLE 3**).[4] VARS assesses for 5 characteristics of a visual aura, and each characteristic is associated with a weighted risk score. The 5 symptoms assessed include:

1. duration of visual symptom between 5 and 60 minutes (3 points)
2. visual symptom develops gradually over 5 minutes (2 points)
3. scotoma (2 points)
4. zig-zag line (2 points)
5. unilateral (1 point).

Of note, visual aura is usually slow-spreading and persists for more than 5 minutes but less than 60 minutes. If a visual symptom has a sudden onset and persists for much longer than 60 minutes, concern is heightened for a more serious neurologic diagnosis such as transient ischemic attack or stroke. A summed score of 5 or more points supports the diagnosis of migraine with aura. In one study, VARS had a sensitivity of 91% and specificity of 96% for identifying women with migraine with aura diagnosed by the ICHD-3 criteria.[4]

**TABLE 3 Visual Aura Rating Scale (VARS) for the diagnosis of aura**[4]

| Visual symptom characteristic | Risk score |
|---|---|
| Duration of visual symptom of 5 to 60 minutes | 3 |
| Visual symptom develops gradually over ≥ 5 minutes | 2 |
| Scotoma symptom | 2 |
| Zig-zag line (fortification) | 2 |
| Unilateral (homonymous) | 1 |
| Migraine with aura diagnosis | Summed score ≥ 5 |

## Consider using VARS to identify migraine with aura

Epidemiologic studies report that about 17% of adults have migraine, and about 5% have migraine with aura.[10,11] Consequently, migraine with aura is one of the most common medical conditions encountered during contraceptive counseling.

CONTINUED ON PAGE 50

TO AROM OR NOT TO AROM

# Does early amniotomy during induction of labor increase the risk of cesarean delivery?

**No,** according to data from a systematic review and meta-analysis that included 1,273 women in 4 randomized controlled trials. The authors found no significant difference in cesarean delivery (CD) rates between women randomly assigned after cervical ripening for labor induction to early amniotomy or late amniotomy/spontaneous rupture of membranes. However, the women assigned to early amniotomy had a significantly shorter induction-to-delivery interval of about 5 hours.

*De Vivo V, Carbone L, Saccone G, et al. Early amniotomy after cervical ripening for induction of labor: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol. 2019. doi: 10.1016/j.ajog.2019.07.049.*

EXPERT COMMENTARY

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Induction of labor has doubled over the past 2 decades, with almost 25% of parturients currently undergoing induction in the United States.[1] Labor induction at term is associated with perinatal outcomes similar to those with spontaneous labor, without an increase in the CD rate.[1-3] Although numerous methods for cervical ripening have been evaluated, the safest and most effective method has yet to be determined.[2]

Amniotomy—or artificial rupture of membranes (AROM)—has long been used as a technique for labor induction and for augmentation in women in spontaneous labor. Purported benefits include an increased responsiveness to exogenous oxytocin, decreased interval to delivery, and an increased likelihood of spontaneous vaginal delivery. Risks of amniotomy include injury to the fetus or surrounding tissues, bleeding, nonreassuring fetal testing, cord prolapse, and prolonged rupture of membranes (defined as longer than 18 hours), which is a risk factor for intra-amniotic infection.

The optimal timing of amniotomy is not known. The recent study by De Vivo and colleagues was designed to better understand the risk/benefit ratio of early amniotomy after cervical ripening in women undergoing induction of labor.

## Details of the study

The authors conducted a systematic review and meta-analysis that included 1,273 women

*The authors report no financial relationships relevant to this article.*

FAST TRACK

*Purported benefits of AROM include an increased responsiveness to exogenous oxytocin, decreased interval to delivery, and increased likelihood of spontaneous vaginal delivery*

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

This is the first systematic review to evaluate early versus late amniotomy/spontaneous rupture of membranes after cervical ripening for induction of labor. The study results suggest that amniotomy soon after cervical ripening does not change the likelihood of CD, but it does shorten the induction-to-delivery interval by around 5 hours. Prior studies have shown that early amniotomy in women in spontaneous labor decreases time to delivery by an average of 3 hours.[4] Now we know that this is true also of early amniotomy following cervical ripening for induction of labor.

A number of questions still remain before early amniotomy is introduced into routine practice: Does group B streptococcus colonization status matter? Does this practice increase the risk of chorioamnionitis? At this time, it seems most prudent to individualize amniotomy timing based on a woman's obstetric history, indication for induction, and response to cervical ripening.

**ERROL R. NORWITZ, MD, PHD, MBA, AND DIANA KOLETTIS, MD**

in 4 randomized controlled trials to determine the effectiveness of routine early amniotomy versus late amniotomy/spontaneous rupture of membranes after cervical ripening (with either a Foley catheter or prostaglandins) in women with a singleton vertex fetus undergoing induction of labor in the term or late preterm period.

Early amniotomy was defined as AROM "soon after cervical ripening" (cases); late amniotomy was defined as AROM after the active phase of labor or spontaneous rupture of membranes (controls).

The primary outcome was the incidence of CD. Secondary outcomes included the overall length of labor, latency from induction to delivery, and neonatal morbidity (a composite of birth weight, Apgar scores, meconium-stained amniotic fluid, neonatal sepsis, need for resuscitation, and admission to the neonatal intensive care unit).

**Findings.** Women randomly assigned to early amniotomy had a similar risk of CD compared with controls (31.1% vs 30.9% [relative risk (RR), 1.05; 95% confidence interval (CI), 0.71–1.56]) and a shorter interval from induction to delivery of about 5 hours (mean difference, -4.95 hours [95% CI, -8.12 to -1.78]).

There was no difference in any of the secondary outcome measures, although the number of events was small. Specifically, there was no significant difference in rates of chorioamnionitis between the early and late amniotomy cohorts (7.3% vs 4.8% [RR, 1.47; 95% CI, 0.95–2.28]).

### Study strengths and limitations

This is the first systematic review to evaluate early versus late amniotomy after cervical ripening for induction of labor. "Systematic review and meta-analysis" is not synonymous with a review of the literature. It has its own methodology and is regarded as original research. A strength of this study is that it was performed by a highly credible team who followed established Cochrane and PRISMA methodological and reporting guidelines.

Study weaknesses include the fact that the meta-analysis contained a relatively small number of trials and study participants. It was significantly underpowered to address issues related to neonatal outcome. The 4 trials included were highly variable in terms of maternal parity and indications for labor induction and CD. The definition of "early amniotomy" was inconsistent, and the overall rate of CD varied greatly among the studies (7.9%–41.1%). Multiple pregnancies were excluded. Taken together, these findings may have limited generalizability. ●

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PB-2012116 Rev A

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Although continuation rates and user satisfaction with LARC methods are high, a common reason for discontinuation is unfavorable bleeding patterns. Here, with an eye toward improved patient counseling, we examine recent data on bleeding rates with 3 hormone-releasing IUDs, discuss how early bleeding patterns with the etonogestrel implant correlate with long-term patterns, and address how postpartum timing of etonogestrel implant insertion might—or might not—impact bleeding patterns.

**IN THIS ARTICLE**



**ON THE WEB**

at mdedge.com/obgyn
**Don't miss the tables on LARC discontinuation rates and Belsey definitions of bleeding patterns**

Long-acting reversible contraception (LARC) use continues to increase in the United States. According to the most recent estimates from 2014, 14% of women use either an intrauterine device (IUD) or the etonogestrel implant.[1] Forms of LARC currently available in the United States include:

- 4 hormone-releasing IUDs
- 1 nonhormonal copper IUD, and
- 1 hormonal subdermal implant.

The hormone-releasing IUDs all contain levonorgestrel (LNG). These include two 52-mg LNG products and a 19.5-mg LNG IUD, which are currently approved by the US Food and Drug Administration (FDA) for contraception for 5 continuous years of use. In addition, a 13.5-mg LNG IUD is FDA-approved for 3 years of use. The hormonal subdermal implant, which contains etonogestrel, is FDA-approved for 3 years of use. Although major complications with IUDs (perforation, expulsion, intrauterine infection) and implants (subfascial implantation, distant migration) are rare, adverse effects that can affect continuation—such as irregular bleeding—are more common.[2,3]

Contraceptive discontinuation due to bleeding concerns occurs more frequently with the etonogestrel implant than with LNG IUDs. In a large prospective study in the United States, 13% of women discontinued the implant during 3 years of follow-up due to bleeding pattern changes.[4] In comparison, the 3-year discontinuation rate for bleeding complaints with the 52-mg LNG IUD is 1.5%.[5] The 3-year discontinuation rate is higher with the 19.5-mg and 13.5-mg LNG IUDs (4.9% and 4.7%, respectively).[6] The discontinuation rate for bleeding complaints within 5 years of use remains higher for the 19.5-mg LNG IUD (5.2%) compared with the 52-mg LNG IUD (2.2%).[7,8]

Notably, it is important to use standardized definitions to understand and compare bleeding concerns with LARC use. The Belsey criteria of the World Health Organization (WHO), a standard used for decades, describe bleeding patterns using 90-day reference periods or intervals.[9] Bleeding patterns that

decrease flow (amenorrhea, infrequent bleeding) often are considered favorable, and those that increase bleeding or irregularity often are considered unfavorable. These criteria are commonly used in package labeling to describe bleeding patterns with extended use.

In this Update, we examine recent data evaluating differences in bleeding patterns with the 3 doses of the LNG IUD, predictors of abnormal bleeding with the etonogestrel implant, and the impact of timing on postpartum etonogestrel implant placement.

# Bleeding patterns with progestin-containing IUDs vary according to the LNG dose

*Goldthwaite LM, Creinin MD. Comparing bleeding patterns for the levonorgestrel 52 mg, 19.5 mg, and 13.5 mg intrauterine systems. Contraception. 2019;100:128-131.*

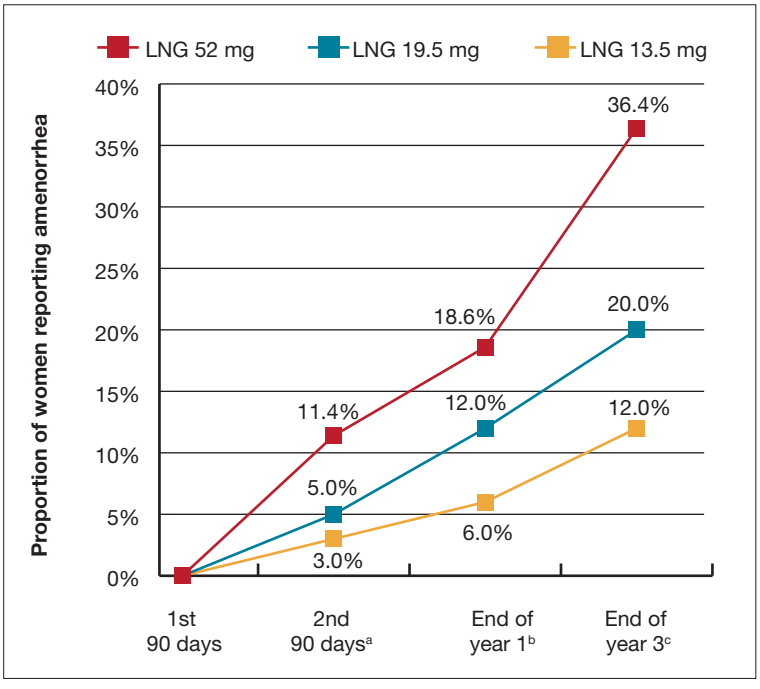
Counseling on IUDs' different hormonal doses requires an understanding of patients' desires for contraceptive efficacy and bleeding expectations. A recent study provides guidance on what patients typically can expect for their bleeding patterns over the first few years with the 3 different doses of LNG IUDs.

Goldthwaite and Creinin used existing published or publicly available data to analyze differences in bleeding patterns associated with the 52-mg, 19.5-mg, and 13.5-mg LNG IUDs. Although two 52-mg LNG IUDs are available, published data using the WHO Belsey criteria are available only for one (Liletta; Allergan, Medicines360). The 2 products have been shown previously to have similar drug-release rates and LNG levels over 5 years.[8]

## Comparing favorable bleeding patterns: Amenorrhea and infrequent bleeding

Among favorable bleeding patterns, amenorrhea was uncommon in the first 90 days and increased over time for all 3 IUDs. However, starting as soon as the second 90-day reference period, amenorrhea rates were significantly higher with the 52-mg LNG IUD compared

**FIGURE 1 Amenorrhea in users of the 52-mg, 19.5-mg, and 13.5-mg LNG IUD**




[a] 52 mg vs 19.5 mg: RR, 1.83 (95% CI, 1.57–2.12)
52 mg vs 13.5 mg: RR, 3.13 (95% CI, 2.56–3.82)
19.5 mg vs 13.5 mg: RR, 1.78 (95% CI, 1.24–2.55)

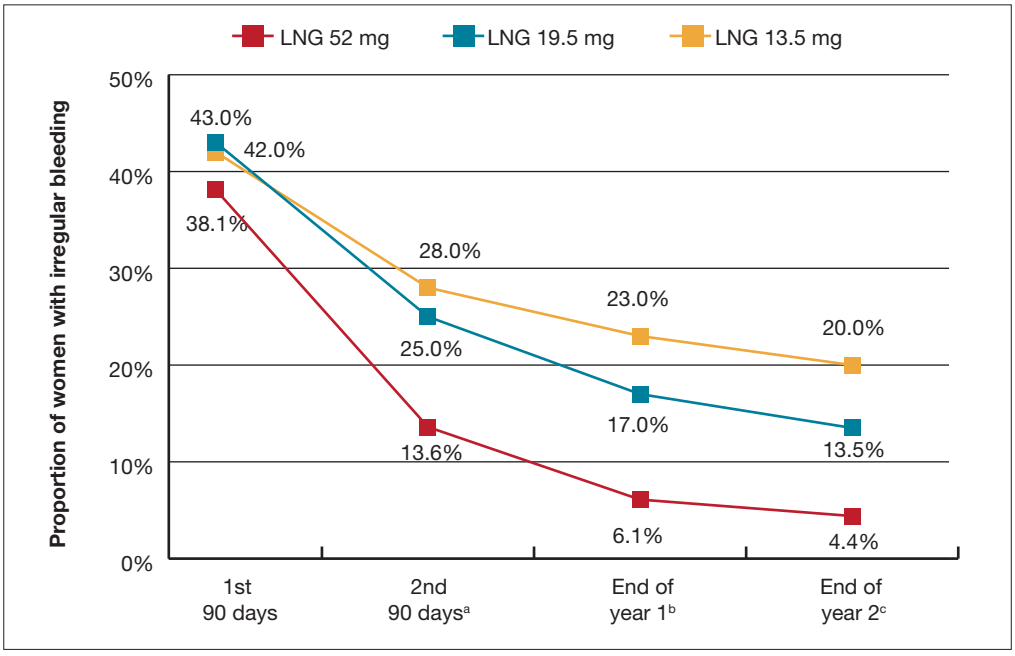
[b] 52 mg vs 19.5 mg: RR, 1.52 (95% CI, 1.27–1.81)
52 mg vs 13.5 mg: RR, 2.98 (95% CI, 2.35–3.76)
19.5 mg vs 13.5 mg: RR, 1.96 (95% CI, 1.52–2.52)

[c] 52 mg vs 19.5 mg: RR, 1.83 (95% CI, 1.57–2.13)
52 mg vs 13.5 mg: RR, 3.13 (95% CI, 2.56–3.82)
19.5 mg vs 13.5 mg: RR, 1.71 (95% CI, 1.37–2.13)

Abbreviations: CI, confidence interval; IUD, intrauterine device; LNG, levonorgestrel; RR, relative risk.

Adapted from Goldthwaite LM, Creinin MD. Comparing bleeding patterns for the levonorgestrel 52 mg, 19.5 mg, and 13.5 mg intrauterine systems. *Contraception*. 2019;100:128-131.

## FIGURE 2 Irregular bleeding rates for users of the 52-mg, 19.5-mg, and 13.5-mg LNG IUD




[a] 52 mg vs 19.5 mg: RR, 0.54 (95% CI, 0.47–0.63)
52 mg vs 13.5 mg: RR, 0.48 (95% CI, 0.42–0.56)
19.5 mg vs 13.5 mg: RR, 0.89 (95% CI, 0.79–1.00)
[b] 52 mg vs 19.5 mg: RR 0.37 (95% CI, 0.30–0.47)
52 mg vs 13.5 mg: RR, 0.27 (95% CI, 0.21–0.34)
19.5 mg vs 13.5 mg: RR, 0.73 (95% CI, 0.63–0.85)
[c] Year 2 estimated by interpolation (data available only for year 1 and year 3). Therefore, statistical testing at end-of-year 2 not calculated.
Abbreviations: CI, confidence interval; IUD, intrauterine device; LNG, levonorgestrel; RR, relative risk.
Adapted from Goldthwaite LM, Creinin MD. Comparing bleeding patterns for the levonorgestrel 52 mg, 19.5 mg, and 13.5 mg intrauterine systems. *Contraception*. 2019;100:128-131.

**FAST TRACK**

*At the end of year 1, 30% of the 52-mg LNG IUD users had infrequent bleeding compared with 26% of the 19.5-mg users (P = .01) and 20% of the 13.5-mg users (P<.0001)*

with both of the lower-LNG dose IUDs, and this difference increased through 3 years of use (**FIGURE 1**, page 17).

Similarly, the 19.5-mg LNG IUD users had significantly higher rates of amenorrhea than the 13.5-mg LNG IUD users for all periods starting with the second 90-day reference period. At 3 years, 36% of women using the 52-mg LNG IUD had amenorrhea compared with 20% of those using the 19.5-mg LNG IUD ($P<.0001$) and 12% of those using the 13.5-mg LNG IUD ($P<.0001$).

Infrequent bleeding was similar for all 3 LNG IUDs in the first 90-day period, and it then increased most rapidly in the 52-mg LNG IUD users. At the end of year 1, 30% of the 52-mg LNG IUD users had infrequent bleeding compared with 26% of the 19.5-mg users ($P = .01$) and 20% of the 13.5-mg users ($P<.0001$). Although there was no difference in infrequent bleeding rates between the 52-mg and the 19.5-mg LNG IUD users at the end of year 1, those using a 52-mg LNG IUD had significantly higher rates of infrequent bleeding compared with the 13.5-mg LNG IUD at all time points.

## Comparing unfavorable bleeding patterns: Frequent, prolonged, and irregular bleeding

Frequent and prolonged bleeding were uncommon with all LNG doses. Irregular bleeding rates declined for users of the 3 IUDs over time. However, significantly fewer users of the 52-mg LNG IUD reported irregular

CONTINUED ON PAGE 26


Symptoms of **postpartum depression** (PPD) can have a negative impact on mothers. If left untreated, these symptoms may persist for months or up to a year.[1]

Not an actual patient.

**INDICATION**

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

**Select IMPORTANT SAFETY INFORMATION for ZULRESSO**

**WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS**

**Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.**

**Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).**

**Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.**

Zulresso™
(brexanolone) injection IV
for intravenous use 100mg/20mL

**Please see Full Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warning, on adjacent pages.**


**Individual results may vary.**

Not an actual patient.

STUDY DESIGN[2,3]

The efficacy of ZULRESSO in the treatment of PPD was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies (referred to as Studies 1 and 2) in women (18 to 45 years) with PPD who met the *Diagnostic and Statistical Manual of Mental Disorders* criteria for a major depressive episode (*DSM-IV*) with onset of symptoms in the third trimester or within 4 weeks of delivery. Women were enrolled up to 6 months postpartum. In these studies, patients received a 60-hour continuous intravenous infusion of ZULRESSO or placebo and were then followed for 4 weeks. Study 1 (NCT02942004) included patients with severe PPD (HAM-D score ≥26), and Study 2 (NCT02942017) included patients with moderate PPD (HAM-D score of 20 to 25). A titration to the recommended target dosage of 90 mcg/kg/hour was evaluated in both studies (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 20 hours, 90 mcg/kg/hour for 28 hours, followed by a taper to 60 mcg/kg/hour for 4 hours and then 30 mcg/kg/hour for 4 hours). A titration to a target dosage of 60 mcg/kg/hour (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 52 hours, then 30 mcg/kg/hour for 4 hours) was also evaluated in Study 1.

The safety of ZULRESSO was evaluated across 3 clinical trials (a Phase II study, Study 1, and Study 2) in 140 women who were exposed to ZULRESSO. The Phase II study evaluated 21 women with severe PPD, 10 of whom received a dose of 90 mcg/kg/hour of ZULRESSO. Baseline oral antidepressant use was reported for 23% of patients.

The primary endpoint was the mean change from baseline in depressive symptoms as measured by the HAM-D total score at the end of the infusion (Hour 60). A pre-specified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at Day 30.

**Select IMPORTANT SAFETY INFORMATION**
**WARNINGS AND PRECAUTIONS**

**Excessive Sedation and Sudden Loss of Consciousness:**
In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

ZULRESSO, the **FIRST AND ONLY** FDA-approved treatment indicated for postpartum depression.

Zulresso™
(brexanolone) injection IV
for intravenous use 100mg/20mL

# Each. Day. Matters.

## RAPID AND SIGNIFICANT IMPROVEMENT OF DEPRESSIVE SYMPTOMS IN 2.5* DAYS[2]

### Study 1

**62.3%** reduction in mean HAM-D total score at Hour 60 with ZULRESSO 90 mcg/kg/hour (n=41)† vs 49.0% with placebo (n=43†; *P*=0.0252‡)

In a group of 38 patients in Study 1, a ZULRESSO titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms.

The recommended dosage of ZULRESSO is 90 mcg/kg/hour.
HAM-D=Hamilton Depression Rating Scale.

### Study 2

**64.6%** reduction in mean HAM-D total score at Hour 60 with ZULRESSO 90 mcg/kg/hour (n=51)† vs 53.3% with placebo (n=53†; *P*=0.0160‡)

*2.5 days=Hour 60.
†Intention to treat population.
‡Statistically significant after multiplicity adjustments.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.

Warnings and precautions for ZULRESSO include: risk of excessive sedation, risk of sudden loss of consciousness, and suicidal thoughts and behaviors.

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

Use in specific populations:

- Pregnancy: May cause fetal harm
- Avoid use in patients with end stage renal disease (ESRD)

**Select IMPORTANT SAFETY INFORMATION**

**ZULRESSO Risk Evaluation and Mitigation Strategy (REMS):**
Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379

**For more information about ZULRESSO treatment and access, visit ZulressoHCP.com**

**Please see Full Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages.**

**References: 1.** Vliegen N, Casalin S, Luyten P. The course of postpartum depression: a review of longitudinal studies. *Harv Rev Psychiatry*. 2014;22(1):1-22. **2.** ZULRESSO Prescribing Information. Cambridge, MA: Sage Therapeutics, Inc; 6/2019. **3.** Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018;392(10152):1058-1070.

## INDICATION

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

## IMPORTANT SAFETY INFORMATION for ZULRESSO

**WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS**

**Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.**

**Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).**

**Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.**

## WARNINGS AND PRECAUTIONS

**Excessive Sedation and Sudden Loss of Consciousness:**
In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

**ZULRESSO Risk Evaluation and Mitigation Strategy (REMS): ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm.**

Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

**SUICIDAL THOUGHTS AND BEHAVIORS**

In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that include approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD).

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. If depression becomes worse or patients experience emergent suicidal thoughts and behaviors, consider changing the therapeutic regimen, including discontinuing ZULRESSO.

**ADVERSE REACTIONS**

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy:** Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm

  There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including ZULRESSO, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/
- **Lactation:** Brexanolone is transferred to breastmilk in nursing mothers. There are no data on the effects of ZULRESSO on a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition
- **Pediatric Use:** The safety and effectiveness of ZULRESSO in pediatric patients have not been established
- **Renal Impairment:** No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment. Avoid use of ZULRESSO in patients with end stage renal disease (ESRD)

**CONTROLLED SUBSTANCE**

ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Zulresso™ (brexanolone) injection IV
for intravenous use 100mg/20mL

**For more information about ZULRESSO treatment and access, visit ZulressoHCP.com**

Sage Therapeutics™



**Please see Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages.**

# ZULRESSO™ (brexanolone) injection (IV), for intravenous use

**Rx only**

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

(For complete details, please see *Full Prescribing Information, including Boxed Warning, and Medication Guide.*)

**WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS**

- **Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO.**
- **Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).**
- **Because of these risks, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.**

**1 INDICATIONS AND USAGE:** ZULRESSO™ is indicated for the treatment of postpartum depression (PPD) in adults.

## 2 DOSAGE AND ADMINISTRATION

A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion.

Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:

- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
- 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
- 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

Dilution required prior to administration.

**4 CONTRAINDICATIONS:** None.

## 5 WARNINGS AND PRECAUTIONS

**5.1 Excessive Sedation and Sudden Loss of Consciousness** In clinical studies, ZULRESSO caused sedation and somnolence that required dose interruption or reduction in some patients during the infusion (5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients). Some patients were also reported to have loss of consciousness or altered state of consciousness during the ZULRESSO infusion (4% of the ZULRESSO-treated patients compared with 0% of the placebo-treated patients). Time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. A healthy 55-year-old man participating in a cardiac repolarization study experienced severe somnolence and <1 minute of apnea while receiving two times the maximum recommended dosage of ZULRESSO (180 mcg/kg/hour). All patients with loss of or altered state of consciousness recovered with dose interruption.

There was no clear association between loss or alteration of consciousness and pattern or timing of dose. Not all patients who experienced a loss or alteration of consciousness reported sedation or somnolence before the episode.During the infusion, monitor patients for sedative effects every 2 hours during planned, non sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation.

After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate.

Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia,the infusion should not be resumed.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving after infusion until any sedative effects of ZULRESSO have dissipated. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness. Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

**5.2 ZULRESSO Risk Evaluation and Mitigation Strategy (REMS)** ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm. Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO.
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

**5.3 Suicidal Thoughts and Behavior** In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

**Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients**

| Age Range (years) | Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated |
|---|---|
| | **Increases Compared to Placebo** |
| <18 | 14 additional patients |
| 18-24 | 5 additional patients |
| | **Decreases Compared to Placebo** |
| 25-64 | 1 fewer patient |

*ZULRESSO is not approved in pediatric patients.

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.

**6 ADVERSE REACTIONS** The following adverse reactions are discussed in more detail in other sections of the labeling:

- Excessive Sedation and Sudden Loss of Consciousness

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

The data described below reflect exposure to ZULRESSO in 140 patients with postpartum depression (PPD). A titration to a target dosage of 90 mcg/kg/hour was evaluated in 102 patients and a titration to a target dose of 60 mcg/kg/hour was evaluated in 38 patients. Patients were then followed for 4 weeks.

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush (Table 2).

*Adverse Reactions Leading to Discontinuation, Dosage Interruption, or Dosage Reduction*

In the pooled placebo controlled-studies, the incidence of patients who discontinued due to any adverse reaction was 2% of ZULRESSO-treated patients compared to 1% of placebo treated patients. The adverse reactions leading to treatment discontinuation in ZULRESSO-treated patients were sedation-related (loss of consciousness, vertigo, syncope, and presyncope) or infusion site pain.

In the pooled placebo controlled-studies, the incidence of patients who had an interruption or reduction of the dosage due to any adverse reaction was 7% of ZULRESSO treated patients compared to 3% of placebo-treated patients. The adverse reactions leading to dose reduction or interruption in ZULRESSO-treated patients were sedation-related (loss of consciousness, syncope, somnolence, dizziness, fatigue), infusion site events, changes in blood pressure, or medication error due to infusion pump malfunction. Three ZULRESSO-treated patients who had a dosage interruption because of loss of consciousness subsequently resumed and completed treatment after resolution of symptoms; two patients who had dosage interruption because of loss of consciousness did not resume the infusion.

Table 2 presents the adverse reactions that occurred in ZULRESSO-treated PPD patients at a rate of at least 2% and at a higher rate than in the placebo-treated patients during the 60 hour treatment period.

**Table 2: Adverse Reactions in Placebo-Controlled Studies in Patients with PPD Reported in ≥ 2% of ZULRESSO-Treated Patients and Greater than Placebo-Treated Patients**

| | Placebo (n=107) | Maximum dosage 60 mcg/kg/hour (n=38) | Maximum dosage 90 mcg/kg/hour (Recommended dosage) (n=102) |
|---|---|---|---|
| **Cardiac Disorders** | | | |
| Tachycardia | - | - | 3% |
| **Gastrointestinal Disorders** | | | |
| Diarrhea | 1% | 3% | 2% |
| Dry mouth | 1% | 11% | 3% |
| Dyspepsia | - | - | 2% |
| Oropharyngeal pain | - | 3% | 2% |
| **Nervous System Disorders** | | | |
| Dizziness, presyncope, vertigo | 7% | 13% | 12% |
| Loss of consciousness | - | 5% | 3% |
| Sedation, somnolence | 6% | 21% | 13% |
| **Vascular Disorders** | | | |
| Flushing, hot flush | - | 5% | 2% |

## 7 DRUG INTERACTIONS

**7.1 CNS Depressants** Concomitant use of ZULRESSO with CNS depressants (e.g., opioids, benzodiazepines) may increase the likelihood or severity of adverse reactions related to sedation.

**7.2 Antidepressants** In the placebo-controlled studies, a higher percentage of ZULRESSO-treated patients who used concomitant antidepressants reported sedation-related events.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Exposure

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.

Risk Summary

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. There are no available data on ZULRESSO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, malformations were not seen in rats or rabbits at plasma levels up to 5 and 6 times the maximum recommended human dose (MRHD), respectively. Developmental toxicities were seen in the fetuses of rats and rabbits at 5 and ≥3 times the plasma levels at the MRHD, respectively. Reproductive toxicities were seen in rabbits at ≥3 times the plasma levels at the MRHD. These effects were not seen in rats and rabbits at 2 and 1.2 times the plasma levels at the MRHD. Brexanolone administered to pregnant rats during pregnancy and lactation resulted in lower pup survival at doses which were associated with ≥2 times the plasma levels at the MRHD and a neurobehavioral deficit in female offspring at 5 times the plasma levels at the MRHD. These effects were not seen at 0.8 times and 2 times the plasma levels at the MRHD, respectively.

In published animal studies, administration of other drugs that enhance GABAergic inhibition to neonatal rats caused widespread apoptotic neurodegeneration in the developing brain. The window of vulnerability to these changes in rats (postnatal days 0-14) corresponds to the period of brain development that takes place during the third trimester of pregnancy in humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

*Animal Data*

In pregnant rats and rabbits, no malformations were seen when brexanolone was given during the period of organogenesis at continuous intravenous doses up to 60 and 30 mg/kg/day, respectively. These doses were associated with maternal plasma levels 5 and 6 times the plasma levels at the MRHD of 90 mcg/kg/hour, in rats and rabbits, respectively. In rats, a decrease in fetal body weights was seen at 60 mg/kg/day (5 times the plasma level at the MRHD). In rabbits, increased numbers of late resorptions and a decrease in fetal body weights were seen at doses equal to and greater than 15 mg/kg/day (3 times the plasma levels at the MRHD) with fewer live fetuses and a higher post implantation loss seen at 30 mg/kg/day (6 times the plasma levels at the MRHD) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain and/or body weight loss). Effects in rats and rabbits were not seen at 2 and 1.2 times the plasma levels at the MRHD, respectively.

When brexanolone was administered to pregnant rats by continuous intravenous administration at 30 and 60 mg/kg/day (2 and 5 times plasma levels at the MRHD, respectively) during the period of organogenesis and throughout pregnancy and lactation, increased numbers of dead pups and fewer live pups at birth were seen. This effect was not seen at 0.8 times the plasma levels at the MRHD. Decreased pup viability between postnatal day 0 and 4 in the presence of maternal toxicity (decreased body weight gain and food consumption during lactation) was seen at 5 times the plasma levels at the MRHD. These effects were not seen at 2 times the plasma levels at the MRHD. A neurobehavioral deficit, characterized by slower habituation in the maximal startle response in the auditory startle test, was seen in female offspring of dams dosed at 5 times the plasma levels at the MRHD. This effect was not seen at 2 times the plasma levels at the MRHD.

### 8.2 Lactation

Risk Summary

Available data from a lactation study in 12 women indicate that brexanolone is transferred to breastmilk in nursing mothers. However, the relative infant dose (RID) is low, 1% to 2% of the maternal weight-adjusted dosage. Also, as ZULRESSO has low oral bioavailability (<5%) in adults, infant exposure is expected to be low. There were no reports of effects of ZULRESSO on milk production. There are no data on the effects of ZULRESSO on a breastfed infant. Available data on the use of ZULRESSO during lactation do not suggest a significant risk of adverse reactions to breastfed infants from exposure to ZULRESSO. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

Data

A study was conducted in twelve healthy adult lactating women treated with intravenous ZULRESSO according to the recommended 60-hour dosing regimen (maximum dosage was 90 mcg/kg/hour). Concentrations of ZULRESSO in breast milk were at low levels (<10 ng/mL) in >95% of women by 36 hours after the end of the infusion of ZULRESSO. The calculated maximum relative infant dose for ZULRESSO during the infusion was 1% to 2%.

**8.4 Pediatric Use** The safety and effectiveness of ZULRESSO in pediatric patients have not been established.

**8.5 Geriatric Use** PPD is a condition associated with pregnancy; there is no geriatric experience with ZULRESSO.

**8.6 Hepatic Impairment** Dosage adjustment in patients with hepatic impairment is not necessary. Modest increases in exposure to unbound brexanolone and modest decreases in exposure to total brexanolone were observed in patients with moderate to severe hepatic impairment (Child-Pugh≥7) with no associated change in tolerability.

**8.7 Renal Impairment** No dosage adjustment is recommended in patients with mild (eGFR 60 to 89 mL/minute/1.73 $m^2$), moderate (eGFR 30 to 59 mL/minute/1.73 $m^2$) or severe (eGFR 15 to 29 mL/minute/1.73 $m^2$) renal impairment.

Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/minute/1.73 $m^2$ because of the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium.

## 9 DRUG ABUSE AND DEPENDENCE

**9.1 Controlled Substance** ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

**9.2 Abuse** In a human abuse potential study, 90 mcg/kg, 180 mcg/kg (two times the maximum recommended infusion rate), and 270 mcg/kg (three times the maximum recommended infusion rate) ZULRESSO infusions over a one hour period were compared to oral alprazolam administration (1.5 mg and 3 mg). On positive subjective measures of "drug liking", "overall drug liking", "high" and "good drug effects", the 90 mcg/kg dosage produced scores that were similar to placebo. Scores on these positive subjective measures for both dosages of ZULRESSO 90 mcg/kg and 180 mcg/kg were lower than both alprazolam doses. However, the scores on the positive subjective measures for ZULRESSO 270 mcg/kg dosage were similar to those produced by both doses of alprazolam. In this study, 3% of subjects administered ZULRESSO 90 mcg/kg and 13% administered ZULRESSO 270 mcg/kg reported euphoric mood, compared to none administered placebo during the one-hour administration.

**9.3 Dependence** In the PPD clinical studies conducted with ZULRESSO, end of treatment occurred through tapering. Thus, in these studies it was not possible to assess whether abrupt discontinuation of ZULRESSO produced withdrawal symptoms indicative of physical dependence. It is recommended that ZULRESSO be tapered according to the dosage recommendations, unless symptoms warrant immediate discontinuation.

## 10 OVERDOSAGE

Human Experience

There is limited clinical trial experience regarding human overdosage with ZULRESSO. In premarketing clinical studies, two cases of accidental overdosage due to infusion pump malfunction resulted in transient loss of consciousness. Both patients regained consciousness approximately 15 minutes after discontinuation of the infusion without supportive measures. After full resolution of symptoms, both patients subsequently resumed and completed treatment. Overdosage may result in excessive sedation, including loss of consciousness and the potential for accompanying respiratory changes.

Management of Overdose

In case of overdosage, stop the infusion immediately and initiate supportive measures as necessary. Brexanolone is rapidly cleared from plasma. Consult a Certified Poison Control Center at **1-800-222-1222** for latest recommendations.

## PATIENT COUNSELING INFORMATION

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

Manufactured for:
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CONTINUED FROM PAGE 18

bleeding at 1 year (6%) compared with users of the 19.5-mg (16.5%, *P*<.0001) and 13.5-mg (23%, *P*<.0001) LNG IUD (**FIGURE 2,** page 18).

### Study limitations

Comparing the data from different studies has limitations. For example, the data were collected from different populations, with the lower-dose LNG products tested in women who had a lower body mass index (BMI) and higher parity. However, prior analysis of the data on the 52-mg LNG IUD demonstrated that bleeding pattern changes did not vary based on these factors.[10]

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

When considering the different progestin-based IUD options, it is important to counsel patients according to their preferences for potential adverse effects. A randomized trial during product development found no difference in systemic adverse effects with the 3 doses of LNG IUD, likely because the systemic hormone levels are incredibly low for all 3 products.[11] The summary data in this report helps explain why women using the lower-dose LNG products have slightly higher discontinuation rates for bleeding complaints, a fact we can explain to our patients during counseling.

Overall, the 52-mg LNG IUD is associated with a higher likelihood of favorable bleeding patterns over the first few years of use, with higher rates of amenorrhea and infrequent bleeding and lower rates of irregular bleeding. For women who prefer to not have periods or to have infrequent periods, the 52-mg LNG IUD is most likely to provide that outcome. For a patient who prefers to have periods, there is no evidence that the lower-dose IUDs result in "regular" or "normal" menstrual bleeding, even though they do result in more bleeding/spotting days overall. To the contrary, the available data show that these women have a significantly higher likelihood of experiencing prolonged, frequent, and irregular bleeding. In fact, no studies have reported rates of "normal" bleeding with the progestin IUDs, likely because women uncommonly have "normal" bleeding with these contraception methods. If a patient does not desire amenorrhea or strongly prefers to have "regular bleeding," alternative methods such as a copper IUD should be considered rather than counseling her toward a lower-dose progestin IUD.

# Predicting long-term bleeding patterns after etonogestrel implant insertion

*Mansour D, Fraser IS, Edelman A, et al. Can initial vaginal bleeding patterns in etonogestrel implant users predict subsequent bleeding in the first two years of use? Contraception. 2019. doi: 10.1016/j.contraception.2019.05.017.*

Data from 2014 indicate that the etonogestrel implant was used by nearly 1 million women in the United States and by 3% of women using contraception.[1] The primary reason women discontinue implant use is because of changes in bleeding patterns. Given the high prevalence of bleeding concerns with the etonogestrel implant, we need more data to help counsel our patients on how they can expect their bleeding to change with implant use.

## Etonogestral implant and bleeding pattern trends

Mansour and colleagues completed a secondary analysis of 12 phase 3 studies to evaluate the correlation between bleeding patterns early after placement of the etonogestrel implant (days 29–118) compared with bleeding patterns through 90-day intervals during the rest of the first year of use. To account for

differences in timing of etonogestrel implant placement relative to the menstrual cycle and discontinuation of other methods like oral contraceptives, bleeding outcomes on days 0–28 were excluded. They also sought to investigate the correlation between bleeding patterns in year 1 compared with those in year 2.

Overall, these studies included 923 individuals across 11 countries; however, for the current analysis, the researchers excluded women from Asian countries who comprised more than 28% of the study population. These women report significantly fewer bleeding/spotting days with the etonogestrel implant and have a lower average body weight compared with European and American women.[12]

A prior analysis of the same data set looked at the number of bleeding/spotting days in groups of users rather than trends in individual patients, and, as mentioned, it also included Asian women, which diluted the overall number of bleeding days.[12] In this new analysis, Mansour and colleagues used the Belsey criteria to analyze individual bleeding patterns as favorable (amenorrhea, infrequent bleeding, normal bleeding) or unfavorable (prolonged and/or frequent bleeding) from a patient perspective. In this way, we can understand trends in bleeding patterns for each patient over time, rather than seeing a static (cross-sectional) report of bleeding patterns at one point in time. Data were analyzed from 537 women in year 1 and 428 women in year 2. During the first 90-day reference period (days 29–118 after implant insertion), 61% of women reported favorable bleeding, and 39% reported unfavorable bleeding.

## Favorable bleeding correlates with favorable patterns later

A favorable bleeding pattern in this first reference period correlated with favorable bleeding patterns through year 1, with 85%, 80%, and 80% of these women having a favorable pattern in reference periods 2, 3, and 4, respectively. Overall, 61% of women with a favorable pattern in reference period 1 had favorable bleeding throughout the entire first year of use. Only 3.7% of women with favorable bleeding in the first reference period discontinued the implant for bleeding in year 1. Further, women with favorable bleeding at year 1 commonly continued to have favorable bleeding in year 2, with a low discontinuation rate (2.5%) in year 2.

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

Individual patients who have a favorable bleeding pattern initially with etonogestrel implant placement are highly likely to continue having favorable bleeding at year 1 and year 2. Notably, of women with a favorable bleeding pattern in any 90-day reference period, about 80% will continue to have a favorable bleeding pattern in the next reference period. These women can be counseled that, even if they have a 90-day period with unfavorable bleeding, about two-thirds will have a favorable pattern in the next reference period. For those with initial unfavorable patterns, about one-third to one-half change to a favorable pattern in subsequent 90-day reference periods. For women who require intervention for unfavorable bleeding but wish to keep their etonogestrel implant, prior data support use of combined oral contraceptive pills, although bleeding resolution seems to be temporary, with 86% of women having bleeding recurrence within 10 days after treatment.[13]

## Initial unfavorable bleeding portends less favorable patterns later

Women who had an unfavorable bleeding pattern initially, however, had a less predictable course over the first year. For those with an initial unfavorable pattern, only 37%, 47%, and 51% reported a favorable pattern in reference periods 2, 3, and 4. Despite these relatively low rates of favorable bleeding, only 13% of the women with an initial unfavorable bleeding pattern discontinued implant use for a bleeding complaint by the end of year 1; this rate was significantly higher than that for women with a favorable initial bleeding pattern ($P<.0001$). The discontinuation rate for bleeding complaints also remained higher in year 2, at 16.5%.

### Limitations and strengths to consider

Although the etonogestrel implant is FDA-approved for 3 years of use, the bleeding data

**FAST TRACK**

*Overall, 61% of women with a favorable pattern in reference period 1 had favorable bleeding throughout the entire first year of use*

from the combined trials included information for only up to 2 years after placement. The studies included also did not uniformly assess BMI, which makes it difficult to find correlations between bleeding patterns and BMI. Importantly, the studies did not include women who were more than 30% above their ideal body weight, so these assessments do not apply to obese users.[12] Exclusion of women from Southeast Asia in this analysis makes this study's findings more generalizable to populations in the United States and Europe.

# Early versus delayed postpartum etonogestrel implant insertion: Similar impacts on 12-month bleeding patterns

**FAST TRACK**

*Twelve-month implant continuation rates were high in both groups: 98% in the early- and 100% in the delayed-insertion group*

*Vieira CS, de Nadai MN, de Melo Pereira do Carmo LS, et al. Timing of postpartum etonogestrel-releasing implant insertion and bleeding patterns, weight change, 12-month continuation and satisfaction rates: a randomized controlled trial. Contraception. 2019. doi:10.1016/j.contraception.2019.05.007.*

Initiation of a desired LARC method shortly after delivery is associated with significant reductions in short interpregnancy intervals.[14] With that goal in mind, Vieira and colleagues compared bleeding patterns in women who received an etonogestrel implant within 48 hours of delivery with those who received an implant at 6 weeks postdelivery.

The study was a secondary analysis of data from a randomized controlled trial of early versus delayed postpartum insertion of the etonogestrel implant conducted in Sao Paulo, Brazil. That primary trial's goal was to examine the impact of early versus delayed implant insertion on infant growth (100 women were randomly assigned to the 2 implant groups); no difference in infant growth at 12 months was seen in the 2 groups.[15] In the secondary analysis, bleeding patterns and BMI were evaluated every 90 days for 12 months. The mean BMI at enrollment postpartum was 29.4 kg/m$^2$ in the early-insertion group and 30.2 kg/m$^2$ for the delayed-insertion group.

## Bleeding patterns with early or delayed implant insertion were similar

Vieira and colleagues found similar bleeding patterns between the groups over 12 months of follow-up. Amenorrhea was reported by 56% of the early-insertion group in the first 90 days and by 62% in the delayed-insertion group. During the last 90 days of the year, 52% of the early-insertion and 46% of the delayed-insertion group reported amenorrhea. Amenorrhea rates did not differ between women who were exclusively breastfeeding and those nonexclusively breastfeeding.

## Continuation rates were high at 1 year

Prolonged bleeding episodes were uncommon in both groups, with only 2% of women reporting prolonged bleeding in any given reference period. Twelve-month implant continuation rates were high in both groups: 98% in the early- and 100% in the delayed-insertion group. Additionally, the investigators found that both groups experienced a

BMI decrease, with no difference between groups (10.3% and 11% in the early- and delayed-insertion groups, respectively).

### Study limitations and strengths

This study included a larger number of participants than prior randomized, controlled trials that evaluated bleeding patterns with postpartum etonogestrel implant insertion, and it had very low rates of loss to follow-up. The study's low rate of 12-month implant discontinuation (2%) is lower than that of other studies that reported rates of 6% to 14%.[16,17] Although the authors stated that this low rate may be due to thorough anticipatory counseling prior to placement, it is also possible that this study population does not reflect all populations. Regardless, the data clearly show that placing an etonogestrel implant prior to hospital discharge, compared with waiting for later placement, does not impact bleeding patterns over the ensuing year. ●

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

For patients who desire an etonogestrel implant for contraception postpartum, we now have additional information to counsel about the impact of implant placement on postpartum bleeding patterns. Overall, bleeding patterns are highly favorable and do not vary whether the implant is placed in the hospital or later. Additionally, the timing of placement does not impact implant continuation rates or BMI changes over 1 year. Further, the primary study assessed infant growth in the early- versus delayed-placement groups and found no differences in infant growth. Although the data are limited, immediate postpartum etonogestrel implant placement does not seem to affect the rate of breastfeeding or the volume of breast milk.[18,19] Timing of implant placement, assuming adequate resources, should be based primarily on patient preference. And, given the correlation of immediate postpartum LARC placement to increased interpregnancy interval, particular efforts should be made to provide the implant in the immediate postpartum period, if the patient desires.[20]


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ROUNDTABLE

# The electronic medical record's role in ObGyn burnout and patient care

These experts share the solutions implemented at their institutions to help cope with the EMR–burnout problem

**Megan L. Evans, MD, MPH; John J. Dougherty, MD, MBA; and Mark B. Woodland, MS, MD**

ILLUSTRATION: PAUL ZWOLAK FOR OBG MANAGEMENT

**IN THIS ARTICLE**



Physician burnout has been labeled a public health crisis by the Harvard School of Public Health and other institutions.[1] A 2018 Physician's Foundation survey found that 78% of physicians had symptoms of burnout,[2] which result from chronic workplace stress and include feeling depleted of energy or exhausted, mentally distanced from or cynical about one's job, and problems getting one's job done successfully.[3] Among ObGyns, almost half (46%) report burnout.[4] One-third of ObGyns responded on a recent Medscape Burnout Report that the computerization of practice is contributing to their burnout, and 54% said too many bureaucratic tasks, including charting, were adding to their burnout.[5]

Inefficient electronic medical records (EMRs) have been implicated as one reason for burnout, with improvements in efficiency cited as one of several potential resolutions to the problem. About 96% of hospitals have adopted EMRs today, compared with only 9% in 2008,[6] and many physicians report recognizing value in the technology. For instance, 60% of participants in Stanford Medicine's

2018 National Physician Poll said EMRs had led to improved patient care. At the same time, however, about as many (59%) said EMRs needed a "complete overhaul" and that the systems had detracted from their professional satisfaction (54%) as well as from their clinical effectiveness (49%).[7]

With this roundtable, we explore the concerns with hours spent on the EMR with several experts, and whether it is a problem that has been contributing to burnout among staff at their institutions. In addition, are there solutions that their institutions have implemented that they can share to help to cope with the problem?

**OBG MANAGEMENT:** ObGyns report that the computerization of practice and too many bureaucratic tasks, including charting, are contributing to burnout. Do you see this problem at your institution?

**John J. Dougherty, MD:** Yes, absolutely. There is not a day that goes by that I don't hear about or experience "Epic Fails." (We use Epic's EMR product at our institution.) Too many clicks are needed to navigate even the simplest tasks—finding notes or results, documenting visits, and billing for services are all unnecessarily complex. In addition, we are being held accountable for achieving a long and growing list of "metrics" measures, education projects (HealthStream), and productivity goals. When do we have time to treat patients? And it is not just practicing physicians and clinicians. Our resident physicians spend an inordinate amount of time in front of the computer documenting, placing orders, and transferring patients using a system with a very inefficient user interface, to say the least.

**Megan L. Evans, MD, MPH:** I absolutely agree. Over the years, my institution has created a conglomerate of EMRs, requiring physicians across the hospital to be fluent in a multitude of systems. For example, you finish your clinic notes in one system, sign off on discharge summaries in another, and complete your operative notes in an entirely different system. As busy attendings, it is hard to keep ahead of all of these tasks, especially when the systems do not talk to one another. Fortunately, my hospital is changing our EMR to a single system within the next year. Until then, however, we will work in this piecemeal system.

**Mark Woodland, MS, MD:** EMR and computerization of medicine is the number 1 issue relating to dissatisfaction by ObGyn providers in our institution. Providers are earnest in their attempt to be compliant with EMR requirements, but the reality is that they are dealing with an automated system that does not have realistic expectations for management of results, follow-up tasks, and patient communications for a human provider. The actual charting, ordering of tests and consults, and communication between providers has been enhanced. However, the "in-basket" of tasks to be accomplished are extraordinary and much of it relies on the provider, which requires an inordinate amount of time. Additionally, while other members of the medical staff are stationary at a desk, physicians and other providers are not. They are mobile between inpatient units, labor and delivery, operating rooms, and emergency rooms. Time management does not always allow for providers to access


## OBG MANAGEMENT Expert Panel

**Megan L. Evans, MD, MPH**
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**John J. Dougherty, MD, MBA**
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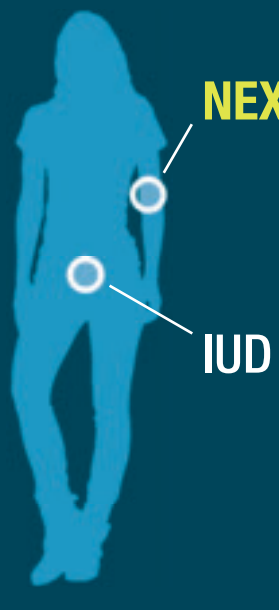
*The authors report no financial relationships relevant to this article.*

**FAST TRACK**

*"EMR and computerization of medicine is the number 1 issue relating to dissatisfaction by ObGyn providers in our institution."*

CONTINUED ON PAGE 36




# Help your patients understand both of their LARC location options[1]

IUD, intrauterine device; LARC, long-acting reversible contraceptive.

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 thrombotic 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 emboli (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.



US-XPL-00588 05/19

# NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

Up to **3 years** of pregnancy prevention*

**>99%** effective†

**Reversible** if her plans change

Placed subdermally just under the skin in the inner upper arm

*NEXPLANON must be removed by the end of the third year and may be replaced by another NEXPLANON at the time of removal, if continued contraceptive protection is desired.

†Less than 1 pregnancy per 100 women who used NEXPLANON for 1 year.

(Actual implant shown; actual implant is 4 cm)

## 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:**

**1.** American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 186: Long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol.* 2017;130(5):e251–e269.

MERCK

# 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.**

**INDICATION AND USAGE**

NEXPLANON is indicated for use by women to prevent pregnancy.

**DOSAGE AND ADMINISTRATION**

The efficacy 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 single NEXPLANON implant is inserted subdermally just under the skin at the inner side of the non-dominant upper arm. The insertion site is overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 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 *[see Dosage and Administration and Warnings and Precautions]*. NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

**CONTRAINDICATIONS**

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
- Allergic reaction to any of the components of NEXPLANON *[see Adverse Reactions]*

**WARNINGS AND PRECAUTIONS**

**The following information is based on experience with the etonogestrel implants (IMPLANON® [etonogestrel implant] and/or NEXPLANON), other progestin-only contraceptives, or experience with combination (estrogen plus progestin) oral contraceptives.**

**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 an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, scarring or infection, may occur.

If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To help reduce the risk of neural or vascular injury, NEXPLANON should be inserted subdermally just under the skin at the inner side of the non-dominant upper arm overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 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 paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable 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, encased in fibrous tissue, or has migrated.

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 deep insertions or intravascular insertion. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed 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 deeply inserted 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 anatomy of the arm. If the implant is located in the chest, healthcare providers familiar with the anatomy of 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 drug-related 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 (absent, 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/or 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 changes 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 (11.1%). Irregular bleeding (10.8%) was the single most common reason women stopped 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 percentages 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.

**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)**

| Total Days of Spotting or Bleeding | Percentage of Patients | | |
|---|---|---|---|
| | Treatment Days 91-180 (N = 745) | Treatment Days 271-360 (N = 657) | Treatment Days 631-720 (N = 547) |
| 0 Days | 19% | 24% | 17% |
| 1-7 Days | 15% | 13% | 12% |
| 8-21 Days | 30% | 30% | 37% |
| >21 Days | 35% | 33% | 35% |

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 2.

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

| Bleeding Patterns | Definitions | %† |
|---|---|---|
| Infrequent | Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea) | 33.6 |
| Amenorrhea | No bleeding and/or spotting in 90 days | 22.2 |
| Prolonged | Any bleeding and/or spotting episode lasting more than 14 days in 90 days | 17.7 |
| Frequent | More than 5 bleeding and/or spotting episodes in 90 days | 6.7 |

* Based on 3315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion

† % = Percentage of 90-day intervals with this pattern

In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

**Ectopic Pregnancies**

As with all 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 venous 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 venous and arterial thromboembolism be carefully assessed. There have been postmarketing reports of serious arterial and venous thromboembolic 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 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, proptosis, diplopia, papilledema, or retinal vascular lesions. 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 are 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 methods like NEXPLANON. The progestin in NEXPLANON may be poorly 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 non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for having the non-radiopaque etonogestrel implant removed.

**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 combination hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

**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 hyperlipidemia 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 etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were 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.

# Nexplanon®
(etonogestrel implant) 68mg

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

***In Situ* 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. Thyroxine 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 (IMPLANON® [etonogestrel implant]) (11.1% 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 (IMPLANON)**

| Adverse Reactions | All Studies N = 942 |
|---|---|
| Bleeding Irregularities* | 11.1% |
| Emotional Lability† | 2.3% |
| Weight Increase | 2.3% |
| Headache | 1.6% |
| Acne | 1.3% |
| Depression‡ | 1.0% |

*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.
‡ Among US subjects (N=330), 2.4% experienced depression 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 (IMPLANON)**

| Adverse Reactions | All Studies N = 942 |
|---|---|
| Headache | 24.9% |
| Vaginitis | 14.5% |
| Weight increase | 13.7% |
| Acne | 13.5% |
| Breast pain | 12.8% |
| Abdominal pain | 10.9% |
| Pharyngitis | 10.5% |
| Leukorrhea | 9.6% |
| Influenza-like symptoms | 7.6% |
| Dizziness | 7.2% |
| Dysmenorrhea | 7.2% |
| Back pain | 6.8% |
| Emotional lability | 6.5% |
| Nausea | 6.4% |
| Pain | 5.6% |
| Nervousness | 5.6% |
| Depression | 5.5% |
| Hypersensitivity | 5.4% |
| Insertion site pain | 5.2% |

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, hematoma (3.0%), bruising (2.0%), pain (1.0%), and swelling (0.7%) were reported.

**Effects of Other Drugs on Hormonal Contraceptives**
***Substances decreasing the plasma concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs:*** Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding.
Some drugs or herbal products that may decrease the effectiveness of HCs include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

***Substances increasing the plasma concentrations of HCs:*** Co-administration of certain HCs and strong or moderate CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole 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:*** Significant changes (increase or decrease) in the plasma concentrations of progestin have been noted in cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine, efavirenz] or increase [e.g., etravirene]). 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 (for example, cyclosporine) or decrease (for example, lamotrigine). Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

**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 etonogestrel during organogenesis at doses of 315 or 781 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. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers.This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

**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 130% 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 time 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**
Overdosage 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 a record of the location of the implant in the upper arm and when it should be removed.
- 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 STDs.
- 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.

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**MERCK & CO., INC.,** Whitehouse Station, NJ 08889, USA.

**For more detailed information, please read the Prescribing Information.**
USPI-MK8415-IPTX-1810r020
Revised: 10/2018



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CONTINUED FROM PAGE 31

computers from all of these areas to facilitate their managing the expectations of the EMR. This requires providers to access the EMR at off hours, extending their workload. Finally, the EMR is neither personal nor friendly. It is not designed with the clinician in mind, and it is not fun or engaging for a provider.

**OBG MANAGEMENT:** What solutions have been instituted in order to help physicians with data entry into the EMR?

**Dr. Dougherty:** When our institution compared EMR offerings, EMR companies put their best collective marketing feet forward. The general notion, at least with the Epic

## Can EMRs be a safety hazard for patients?

EMRs are not just inefficient and contributing to physician burnout, according to a joint report from Kaiser Health News (KHN) and *Fortune* magazine, they are inadequate and contributing to patient safety concerns.[1] This was not the intended goal of the HITECH Act, signed into law in 2009 as part of the stimulus bill. HITECH was intended to promote the adoption of meaningful use of health information technology by providing financial incentives to clinicians to adopt electronic medical records (EMRs). It also intended to increase security for health care data—achieved through larger penalties for HIPAA violations.[2]

Ten years later, however, "America has little to show" for its $36 billion investment, according to KHN and *Fortune*. Yes, 96% of hospitals have one of the currently available EMRs, among thousands, but they are disconnected. And they are "glitchy." At least 2 EMR vendors have reached settlements with the federal government over egregious patient errors. At least 7 deaths have resulted from errors related to the EMR, according to the firm Quantros, reports KHN and *Fortune*, and the number of EMR-related safety events tops 18,000. The problem is that information, critical to a patient's well-being, may get buried in the EMR. Clinicians may not have been aware of, because they did not see, a critical medication allergy or piece of patient history.[1]

The problems with health information technology usability do have solutions, however, asserts Raj M. Ratwani, MD, and colleagues. In a recent article published in the *Journal of the American Medical Association*, the researchers propose 5 priorities for achieving progress[3]:

- Establishment of a national database of usability and safety issues. This database should allow sharing of safety information among EMR vendors, hospitals, and clinicians, and make the public aware of any technology risks.
- Establishment of basic design standards, which should promote innovation and be regulated by a board composed of all stakeholders: EMR vendors, researchers, clinicians, and health care organizations.
- Addressing unintended harms. Causes of harm could include "vendor design and development, vendor and health care organization implementation, and customization by the health care organization." Along with shared responsibility and collaboration comes shared liability for harms caused by inadequate usability.
- Simplification of mandated documentation requirements that affect usability. Reducing clinician's "busy work" would go a long way toward simplifying documentation requirements.
- Development of standard usability and safety measures so that progress can be tracked and the market can react. EMR vendors cannot be directly compared currently, since no standards for usability are in place.

Ratwani and colleagues cite shared responsibility and commitment among all of the parties invested in EMR usability success as keys to solving the current challenges affecting health information technology, with policy makers at the helm.[3] The federal government is attempting to respond: As part of the 2016 21st Century Cures Act and with an aim toward alleviating physician time spent on the EMR, the Department of Health and Human Services is required to recommend reductions to current EMR burdens required under the HITECH Act. It plans to revise E&M codes, lessening documentation. And the Centers for Medicare and Medicaid Services aims to make meaningful use requirements more flexible, require information exchange between providers and patients, and provide incentive to clinicians to allow patient access to EMRs.[4,5]

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1. Fry E, Schulte F. Death by a thousand clicks. *Fortune*. March 18, 2019. http://fortune.com/longform/medical-records/. Accessed September 9, 2019.
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3. Ratwani R, Reider J, Singh H. A decade of health information technology usability challenges and the path forward. *JAMA*. 2019;321:743-744.
4. Hoffman S. Healing the healers: legal remedies for physician burnout. Case Western Reserve University School of Law. September 2018.
5. Morris G, Anthony ES. 21st Century Cures Act overview for states. Office of the National Coordinator for Health Information Technology. https://www.healthit.gov/sites/default/files/curesactlearningsession_1_v6_10818.pdf. Accessed September 11, 2019.

CONTINUED ON PAGE 37

2019

# PAGS PELVIC ANATOMY and GYNECOLOGIC SURGERY SYMPOSIUM

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## ENCORE AT WYNN Las Vegas

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**December 12-14, 2019**

### OPTIONAL HANDS-ON WORKSHOPS
**December 11, 2019**

**OPTIONAL HANDS-ON WORKSHOPS**
**Limited Space Available. First come. First served!**

- Energy-Based Devices for Hysterectomy and Tissue Extraction Techniques **NEW!**
- Laparoscopic Suturing
- Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
- Office-Based Gynecologic Procedures

**SCIENTIFIC SESSION TOPICS INCLUDE:**

- Hysterectomy Techniques
- Incontinence and Prolapse Surgery
- Avoiding and Managing Complications
- Gynecologic Oncology for the Generalist
- Management of Endometriosis
- Medical Legal Cases
- Enhanced Recovery after Surgery
- Benign Gynecology
- Is there any Role for Vaginal Mesh?
- Surgical Tips for Successful Pelvic Surgery Video Session

**PLUS, SPECIAL KEYNOTES**

- The Evolution of Surgical Procedures Used to Correct Pelvic Organ Prolapse
- Techniques to Preserve Level 1 Support at the Time of Vaginal Laparoscopic and Robotic Hysterectomy

**AND,** Optional Post-Conference P.E.P. Practice Management Workshop

## COURSE CHAIRS

**Tommaso Falcone, MD**
Cleveland Clinic London

**Mickey M. Karram, MD**
The Christ Hospital

## SPECIAL KEYNOTE SPEAKER

**Mark D. Walters, MD**
Cleveland Clinic

## Faculty

**Michael S. Baggish, MD**
St. Helena Hospital

**Linda D. Bradley, MD**
Cleveland Clinic

**Andrew I. Brill, MD**
California Pacific Medical Center

**Amanda Nickles Fader, MD**
Johns Hopkins Hospital

**John B. Gebhart, MD, MS**
Mayo Clinic

**Rosanne M. Kho, MD**
Cleveland Clinic

**Javier F. Magrina, MD**
Mayo Clinic Phoenix

**Beri M. Ridgeway, MD**
Cleveland Clinic

For complete information and to register please see our website: **PAGS-cme.org**.

# PAGS AGENDA

Agenda and faculty is subject to change. Please see website for updates.

## WEDNESDAY, DECEMBER 11, 2019

**PRE-CONFERENCE WORKSHOPS**
(Optional, Separate fee required)

**WORKSHOP A** 8:30 AM – 12:30 PM
**Energy-Based Devices for Hysterectomy and Tissue Extraction Techniques NEW!**
Led by: Rosanne M. Kho, MD
4 CME Credits Available

**WORKSHOP B** 8:30 AM – 12:30 PM
**Hands-On Laparoscopic Suturing - The "Vertical Zone" (Simulation Lab)**
Led by: Charles H. Koh, MD
4 CME Credits Available

**WORKSHOP C** 8:30 AM – 5:30 PM
**Office-Based Gynecologic Procedures**
All day workshop (Includes a morning lecture series and afternoon practicum.)
Led by: Tommaso Falcone, MD
8 CME Credits Available

**WORKSHOP D** 1:30 PM – 5:30 PM
**Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist**
Led by: Mickey M. Karram, MD
4 CME Credits Available

### GENERAL SCIENTIFIC SESSIONS

## THURSDAY, DECEMBER 12, 2019

6:45 AM **Registration/Breakfast/Exhibits**

7:50 AM **Course Overview**
Mickey M. Karram, MD

### PELVIC ANATOMY

8:00 AM **Pelvic and Abdominal Anatomy from the Laparoscopic Surgeon's View**
Tommaso Falcone, MD

8:40 AM **Anatomic Considerations: Facilitating Vaginal Procedures Safely and Effectively**
Mickey M. Karram, MD

### INCONTINENCE AND PROLAPSE SURGERY

9:10 AM **Panel Discussion: Evaluation and Non-Surgical Management of Female Pelvic Floor Disorders: What Every Generalist Should Know**
John B. Gebhart, MD, MS
Mickey M. Karram, MD
Beri M. Ridgeway, MD

9:55 AM **Question and Answer Session**

10:25 AM **Break/Exhibits**

11:25 AM **Surgery for Stress Incontinence and the Future of Synthetic Slings**
Beri M. Ridgeway, MD

12:05 PM **Surgery for Pelvic Organ Prolapse: Do We Need to Perform and Teach More Transvaginal Native Tissue Suture Repairs?**
John B. Gebhart, MD, MS

12:25 PM **Mesh-Augmented Prolapse Repair: Is There Any Role for Vaginal Mesh: Indication and Technique of Sacral Colpopexy**
Beri M. Ridgeway, MD

12:55 PM **Question and Answer Session**

1:10 PM **Lunch**

1:25 PM **Luncheon Symposium**

2:10 PM **Dessert Break/ Exhibits**

### THURSDAY'S KEYNOTE LECTURE

2:40 PM **The Evolution of Surgical Procedures Used to Correct Pelvic Organ Prolapse**
Mark D. Walters, MD

### BENIGN GYNECOLOGY

3:25 PM **Safe Use of Energy-Based Devices for Gynecologic Surgery**
Andrew I. Brill, MD

3:55 PM **Management of Endometriosis**
Tommaso Falcone, MD

4:40 PM **The Hysteroscopic Treatment of Submucosal Fibroids and Polyps**
Linda D. Bradley, MD

5:10 PM **Question and Answer Session**

## FRIDAY, DECEMBER 13, 2019

6:45 AM **Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

### HYSTERECTOMY - TECHNIQUE

8:15 AM **The Difficult Vaginal Hysterectomy**
Rosanne M. Kho, MD

8:45 AM **When is it Appropriate to Remove Ovaries at Hysterectomy?**
Amanda Nickles Fader, MD

9:15 AM **Total Laparoscopic Hysterectomy**
Andrew I. Brill, MD

9:45 AM **Break /Exhibits**

10:30 AM **Robotic Hysterectomy**
Javier F. Magrina, MD

11:00 AM **Tissue Extraction Techniques (Morcellation)**
Rosanne M. Kho, MD

11:30 AM **Uterine Preserving Procedures in Patients with Pelvic Organ Prolapse**
Mickey M. Karram, MD
Beri M. Ridgeway, MD

12:00 PM **Enhanced Recovery after Surgery**
Javier F. Magrina, MD

12:30 PM **Question and Answer Session**

1:00 PM **Lunch**

1:15 PM **Luncheon Symposium**

2:00 PM **Dessert Break/Exhibits**

### FRIDAY'S KEYNOTE LECTURE

2:30 PM **Techniques to Preserve Level 1 Support at the Time of Vaginal Laparoscopic and Robotic Hysterectomy**
Mark D. Walters, MD

### ONCOLOGY FOR THE GENERALIST

3:15 PM **Surgical Management of Pre-Cancer Vulvovaginal Lesions**
Amanda Nickles Fader, MD

4:00 PM **Laparoscopic and Robotic Management of the Adnexal Mass**
Javier F. Magrina, MD

4:45 PM **Spectrum of Vulvovaginal Disorders**
Michael S. Baggish, MD

5:30 PM **Question and Answer Session**

## SATURDAY, DECEMBER 14, 2019

6:30 AM **Breakfast**

7:30 AM **Myomectomy: Open to Robotic Approaches**
Tommaso Falcone, MD

8:30 AM **Avoiding and Managing Urogynecologic Complications**
John B. Gebhart, MD, MS
Mickey M. Karram, MD

9:30 AM **Avoiding and Managing Laparoscopic Complications**
Tommaso Falcone, MD

10:30AM **Break**

10:45AM **Interesting Case Presentations in Medical Legal**
Michael S. Baggish, MD
Tommaso Falcone, MD

11:30 AM **Surgical Tips for Successful Pelvic Surgery: Video Session**
Surgical Management of Cornual Ectopic & Dermoid Cysts
Tommaso Falcone, MD

Techniques to Suspend the Apex at the Time of Vaginal Surgery
Mickey M. Karram, MD

1:00 PM **Question and Answer Session**

1:15 PM **PAGS Scientific Program Adjournment**

## P.E.P. PRACTICE ENHANCEMENT PROGRAM AGENDA (Optional)

Open to Non-Attendees So bring your staff!

3.25 CME Credits Available

Make Your Practice More Profitable, Efficient, and Productive!

**Director**
**Neil H. Baum, MD**
Former Associate Clinical Professor of Urology
Tulane Medical School and Louisiana State University, New Orleans, Louisiana

Author, *The Complete Business Guide to a Successful Medical Practice* and *3-Stages of a Physician's Career*

**Faculty**
**Stephanie Stinchcomb Storck, CPC, CCS-P, ACS-UR**

## SATURDAY, DECEMBER 14, 2019 Encore at Wynn Las Vegas

2:00 PM **Course Overview**

2:10 PM
- Improving the efficiency and the productivity of the gynecologic practice
- Harnessing social media for the gynecologic practice
- Financial planning for gynecologists

3:30 PM **Break**

3:45 PM
- Coding update for gynecologists
- Numbers you should know
- Mindfulness for doctors
* Physician burnout

5:00 PM **Q and A**

5:30 PM **P.E.P. Adjournment**

# PAGS Scientific Faculty

## Course Chairs

**Tommaso Falcone, MD**
Chief of Staff
Chief Academic Officer
Medical Director
Cleveland Clinic London
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
London, UK

**Mickey M. Karram, MD**
Director of Urogynecology
The Christ Hospital
Volunteer Professor of Ob/Gyn
University of Cincinnati
Cincinnati, Ohio

## Special Keynote Speaker

**Mark D. Walters, MD**
Professor and Vice-Chair of Gynecology
Department of Obstetrics and Gynecology
Cleveland Clinic
Cleveland, Ohio

## Faculty

**Michael S. Baggish, MD**
Professor of Obstetrics and Gynecology
University of California San Francisco
St. Helena, California

**Linda D. Bradley, MD**
Vice Chair
Obstetrics, Gynecology, and Women's Health Institute
Director
Center for Menstrual Disorders
Professor of Surgery
Cleveland Clinic
Cleveland, Ohio

**Andrew I. Brill, MD**
Director
Minimally Invasive Gynecology & Surgical Education
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San Francisco, California

**Amanda Nickles Fader, MD**
Associate Professor and Director
Kelly Gynecologic Oncology Service
Director of Minimally Invasive Surgery
Department of Gynecology/Obstetrics
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Baltimore, Maryland

**John B. Gebhart, MD, MS**
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**Rosanne M. Kho, MD**
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Director
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Cleveland, Ohio

**Javier F. Magrina, MD**
Professor of Obstetrics and Gynecology
Barbara Woodward Lips Professor
Mayo Clinic
Phoenix, Arizona

**Beri M. Ridgeway, MD**
Department Chair, Regional Ob/Gyn
Cleveland Clinic
Assistant Professor
Cleveland Clinic Learner College of Medicine
Cleveland, Ohio

# Optional Workshops

For complete information please see PAGS-CME.org.

**Wednesday, December 11, 2019, Encore at Wynn Las Vegas**

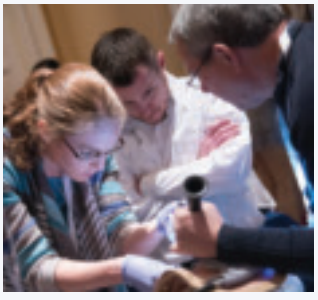
**Optional Hands-on Workshops**

*PAGS hands-on workshops have limited space available and will sell out. First come. First served!*

**(See PAGS website for complete workshop details.)**

**WORKSHOP A**
**ENERGY-BASED DEVICES FOR HYSTERECTOMY AND TISSUE EXTRACTION TECHNIQUES NEW!**
*4 CME Credits Available*
**8:30 AM - 12:30 PM**
**Led by: Rosanne M. Kho, MD**
Faculty: Andrew I. Brill, MD; Keith B. Isaacson, MD

**WORKSHOP B**
**HANDS-ON LAPAROSCOPIC SUTURING - THE "VERTICAL ZONE" (SIMULATION LAB)**
*4 CME Credits Available*
**8:30 AM - 12:30 PM**
**Led by: Charles H. Koh, MD**



**WORKSHOP C**
**OFFICE-BASED GYNECOLOGIC PROCEDURES: THE GYNECOLOGIST OF THE FUTURE**
FULL-DAY WORKSHOP
*8 CME Credits Available*
**8:30 AM - 5:30 PM**
Includes a morning lecture series and afternoon practicum on vulvar/vaginal injections and excisions, ultrasound and hysteroscopy

**Led by: Tommaso Falcone, MD**
Faculty: Andrew Brill, MD; Linda D. Bradley, MD; Mark Dassel, MD; Jeffrey R. Dell, MD; Laura Detti, MD; Oluwatosin Goje, MD; Keith Isaacson, MD; Mickey Karram, MD; James M. Shwayder, MD, JD

**WORKSHOP D**
**TECHNICAL ASPECTS OF VAGINAL HYSTERECTOMY & CYSTOURETHROSCOPY FOR THE GYNECOLOGIST**
*4 CME Credits Available*
**1:30 PM - 5:30 PM**
**Led by: Mickey M. Karram, MD**
Faculty: Rosanne M. Kho, MD; Doug Miyazaki, MD

# Who Should Attend?

The PAGS conference is designed for obstetricians/gynecologists, second, third and fourth-year residents in Ob/Gyn, as well as sub-specialty fellows and advanced practice clinicians. Residents and advanced practice health clinicians are welcome at reduced rates.

## ACCREDITATION

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Cincinnati and Global Academy for Medical Education, LLC. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

The University of Cincinnati designates this Live Activity for 20 *AMA PRA Category 1 credits*™ for the conference and (1) 8-hour pre-conference workshops at 8.0 *AMA PRA Category 1 credits*™, (3) 4-hour pre-conference hands-on workshops at 4.0 *AMA PRA Category 1 credits*™ each and (1) post workshop at 3.25 *AMA PRA Category 1 credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

2019

# PAGS PELVIC ANATOMY and GYNECOLOGIC SURGERY SYMPOSIUM

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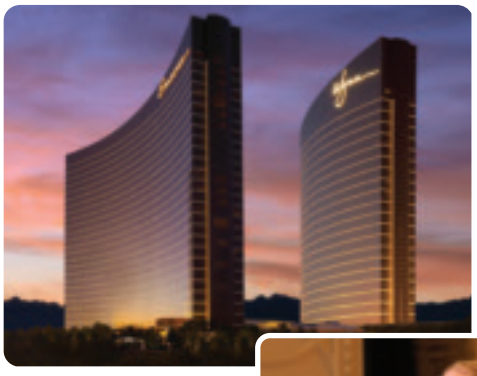
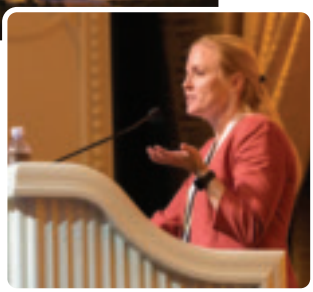




### What Your Colleagues Say About PAGS:

"LOVE this meeting."

"Excellent topics and presentation was superb"

"Enjoy and appreciated attending as have attended twice. Was straightforward and topics covered very well."

"Thank you for an excellent program!"

"This is such good educational time. I love how there is something current and relevant everytime I attend (this is my third time)."

"Continue with what you do and that is provide 2 ½ days of excellent information to the average practicing Ob/Gyn."

"This is a fantastic conference year after year! I have travelled from Australia on three occasions to attend."

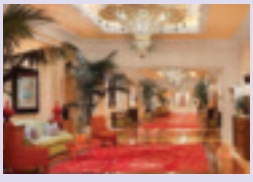
***Optional*** **HANDS-ON WORKSHOPS**
**8 CME Credits Available**
**December 11, 2019**

**SCIENTIFIC SESSIONS**
**20 CME Credits Available**
**December 12-14, 2019**

***Optional*** **"P.E.P." PRACTICE MANAGEMENT PROGRAM**
**3.25 CME Credits Available**
**December 14, 2019**

## About Our Venue

### Encore at Wynn Las Vegas



The 2019 Pelvic Anatomy and Gynecologic Surgery Symposium (PAGS) will take place at the Encore Wynn Las Vegas where we have arranged for a discount room rate of **just $179* a night for PAGS participants.** To make your reservation, please call (866) 770-7555. You must identify yourself as a Pelvic Anatomy and Gynecologic Surgery Symposium 2019 attendee or reference the block code: 6PAG1219 to receive the discounted rate.

**Discount room rate expires November 12, but we urge you to make your arrangements as soon as possible as our room block will sell out.**

*Plus $25 amenity fee

## How to Register for PAGS

**Online: www.PAGS-CME.org**
**Inquiries: PAGS@globalacademycme.com**

| | Until Nov 8 | After Nov 8 |
|---|---|---|
| **PAGS Scientific Program** | | |
| ■ Physicians | $895 | $995 |
| ■ Residents, Fellows, Allied Health | $750 | $795 |
| ■ **P.E.P. Program only**<br>Also open to non-attendees | $395 | $495 |
| ■ **Best Buy!**<br>PAGS + P.E.P. Discount Combination Package | $1,195 | $1,395 |
| ■ **Office-Based Gynecologic Procedures: The Gynecologist of the Future All Day Workshop** | $495 | $545 |
| ■ **Laparoscopic Suturing Morning Workshop** | $275 | $345 |
| ■ **Energy-Based Devices for Hysterectomy and Tissue Extraction Techniques** | $275 | $345 |
| ■ **Vaginal Hysterectomy & Cystourethroscopy Afternoon Workshop** | $350 | $395 |

Cancellation Policy: Full refund less a $50 administrative fee as follows: Cancellations can be made using our online registration system until November 12, 2019. After November 12, 2019 no refunds will be granted. After the refund date, you have two options: you can send someone in your place, or we can mark a credit in the amount you paid minus $50 administration fee, (plus additional $35 administration fee per workshop) to be applied to your registration for next year's conference. Refunds will not be issued to no-shows.

**To register and for complete information please see our website: PAGS-cme.org.**

CONTINUED FROM PAGE 36

EMR, was that "you can customize Epic to your liking." It did not take long for a bunch of motivated Epic users to create "smart" stuff (lists, phrases, and texts) in an effort to customize workflows and create fancy-looking electronic notes. Shortly thereafter, it was obvious that, as an institution, our reporting efforts kept coming up short—our reports lacked accuracy and meaning. Everyone was documenting in different ways and in different areas. Considering that reports are currently generated using (mostly) discrete data entries (data placed in specific fields within the EMR), it became obvious that our data entry paradigm needed to change. Therefore, standardization became the leading buzzword. Our institution recently initiated a project aimed at standardizing our workflows and documentation habits. In addition, we have incorporated a third-party information exchange product into our health system data aggregation and analysis workflow. Much more needs to be done, but it is a start.

**Dr. Evans:** At my institution, as a group, we have created templates for routine procedures and visits that also auto populate billing codes. I know that some departments have used scribes. From the hospital side, there has been improved access to the EMR from home. Some of my colleagues like this feature; however, others, like myself, believe this contributes to some of our burnout. I like to leave work at work. Having the ability to continue working at home is not a solution in my mind.

**Dr. Woodland:** At our institution, we have engaged our chaperones and medical assistants to help facilitate completion of the medical records during the office visit. Providers work with their assistants to accommodate documentation of history and physical findings while also listening to the provider as they are speaking in order to document patient care plans and orders. This saves the clinicians time in reviewing and editing the record as well as making sure the appropriate care plan is instituted. Our EMR provider recently has begun experimenting with personalization of color themes as well as pictures as part of the interface. Having said this, I still ask, "Why have medical professionals allowed non–clinical agencies and information technology groups to run this show?" It is also inconceivable to me that this unfunded mandate—that has increased cost, decreased clinical efficiency, and decreased clinician satisfaction—has not been addressed by national and international medical communities.

CONTINUED ON PAGE 38

## 6 tips for improving use of the EMR

1. **Engage the computer in your patient encounter,** says Rey Wuerth and colleagues. Share the screen, and any test results you are highlighting, with your patient by turning it toward her during your discussion. This can increase patient satisfaction.[1]
2. **Go mobile at the point of care,** suggests Tom Giannulli, MD, MS, Chief Medical Information Officer at Kareo. By using a tablet or mobile device, you can enter data while facing a patient or on the go.[2]
3. **Use templates when documenting data,** advises Wuerth and colleagues, as pre-filled templates, that are provided through the EMR or that you create within the EMR, can reduce the time required to enter patient visits, findings, and referrals.[1]
4. **Delegate responsibility for routing documents,** says Brian Anderson, MD. Hand off to staff administrative duties, such as patient forms and routine negative test results.[3]
5. **Involve medical assistants (MAs) in the process.** Make the MA feel part of the team, says R. Scott Eden, and assign them history-taking responsibilities, utilizing your EMR's templates. Assign them other tasks as well, including medication reconciliation, referrals, refills, routine screening, and patient education.[4]
6. **Employ physical or virtual scribes who are specifically assigned to EMR duty.** Although drawbacks can include patient privacy concerns and reduced practice income due to salary requirements, employing a scribe (often a pre-medical or graduate student), who trails you on patient visits, or who is connected virtually, can leave the clinician free to interact with patients.[5,6]

**References**

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**FAST TRACK**

*"One great piece of advice I received was to be satisfied with good notes, not perfect notes."*

**OBG MANAGEMENT:** What changes do you feel your EMR system needs to undergo?

**Dr. Woodland:** I feel that we need to appropriately manage expectations of the EMR and the institution with relation to EMR and providers. By this I mean that we need to make the EMR more user-friendly and appropriate for different clinicians as well as patients. We also need to manage expectations of our patients. In a digital age where immediate contact is the norm, we need to address the issue that the EMR is not social media but rather a communication tool for routine contact and information transmission. Emergencies are not typically addressed well through the EMR platform; they are better handled with a more appropriate communication interface.

**Dr. Dougherty:** I feel that the biggest change needed is a competent, simple, and standard user-interface. Our old charting methods were great on a number of levels. For instance, if I wanted to add an order, I flipped to the "Orders" tab and entered an order. If I needed to document a note, I flipped to the "Notes" tab and started writing, etc. Obviously, manual charting had its downsides—like trying to decipher handwriting art! EMRs could easily adopt the stuff that worked from our old methods of documentation, while leveraging the advantages that computerized workflows can bring to practitioners, including efficient transfer of records, meaningful reporting, simple electronic ordering, and interprofessional communication portals.

**Dr. Evans:** Our systems need to better communicate with one another. I am in an academic practice, and I should be able to see labs, consultant notes, imaging, all in one spot to improve efficiency and ease with patient visits. Minimizing clicks would be helpful as well. I try to write as much as I can while in the room with a patient to avoid after-hours note writing, but it takes away from my interaction with each patient.

**OBG MANAGEMENT:** With an aim toward alleviating burnout, are there any tips you can offer your colleagues on interfacing with the EMR?

**Dr. Evans:** When I first started as a new attending, it would take me hours to finish my notes, partly because of the level of detail I would write in my history of present illness (HPI) and assessment and plan. One great piece of advice I received was to be satisfied with good notes, not perfect notes. I worked to consolidate my thoughts and use preconstructed phrases/paragraphs on common problems I saw. This saved time to focus on other aspects of my academic job.

**Dr. Dougherty:** We need to refocus on the patient first, and mold our systems to meet that priority. Much too often, we have our backs to the patients or spend too much time interfacing with our EMR systems, and our patients are not happy about it (as many surveys have demonstrated). More importantly, a renewed focus on patient care, not EMR care, would allow our practitioners to do what they signed up for—treating patients. In the meantime, I would suggest that practitioners stay away from EMR gimmicks and go back to old-style documentation practices (like those established by the Centers for Medicare and Medicaid Services in 1997 and 1998), and ask the IT folks to help with molding the EMR systems to meet your own standards, not the standards established by EMR companies. I am also very hopeful that the consumer will drive most of the health care-related data collection in the near future, thereby marginalizing the current generation of EMR systems.

**Dr. Woodland:** I would add that providers need to manage the EMR and not let the EMR manage them. Set up task reminders at point times to handle results and communications from the EMR and set up time in your schedule where you can facilitate meeting these tasks. When providers are out on vacation, make sure to have an out-of-office reminder built into their EMR so that patients and others know timing of potential responses. Try to make the EMR as enjoyable as possible and focus on the good points of the EMR, such as legibility, order verification, safety, and documentation.

**OBG MANAGEMENT:** Do you feel that the EMR has led to improved patient care?

**Dr. Evans:** Yes and no. Yes, in that it can be much easier to follow a patient's health care

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1. Ackerman SJ, Wahl PM, Knight T, Cartwright, CP. Healthcare Resource Utilization and Costs of Amplified Versus Non-amplified Molecular Probe Testing for Vaginitis/Vaginosis: A U. S. Commercial Payer Perspective. LabCorp.

CONTINUED FROM PAGE 38

history from other provider notes or prior surgeries. Information is searchable and legible. If an EMR is built correctly, it can save time for providers, through smart phrases and templates, and it can help providers with proper billing codes and documentation requirements. No, in that it can take away from important patient interaction. We are required to see more patients in less time all while using, at times, a cumbersome EMR system.

**Dr. Woodland:** This is a tricky question because the EMR has both positive and negative attributes. Certainly, the legibility and order verification has improved, but the ease of accessing information in the EMR has changed. Additionally, there has been a drastic increase in provider dissatisfaction that has not been addressed. Provider dissatisfaction can lead to problems in patient care. If there was a clear-cut increased value for the cost, I do not think the EMR would be such a huge focus of negative attention. Providers need to take back control of their EMR and their profession so that they can utilize the EMR as the tool it was supposed to be and not the dissatisfier that it has become.

**Dr. Dougherty:** I do not believe patient care has been improved by EMR systems, for all of the reasons we have discussed, and then some. But there is an enormous amount of potential, *if* we get the interface between humans and EMR systems right! ●

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# Using slings for the surgical management of urinary incontinence: A safe, effective, evidence-based approach

Sling procedures are a mainstay of surgical treatment for SUI. Here, 2 experts offer case vignettes to illustrate the considerations involved in selecting the appropriate sling and counseling the patient.

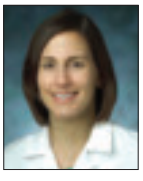
**Nancy Ringel, MD, and Lee A. Richter, MD**

**IN THIS ARTICLE**



Urinary incontinence affects approximately 50% of women, with up to 80% of these women experiencing stress urinary incontinence (SUI) at some point in their lives.[1-3] While conservative measures can offer some improvement in symptoms, the mainstay of treatment for SUI is surgical intervention.[4,5] The lifetime risk of undergoing surgery for SUI is 13.6%, and surgery leads to a major improvement in quality of life and productivity.[1,6]

Dr. Ringel is Clinical Fellow, Section of Female Pelvic Medicine and Reconstructive Surgery, MedStar Georgetown/Washington Hospital Center, Washington, DC.



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*The authors report no financial relationships relevant to this article.*

## Types of slings used for SUI

Sling procedures are the most commonly used surgical approach for the treatment of SUI. Two types of urethral slings are used: the midurethral sling and the autologous fascial (pubovaginal) sling. The midurethral sling, which is the most frequently used sling today, can be further characterized as the retropubic sling, the transobturator sling, and the mini sling (**FIGURE 1**, page 44).

### Retropubic sling

A retropubic sling is a midurethral mesh sling that is placed beneath the urethra at the midpoint between the urethral meatus and the bladder neck. The arms of the sling extend behind the pubic symphysis, providing a hammock-like support that helps prevent leakage with increased abdominal pressures. The retropubic sling is the most commonly used type of sling. For women presenting with uncomplicated SUI who desire surgical correction, it often is the best choice for providing long-term treatment success.[7]

### Transobturator sling

A transobturator sling is a midurethral mesh

sling that is placed beneath the urethra as described above, but the arms of the sling extend outward through the obturator foramen and into the groin. This enables support of the midurethra, but this sling is less likely to result in such complications as bladder perforation or postoperative urinary retention. Transobturator slings also are associated with lower rates of voiding dysfunction and urinary urgency than retropubic slings.[7-9] However, transobturator slings have higher rates of groin pain, and they are less effective in maintaining long-term cure of SUI.[7]

First introduced in 1996, the midurethral sling quickly grew in popularity for the treatment of SUI because of its high success rates and its minimally invasive approach.[10] Both retropubic and transobturator slings are safe, extensively researched surgical approaches for the management of SUI.[3] Midurethral slings have a very high rate of incontinence cure (80%–90%) and extremely high patient satisfaction rates (85%–90%), as even patients without complete cure report meaningful symptomatic improvement.[7,8,11]

### Single-incision (mini) sling

A single-incision sling is a midurethral mesh sling that is designed to be shorter in length than standard midurethral slings. The placed sling lies under the midurethra and extends toward the superior edge of the obturator foramen but does not penetrate it. The sling is held in place by small pledgets on either side of the mesh hammock that anchor it in place to the obturator internus muscular fascia. Because this "mini" sling was introduced in 2006, fewer long-term data are available for this sling than for standard midurethral slings.

### Autologous (fascial) sling

An autologous sling is a retropubic sling made from the patient's own fascia; it is harvested from either the fascia lata of the lateral thigh or the rectus fascia of the abdomen. The sling is placed beneath the urethra in the bladder neck region, and sutures affixed to the sling edges pass behind the pubic symphysis and through the abdominal fascia to anchor it in place.

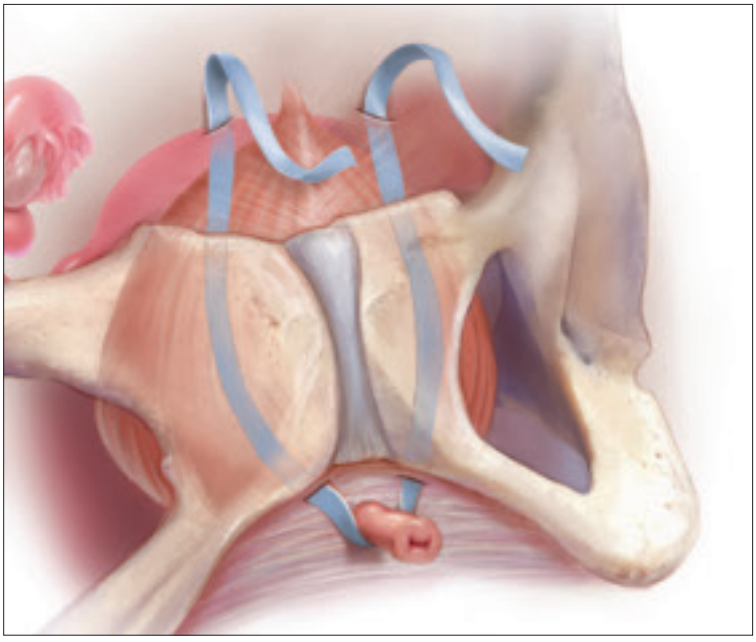


ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

## Choose a sling based on the clinical situation and patient goals

Consider the unique features of each sling when selecting the proper sling; this should be a shared decision with the patient after thorough counseling. Below, we present 4 clinical cases to exemplify scenarios in which different slings are appropriate, and we review the rationale for each selection.

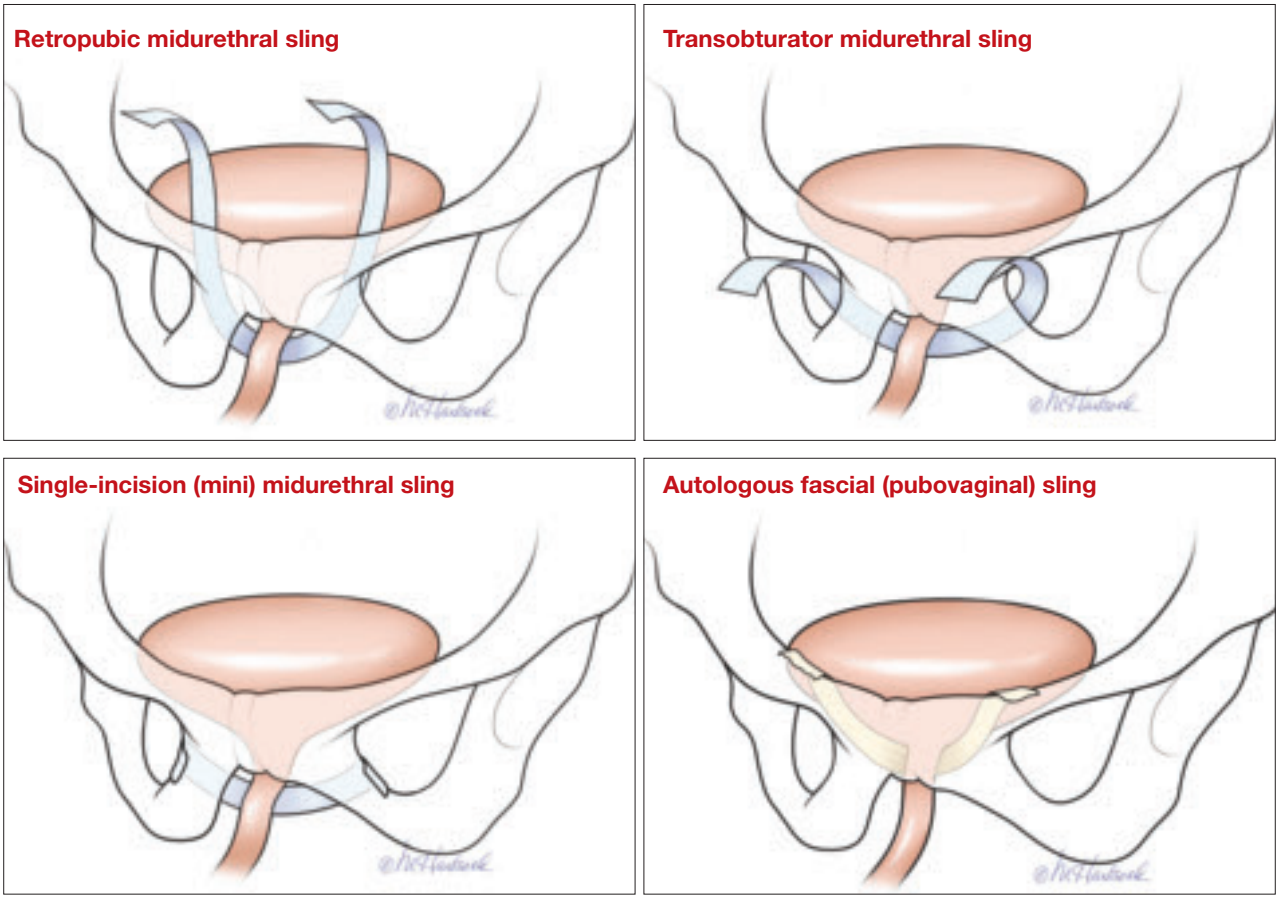
### CASE 1 SUI that interferes with exercise routine

Ms. P. is a 46-year-old (G3P3) active mother. She loves to exercise, but she has been working out less frequently because of embarrassing urinary leakage that occurs with activity. She has tried pelvic floor exercises and changing her fluid intake habits, but improvements have been minimal with these interventions. On evaluation, she has a positive cough stress test with a recently emptied bladder and a normal postvoid residual volume.

What type of sling would be best?

Because this patient is young, active, and has significant leakage with an empty bladder, a sling with good long-term treatment success is likely to provide her with the best results (Figure 1). We therefore offered her a retropubic midurethral sling. The retropubic

## FIGURE 1 Types of slings used in surgical management of SUI

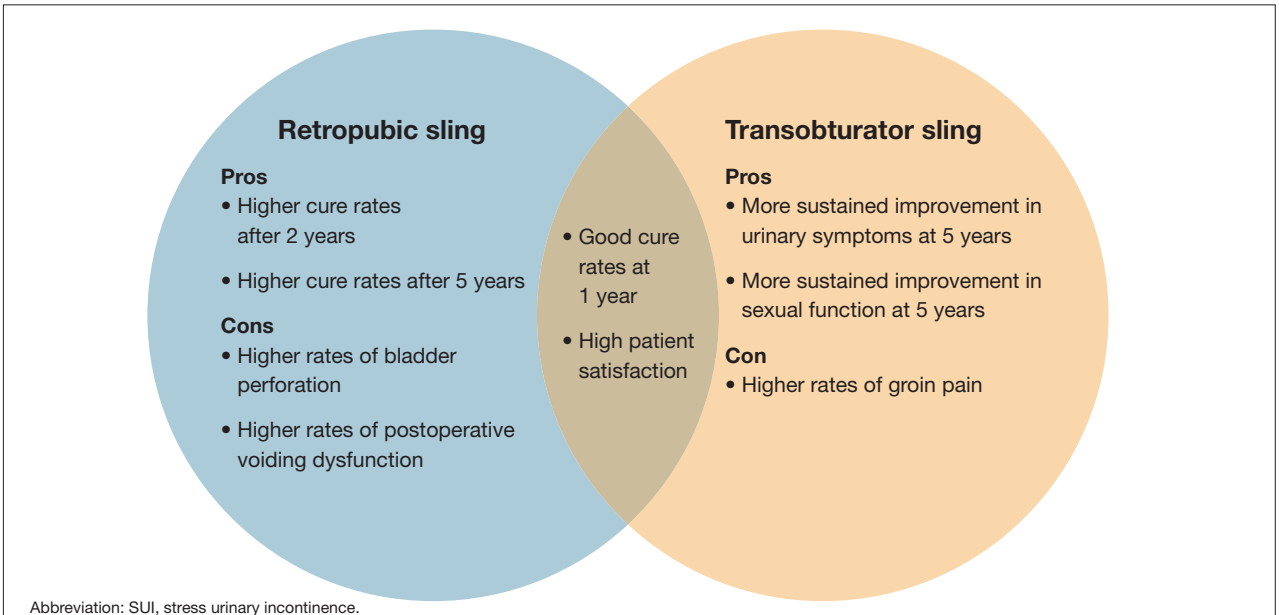



| Type | Retropubic midurethral sling | Transobturator midurethral sling | Single-incision (mini) midurethral sling | Autologous fascial (pubovaginal) sling |
|---|---|---|---|---|
| Description | Mesh sling placed beneath the midurethra with arms extending behind the pubic bone | Mesh sling placed beneath the midurethra with arms through the obturator foramen | Mesh sling placed beneath the midurethra with arms to the obturator foramen | Fascial sling placed beneath the urethra at the level of the bladder neck with arms or suture passing behind the pubic bone |
| Incisions | Anterior vaginal wall<br>Suprapubic | Anterior vaginal wall<br>Groin | Anterior vaginal wall | Anterior vaginal wall<br>Pfannenstiel<br>Lateral thigh (if using fascia lata) |
| Conditions in which to consider use | Uncomplicated SUI<br>Occult SUI<br>Recurrent SUI after prior sling<br>Intrinsic sphincter deficiency | Uncomplicated SUI<br>Occult SUI<br>A need to avoid the retropubic space (eg, patients with renal transplants) | Occult SUI<br>A need to avoid the retropubic space (eg, patients with renal transplants)<br>Desire to minimize incisions | A need to avoid mesh<br>A preference to avoid mesh |

Abbreviation: SUI, stress urinary incontinence.

ILLUSTRATIONS: MARCIA HARTSOCK FOR OBG MANAGEMENT

**FIGURE 2** Pros and cons of the retropubic sling versus the transobturator sling for SUI[7-9]




Abbreviation: SUI, stress urinary incontinence.

approach is preferred here as it is less likely than the transobturator sling to cause groin/thigh pain, which is an important consideration in this young, active patient.

### Further testing is not needed

For women with uncomplicated SUI who demonstrate leakage with stress (coughing, Valsalva stress test) and who have a normal postvoid residual volume, additional testing, such as urodynamic evaluation, is not necessary.[12] These patients can be counseled on the range of conservative management options and as well as surgical inventions.

**CASE 2** Return of SUI symptoms after transobturator sling placement

Ms. E. is a 70-year-old woman who had a transobturator sling placed 5 years ago. Initially, her SUI symptoms improved after surgery. Recently, however, she noticed a return of her SUI, which she finds bothersome and limiting to her quality of life.

How would you manage this patient?

While midurethral slings are highly effective, there are instances in which patients will have symptom recurrence. For women who already have a midurethral sling, consider the following important questions.

### Is this truly recurrent SUI, or is it a new process?

Like any reconstructive procedure, midurethral sling success rates decline over time and recurrent SUI can develop.[7] However, it also is possible for urge urinary incontinence to develop as a new process, and it is important to distinguish which type of urinary incontinence your patient has prior to counseling about treatment options.

To further evaluate patients with recurrent incontinence and a prior sling, we recommend urodynamic studies with cystoscopy (in addition to a detailed history and physical exam). This not only helps rule out other forms of incontinence, such as overactive bladder, but also evaluates for possible mesh erosion into the urethra or bladder, which can cause irritative voiding symptoms and incontinence.

### What type of sling did the patient have initially, and how does this impact a repeat procedure?

Regardless of the initial sling type used, repeat midurethral sling procedures have a

**FAST TRACK**

*Like any reconstructive procedure, midurethral sling success rates decline over time and recurrent SUI can develop*

significantly lower cure rate than primary midurethral sling procedures.[13] Retropubic slings are more effective than transobturator slings for patients with recurrent SUI who have failed a prior sling. When a patient presents with recurrent SUI after a prior transobturator sling, the best option for a repeat procedure is usually a retropubic sling, as it achieves higher objective and subjective cure rates.[13,14] (See **FIGURE 2,** page 45, for a comparison of retropubic and transobturator slings.)

### Should I remove the old sling prior to placing a new one?

While it is recommended to remove the vaginal portion of the sling if the patient has a mesh exposure or is experiencing other symptoms, such as pain or bleeding, removal of the old sling is not necessarily indicated prior to (or during) a repeat incontinence procedure.[15,16] Removing the sling, removing a portion of the sling, or leaving the sling in situ are all reasonable options.

### CASE 3 Treated SUI has mesh exposure

Ms. R. is a 60-year-old woman with a history of SUI that was previously managed with a retropubic midurethral sling placed at an outside hospital. She is a smoker and has developed a vaginal mesh exposure. Although she would like the mesh removed, she does not want her incontinence to come back. She tells you that she does not think she would be able to quit smoking.

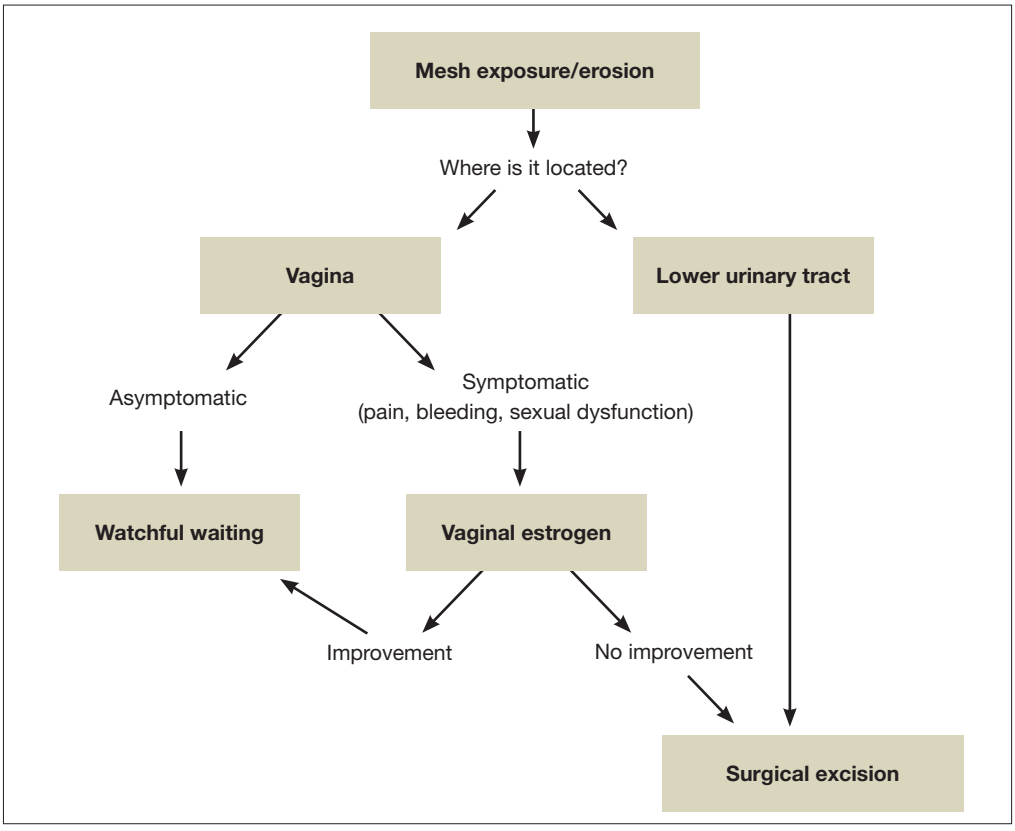
What would be a reasonable next option for Ms. R.?

While complications from a midurethral sling are rare, mesh exposures occur in approximately 2% of patients, and urinary retention requiring release of the sling occurs in about 1% of patients.[3,6] It often helps to clarify for patients that the US Food and Drug Administration public health

**FAST TRACK**

*When a patient presents with recurrent SUI after a prior transobturator sling, the best option for a repeat procedure is usually a retropubic sling, as it achieves higher objective and subjective cure rates*

**FIGURE 3 Mesh complications decision tree**



advisories on the use of transvaginal mesh have been directed specifically toward the use of transvaginal mesh for the treatment of pelvic organ prolapse (POP), *not* the use of mesh for midurethral slings for SUI or transabdominal mesh for POP.[10,17]

When considering use of a mesh sling, a thorough discussion of the potential risks, as well as the benefits and alternatives, is imperative. Patients must personally balance the probability of benefit with the potential risk of complications, and while physicians can help outline the benefits and risks through shared decision-making, ultimately it is the patient who should make this decision.

Certain patient populations may be at higher risk for mesh complications[18] (see box at right). These complications are managed in various ways (**FIGURE 3**). Patients who have experienced mesh complications previously are typically not good candidates for a repeat mesh sling, particularly when the risk factor for complications cannot be modified.

### A mesh sling alternative

The most effective way to manage SUI in patients who are not good candidates for a mesh sling is to consider employing a sling that uses the patient's own tissue.[19-21] Common approaches include harvesting a graft of rectus fascia through a Pfannenstiel skin incision or using fascia lata from the patient's iliotibial band in the lateral thigh. Autologous slings are safe and effective, and even after a mesh sling has failed, autologous slings have an almost 70% cure rate for SUI.[20,21]

### Timing of mesh removal and placement of an autologous fascial sling

Either concomitant or delayed placement of a pubovaginal sling is acceptable when removing mesh, though this should be a joint decision with the patient after counseling. If the risk for surgical complications is modifiable (for example, poorly controlled diabetes that could be improved with blood glucose control), it may be advisable to delay the fascial sling until the risk factors have been addressed. Similarly, if the reason for mesh removal is pain, it may be advisable to remove the mesh prior to placing a new sling to ensure that the pain resolves completely. Otherwise, if pain persists, it can be unclear whether the new sling is contributing to the pain, and this may lead to difficulties treating pain or incontinence in the future.

In this patient, who was an active smoker, we excised the exposed mesh and concomitantly placed an autologous fascial sling utilizing rectus fascia. This maintained continence without introducing mesh in a high-risk patient.

#### Risk factors for mesh-related complications

- Smoking
- Poorly controlled diabetes
- Decreased estrogen status
- Chronic steroid use
- Prior urethral surgery (urethral diverticulum, urethroplasty)

#### CASE 4 POP and occult SUI

Ms. B. is a 79-year-old woman with stage 3 POP planned for surgical repair. While she does not report urinary leakage, preoperative urodynamic testing revealed occult SUI with reduction of her prolapse. Her priorities are to avoid needing another surgery and to limit the chances of postoperative leakage, but she is nervous about her postoperative recovery and wants to avoid pain.

What approach would be appropriate?

### Consider a mini sling for this patient

The single-incision (mini) sling is an option to consider for patients with mild incontinence or for those without evidence of intrinsic sphincter deficiency. It is also a good option for those who want to avoid the additional incisions required for full-length slings.

While currently there is not sufficient evidence to clearly state if single-incision slings are equivalent to other slings, recent studies show that single-incision slings appear to be

**FAST TRACK**

*Common approaches for autologous slings include harvesting a graft of the patient's rectus fascia through a Pfannenstiel incision or using fascia lata from the iliotibial band in the lateral thigh*

safe and effective in the short term, with possibly fewer complications than traditional transobturator slings.[22-24] As patients are often concerned about the potential for groin pain with a transobturator sling, a single-incision sling is an acceptable alternative that avoids groin incisions and also avoids the retropubic space.

## Patient counseling is crucial

Regardless of the route, sling procedures are highly effective and safe for treating women with SUI.[3] Understanding the characteristics of each type of sling and the distinct surgical approaches enables informed counseling for patients who are navigating the treatment options for SUI. ●

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# Can we discern optimal long-term osteoporosis treatment for women?

## The use of osteoporosis drugs in sequence—rather than a single agent for a long time—may be the most effective management strategy

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In a recent systematic review, Fink and colleagues attempted to summarize the published evidence of the efficacy and safety of long-term (> 3 years) therapy for osteoporosis.[1] Unfortunately, they arrived at very limited and tentative conclusions because, as they point out, of the paucity of such evidence.

### Why long-term studies stop short

Only 3 of the several tens of placebo-controlled fracture end-point studies (about 58 trials and observational studies) that Fink and colleagues reviewed evaluated treatment for more than 3 years. The nonavailability of longer-term studies is the direct consequence of a requirement by regulatory agencies for a 3-year fracture end-point study in order to register a new drug for osteoporosis. Hence, longer, placebo-controlled studies do not benefit the industry sponsor, and enrolling patients with osteoporosis or who are at high risk for fracture in any, much less long, placebo-controlled trials is now considered to be unethical.

*The author reports receiving honorarium and consulting fees from Amgen.*

### What the authors did observe

From this limited set of information with which to evaluate, Fink and colleagues observed that long-term therapy with raloxifene reduces the risk of vertebral fractures but is associated with thromboembolic complications. In addition, treatment for more than 3 years with bisphosphonates reduces the risk of vertebral and nonvertebral fractures but may increase risk of rare adverse events (including femoral shaft fractures with atypical radiographic features).

**The bisphosphonate holiday.** The authors refer to the even more limited evidence about the effects of discontinuing bisphosphonate therapy. Unlike the rapid loss of bone mass density (BMD) and fracture protection upon stopping estrogen or denosumab, the offset of these treatment benefits is slower when bisphosphonates are discontinued. This, coupled with concern about increasing risk with long-term bisphosphonate therapy, led to the confusing concept of a "bisphosphonate holiday." While recommendations to consider temporary discontinuation of bisphosphonates in patients at low risk for fracture have been made by expert panels,[2] very little information exists about the benefits/risks of this strategy, how long the treatment interruption should be, or how to decide when and with what to restart therapy.

Unfortunately, overall, Fink and colleagues' observations provide little practical guidance for clinicians.

### What we can learn from longer term and recent studies of ideal treatment

Since we have no "cure" for osteoporosis, and since the benefits of therapy, including protection from fractures, abate upon stopping treatment (as they do when we stop treating hypertension or diabetes), very long term if not lifelong management is required for patients with osteoporosis. Persistent or even greater reduction of fracture risk with treatment up to 10 years, compared with the rate of fracture in the placebo or treated group during the first 3 years of the study, has been observed with zoledronate and denosumab.[3-5] Denosumab was not included in the systematic review by Fink and colleagues since the pivotal fracture trial with that agent was placebo-controlled for only 3 years.[6]

**Sequential drug treatment may be best.** Fink and colleagues also did

not consider new evidence, which suggests that the use of osteoporosis drugs in sequence—rather than a single agent for a long time—may be the most effective management strategy.[7,8]

**More consideration should be given to the use of estrogen and raloxifene** in younger postmenopausal women at risk for vertebral but not hip fracture.

**Only treat high-risk patients.** Using osteoporosis therapies to only treat patients at high risk for fracture will optimize the benefit:risk ratio and cost-effectiveness of therapy.

**Bisphosphonate holidays may not be as important as once thought.** BMD and fracture risk reduction does not improve after 5 years of bisphosphonate therapy, and longer treatment may increase the risk of atypical fractures, while switching to another agent can increase BMD and perhaps mitigate the safety concern, suggesting that there is little justification for continuous use of bisphosphonates for more than 5 years, thereby minimizing the importance of a bisphosphonate holiday.

**Hip BMD may serve as indicator for treatment decisions.** Recent evidence indicating that the change in hip BMD with treatment or the level of hip BMD achieved on treatment correlates with fracture risk reduction may provide a useful clinical target to guide treatment decisions.[9,10]

Because we have a lack of pristine evidence does not mean that we shouldn't treat osteoporosis; we have to do the best we can with the limited evidence we have. Therapy must be individualized, for we are not just treating osteoporosis, we are treating patients with osteoporosis. ●


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## EDITORIAL

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The CDC MEC recommend against the use of estrogen-containing contraceptives in women with migraine with aura (Category 4 rating). The VARS may help clinicians identify those who have migraine with aura who should not be offered estrogen-containing contraceptives. Equally important, the use of VARS could help reduce the number of women who are inappropriately diagnosed as having migraine with aura based on fleeting visual symptoms lasting far less than 5 minutes during a migraine headache. ●


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## MENSTRUAL PAIN RELIEF THROUGH MICRO-PULSES

**Livia**, by **iPulse Medical Ltd**, is a US Food and Drug Administration (FDA) approved, drug-free option to treat menstrual pain through the transmission of electrical pulses. Electrodes are placed on the body at the source of menstrual pain and send a frequency to the nerves to reduce pain. **Livia** was designed based on the principles of the "gate control" theory of pain, says **iPulse Medical**. When the nerves are stimulated by the device's electrodes, the nerve gate is closed, preventing pain signals from being received or felt in the brain.

The device can be worn in public or at home and allows the user to adjust the frequency of the electrical signal to correspond with her pain intensity. According to **iPulse Medical**, there are no adverse effects and the user will not build up a tolerance; however, the device should not be worn if the user has a pacemaker or is undergoing fertility treatment.

**FOR MORE INFORMATION, VISIT:** https://mylivia.com/

## EXPAREL FOR CESAREAN DELIVERY


**Pacira BioSciences** announced completion of their Phase 4 study of **Exparel** (bupivacaine lipsome injectable suspension), a local analgesic given to patients undergoing planned cesarean delivery (CD), aimed at reducing postsurgical pain and total opioid consumption through the first 72 hours postsurgery. **Exparel** is administered through transversus abdominis plane field block.

**Pacira's** multicenter, randomized, double-blind study of 186 patients showed that those receiving **Exparel** plus bupivacaine HCl had a 52% reduction in total opioid consumption and significantly lower pain scores through the first 72 hours after CD, compared with those receiving only bupivacaine HCl. The most common adverse effects are itching and nausea. **Exparel** should not be used for patients under the age of 18 and should be used cautiously in patients with hepatic disease.

**FOR MORE INFORMATION, VISIT:** https://www.exparel.com/

## *M GENITALIUM* ASSAY DETECTS THE STI

**Hologic's Aptima**® *Mycoplasma genitalium* assay is the first FDA-cleared diagnostic test for this sexually transmitted infection (STI), which has been identified by the Centers for Disease Control and Prevention as an emerging public health threat. The assay is an in vitro nucleic acid amplification test that can be used to verify swab or urine samples from women and men. In published studies, the ribosomal RNA-based assay displayed greater sensitivity than lab-developed or CE-marked DNA-based tests. Early detection is important, **Hologic** asserts, because *M genitalium* is increasing in prevalence among higher-risk populations; however, it is not well known and often misdiagnosed, leading to incorrect treatment as well as risk for transmission and recurrence.

**Hologic** cites several studies that have shown *M genitalium* can be asymptomatic; however, it also can be associated with nongonococcal urethritis in men and cervicitis in women, as well as increased risk for pelvic inflammatory disease, preterm birth, spontaneous abortion, and infertility. A high percentage of infected people have an antibiotic-resistant strain, demonstrating a need for early detection and screening.

**FOR MORE INFORMATION, VISIT:** https://www.hologic.com

## NEW ART OPTION

**INVOcell**™ is an intravaginal culture system offering women and their partners another option for proven, effective assisted reproductive technology (ART), says **Ferring Pharmaceuticals**. The **INVOcell** Culture Device uses a woman's own body as a natural incubator during fertilization and early embryo development. It differs from in vitro fertilization, as the incubation happens intravaginally and not in a lab. During the process, the patient undergoes a mild ovarian stimulation and monitoring cycle. After the eggs and sperm are collected, they are placed into the device and then immediately placed into the vaginal cavity to incubate and allow early embryo development to take place. After the incubation period, the **INVOcell** device is removed and the embryos are transferred or frozen, according to **Ferring**. For Important Safety Information, see **INVOcell**'s instructions for use.

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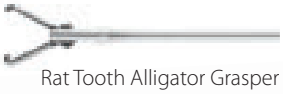

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