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OBG MANAGEMENT

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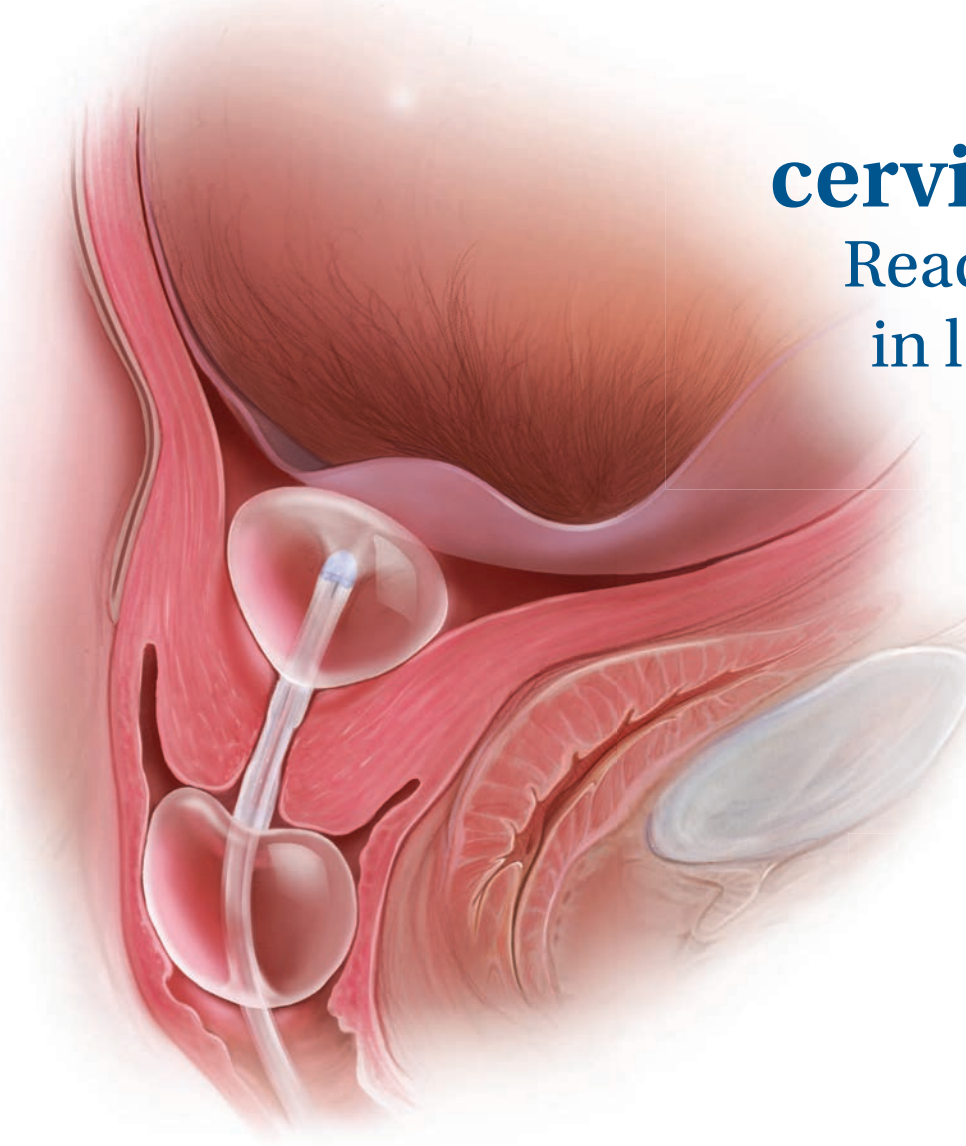
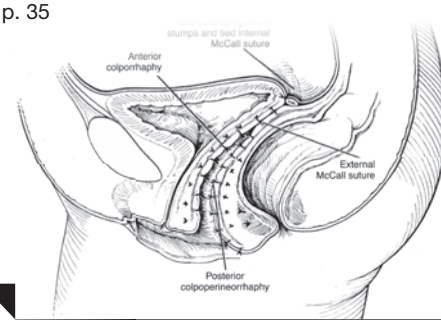


Outpatient cervical ripening

Ready for prime time in low-risk patients?



*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.

abbvie

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

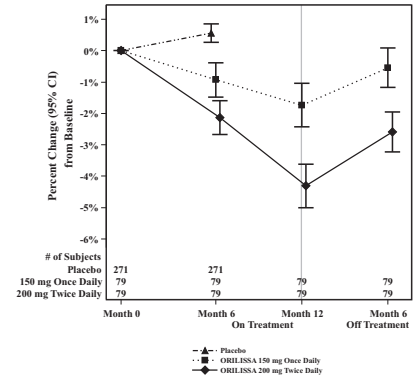
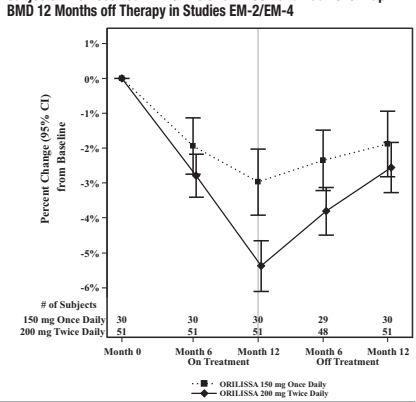


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



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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Ref: 03-B671 Revised: July, 2018

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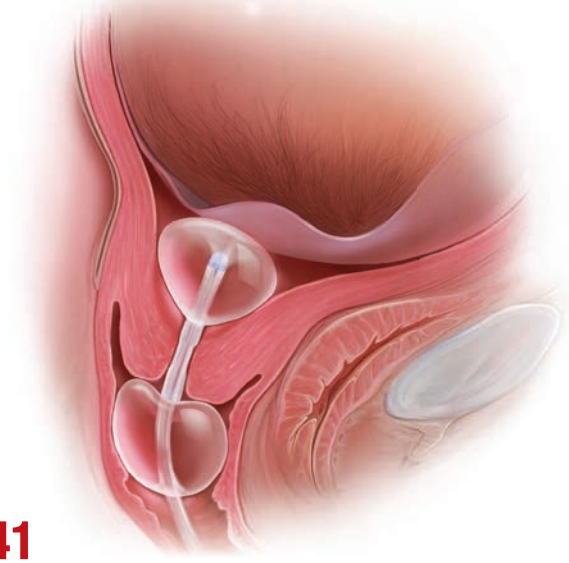

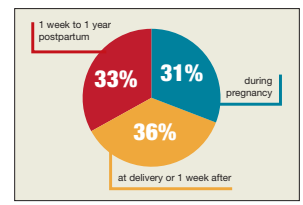

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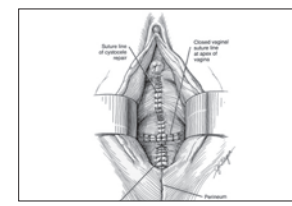

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1. Madsen, Annetta Madeline, et al. Absorbable Subcuticular Staples Compared with Suture for Cesarean Closure. Obstet Gynecol. 2015; vol. 125
2. The International Healthcare Worker Safety Center (University of Virginia Health System)
3. Schrufer-Poland, T. L., Ruiz, M. P., Kassar, S., Tomassian, C., Algren, S. D., & Yeast, J. D. (2016). Incidence of wound complications in cesarean deliveries following closure with absorbable subcuticular staples versus conventional skin closure techniques. European Journal of Obstetrics & Gynecology and Reproductive Biology, 206, 53-56. doi:10.1016/j.ejogrb.2016.07.501

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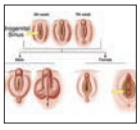

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OLIVIA H. CHANG, MD, MPH;
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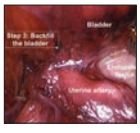

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Women with epilepsy: 5 clinical pearls for contraception and preconception counseling

For women with epilepsy, intrauterine devices are the optimal reversible contraceptive, and, preconception, the use of antiepileptic drugs with the lowest teratogenic potential should be considered

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In 2015, 1.2% of the US population was estimated to have active epilepsy.[1] For neurologists, key goals in the treatment of epilepsy include: controlling seizures, minimizing adverse effects of antiepileptic drugs (AEDs) and optimizing quality of life. For obstetrician-gynecologists, women with epilepsy (WWE) have unique contraceptive, preconception, and obstetric needs that require highly specialized approaches to care. Here, I highlight 5 care points that are important to keep in mind when counseling WWE.

1 Enzyme-inducing AEDs reduce the effectiveness of estrogen-progestin and some progestin contraceptives.

AEDs can induce hepatic enzymes that accelerate steroid hormone metabolism, producing clinically important reductions in bioavailable steroid hormone concentration (**TABLE 1**, page 10). According to Lexicomp, AEDs that are inducers of hepatic enzymes that metabolize steroid hormones include: carbamazepine (Tegretol), eslicarbazepine (Aptiom), felbamate (Felbatol), oxcarbazepine (Trileptal), perampanel (Fycompa), phenobarbital, phenytoin (Dilantin), primidone (Mysoline), rufinamide (Banzel), and topiramate (Topamax) (at dosages >200 mg daily). According to Lexicomp, the following AEDs do not cause clinically significant changes in hepatic enzymes that metabolize steroid hormones: acetazolamide (Diamox), clonazepam (Klonopin), ethosuximide (Zarontin), gabapentin (Neurontin), lacosamide (Vimpat), levetiracetam (Keppra), pregabalin (Lyrica), tiagabine (Gabitril), vigabatrin (Vigadrone), and zonisamide (Zonegran).[2,3] In addition, lamotrigine (Lamictal) and valproate (Depakote) do not significantly influence the metabolism of contraceptive steroids,[4,5] but contraceptive steroids significantly influence their metabolism (**TABLE 2**, page 16).

For WWE taking an AED that accelerates steroid hormone metabolism, estrogen-progestin contraceptive failure is common. In a survey of 111 WWE taking both an oral contraceptive and an AED, 27 reported becoming pregnant while taking the oral contraceptive.[6] Carbamazepine, a strong inducer of hepatic enzymes, was the most frequently used AED in this sample.

Many studies report that carbamazepine accelerates the metabolisms of estrogen and progestins and reduces contraceptive efficacy. For example, in one study 20 healthy women were administered an ethinyl estradiol (20 μg)-levonorgestrel (100 μg) contraceptive, and randomly assigned to either receive carbamazepine 600 mg daily or a placebo pill.[7] In this study, based on serum progesterone measurements, 5 of 10 women in the carbamazepine group ovulated, compared with 1 of 10 women in the placebo group. Women taking carbamazepine had integrated serum ethinyl estradiol and levonorgestrel concentrations approximately 45% lower than women taking placebo.[7] Other studies also report that carbamazepine accelerates steroid hormone metabolism and reduces the circulating concentration of ethinyl estradiol, norethindrone, and levonorgestrel by about 50%.[5,8]

CONTINUED ON PAGE 10

CONTINUED FROM PAGE 9

WWE taking an AED that induces hepatic enzymes should be counseled to use a copper or levonorgestrel (LNG) intrauterine device (IUD) or depot medroxyprogesterone acetate (DMPA) for contraception.[9] WWE taking AEDs that do not induce hepatic enzymes can be offered the full array of contraceptive options, as outlined in Table 1. Occasionally, a WWE taking an AED that is an inducer of hepatic enzymes may strongly prefer to use an estrogen-progestin contraceptive and decline the preferred option of using an IUD or DMPA. If an estrogen-progestin contraceptive is to be prescribed, safeguards to reduce the risk of pregnancy include:

- prescribe a contraceptive with ≥35 µg of ethinyl estradiol
- prescribe a contraceptive with the highest dose of progestin with a long half-life (drospirenone, desogestrel, levonorgestrel)
- consider continuous hormonal contraception rather than 4 or 7 days off hormones and
- recommend use of a barrier contraceptive in addition to the hormonal contraceptive.

The effectiveness of levonorgestrel emergency contraception may also be reduced in WWE taking an enzyme-inducing AED. In these cases, some experts recommend a regimen of two doses of levonorgestrel 1.5 mg, separated by 12 hours.[10] The effectiveness of progestin subdermal contraceptives may be reduced in women taking phenytoin. In one study of 9 WWE using a progestin subdermal implant, phenytoin reduced the circulating levonorgestrel level by approximately 40%.[11]

TABLE 1 Lexicomp risk, severity, and reliability rating of potential interactions between AED and accelerated metabolism of estrogen and progestin contraceptive hormones[2,a]

Is the antiepileptic medication an inducer of hepatic enzymes that can accelerate the inactivation of estrogen and/or progestin contraceptive hormones?			
YES		NO	
Antiepileptic medication	Lexicomp risk (letter grade), severity, and reliability rating for AED interaction with estrogen-progestin contraceptive	Antiepileptic medication	Lexicomp rating- interaction with estrogen-progestin contraceptive
Carbamazepine (Tegretol)	D rating-consider therapy modification, Severity Major, Reliability Good	Acetazolamide (Diamox)	A rating. No known interactions with estrogen or progestin hormones
Eslicarbazepine (Aptiom)	D rating-consider therapy modification, Severity Major, Reliability Good	Clonazepam (Klonopin)	A rating. No known interactions with estrogen or progestin hormones
Felbamate (Felbatol)	D rating-consider therapy modification, Severity Major, Reliability Good	Ethosuximide (Zarontin)	A rating. No known interactions with estrogen or progestin hormones
Oxcarbazepine (Trileptal)	D rating-consider therapy modification, Severity Major, Reliability Good	Gabapentin (Neurontin)	A rating. No known interactions with estrogen or progestin hormones
Perampanel (Fycompa)	D rating-consider therapy modification, Severity Major, Reliability Fair	Lacosamide (Vimpat)	B rating. May increase the serum concentration of ethinyl estradiol by 20%. Severity Minor, Reliability Fair
Phenobarbital	D rating-consider therapy modification, Severity Major, Reliability Fair. Also induces CYP3A4	Levetiracetam (Keppra)	A rating. No known interactions with estrogen or progestin hormones
Phenytoin (Dilantin)	D rating-consider therapy modification, Severity Major, Reliability Fair	Pregabalin (Lyrica)	A rating. No known interactions with estrogen or progestin hormones
Primidone (Mysoline)	D rating-consider therapy modification, Severity Major, Reliability Fair	Tiagabine (Gabitril)	A rating. No known interactions with estrogen or progestin hormones
Rufinamide (Banzel)	D rating-consider therapy modification, Severity Major, Reliability Fair	Vigabatrin (Vigadrone)	A rating. No known interactions with estrogen or progestin hormones
Topiramate (Topamax)	D rating-consider therapy modification, Severity Major, Reliability Good	Zonisamide (Zonegran)	A rating. No known interactions with estrogen or progestin hormones

[a]Lamotrigine (Lamictal) and valproate (Depakote) are not strong inducers of hepatic enzymes. Hence, they do not accelerate the metabolism of estrogen and progestin contraceptive hormones. However, the metabolism of lamotrigine and valproate is accelerated by estrogen (see Table 2).

Abbreviation: AED, antiepileptic drug.

CONTINUED ON PAGE 16

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

NOW APPROVED

FIRST AND ONLY FDA-APPROVED
TREATMENT FOR POSTPARTUM DEPRESSION.[1]

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.[1]

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. Please see Important Safety Information including Boxed Warning below.[1]

To learn more, please visit ZulressoHCP.com

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.

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

IMPORTANT SAFETY INFORMATION for ZULRESSO (CONT'D)

Excessive Sedation and Sudden Loss of Consciousness (cont'd): 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.

Please also see Full Prescribing Information including Boxed Warning and Medication Guide for ZULRESSO.

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.

Reference: 1. ZULRESSO Prescribing Information. Cambridge, MA: Sage Therapeutics, Inc; 6/2019.

Sage Therapeutics™

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

Please see Brief Summary of 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 m2), moderate (eGFR 30 to 59 mL/minute/1.73 m2) or severe (eGFR 15 to 29 mL/minute/1.73 m2) renal impairment.

Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/minute/1.73 m2 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).

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TABLE 2 Metabolism effects of lamotrigine and valproate by estrogen medications[a]

Antiepileptic medication	Lexicomp risk (letter grade), severity, and reliability rating
Lamotrigine (Lamictal)	Estrogen may reduce lamotrigine levels. D rating-consider therapy modification, Severity Major, Reliability Good
Valproate (Depakote)	Estrogen may reduce valproate levels. C rating-monitor therapy. Severity Moderate, Reliability Fair

[a]The metabolism of lamotrigine and valproate is accelerated by estrogen medications, resulting in a possible reduction in circulating medication concentration, increasing the risk of seizure. Lamotrigine and valproate do not significantly accelerate the metabolism of ethinyl estradiol or levonorgestrel.

2 Do not use lamotrigine with cyclic estrogen-progestin contraceptives.

Estrogens, but not progestins, are known to reduce the serum concentration of lamotrigine by about 50%.[12,13] This is a clinically significant pharmacologic interaction. Consequently, when a cyclic estrogen-progestin contraceptive is prescribed to a woman taking lamotrigine, oscillation in lamotrigine serum concentration can occur. When the woman is taking estrogen-containing pills, lamotrigine levels decrease, which increases the risk of seizure. When the woman is not taking the estrogen-containing pills, lamotrigine levels increase, possibly causing such adverse effects as nausea and vomiting. If a woman taking lamotrigine insists on using an estrogen-progestin contraceptive, the medication should be prescribed in a continuous regimen and the neurologist alerted so that they can increase the dose of lamotrigine and intensify their monitoring of lamotrigine levels. Lamotrigine does not change the metabolism of ethinyl estradiol and has minimal impact on the metabolism of levonorgestrel.[4]

3 Estrogen-progestin contraceptives require valproate dosage adjustment.

A few studies report that estrogen-progestin contraceptives accelerate the metabolism of valproate and reduce circulating valproate concentration,[14,15] as noted in Table 2. In one study, estrogen-progestin contraceptive was associated with 18% and 29% decreases in total and unbound valproate concentrations, respectively.[14] Valproate may induce polycystic ovary syndrome in women.[16] Therefore, it is common that valproate and an estrogen-progestin contraceptive are co-prescribed. In these situations, the neurologist should be alerted prior to prescribing an estrogen-progestin contraceptive to WWE taking valproate so that dosage adjustment may occur, if indicated. Valproate does not appear to change the metabolism of ethinyl estradiol or levonorgestrel.[5]

4 Preconception counseling: Before conception consider using an AED with low teratogenicity.

Valproate is a potent teratogen, and consideration should be given to discontinuing valproate prior to conception. In a study of 1,788 pregnancies exposed to valproate, the risk of a major congenital malformation was 10% for valproate monotherapy, 11.3% for valproate combined with lamotrigine, and 11.7% for valproate combined with another AED, but not lamotrigine.[17] At a valproate dose of ≥1,500 mg daily, the risk of major malformation was 24% for valproate monotherapy, 31% for valproate plus lamotrigine, and 19% for valproate plus another AED, but not lamotrigine.[17] Valproate is reported to be associated with the following major congenital malformations: spina bifida, ventricular and atrial septal defects, pulmonary valve atresia, hypoplastic left heart syndrome, cleft palate, anorectal atresia, and hypospadias.[18]

In a study of 7,555 pregnancies in women using a single AED, the risk of major congenital anomalies varied greatly among the AEDs, including:valproate(10.3%),phenobarbital (6.5%), phenytoin (6.4%), carbamazepine (5.5%), topiramate (3.9%), oxcarbazepine (3.0%), lamotrigine (2.9%), and levetiracetam (2.8%).[19] For WWE considering pregnancy, many experts recommend use of lamotrigine, levetiracetam, or oxcarbazepine to minimize the risk of fetal anomalies.

5 Folic acid: Although the optimal dose for WWE taking an AED and planning to become pregnant is unknown, a high dose is reasonable.

The American College of Obstetricians and Gynecologists (ACOG) recommends that women planning pregnancy take 0.4 mg of folic acid daily, starting at least 1 month before pregnancy and continuing through at least the 12th week of gestation.[20] ACOG also recommends that women at high risk of a neural tube defect should take 4 mg of folic acid daily. WWE taking a teratogenic AED are known to be at increased risk for fetal malformations, including neural tube defects. Should these women take 4 mg of folic acid daily?

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Epilepsy and operation of a motor vehicle

For most women with epilepsy, maintaining a valid driver's license is important for completion of daily life tasks. Most states require that a patient with seizures be seizure-free for 6 to 12 months to operate a motor vehicle. Estrogen-containing hormonal contraceptives can reduce the concentration of some AEDs, such as lamotrigine. Hence, it is important that the patient be aware of this interaction and that the primary neurologist be alerted if an estrogen-containing contraceptive is prescribed to a woman taking lamotrigine or valproate. Specific state laws related to epilepsy and driving are available at the Epilepsy Foundation website (https://www.epilepsy.com/driving-laws).

ACOG notes that, for women taking valproate, the benefit of high-dose folic acid (4 mg daily) has not been definitively proven,[21] and guidelines from the American Academy of Neurology do not recommend high-dose folic acid for women receiving AEDs.[22] Hence, ACOG does not recommend that WWE taking an AED take high-dose folic acid.

By contrast, the Royal College of Obstetricians and Gynecologists (RCOG) recommends that all WWE planning a pregnancy take folic acid 5 mg daily, initiated 3 months before conception and continued through the first trimester of pregnancy.[23] The RCOG notes that among WWE taking an AED, intelligence quotient is greater in children whose mothers took folic acid during pregnancy.[24] Given the potential benefit of folic acid on long-term outcomes and the known safety of folic acid, it is reasonable to recommend high-dose folic acid for WWE.

Final takeaways

Surveys consistently report that WWE have a low-level of awareness about the interaction between AEDs and hormonal contraceptives and the teratogenicity of AEDs. For example, in a survey of 2,000 WWE, 45% who were taking an enzyme-inducing AED and an estrogen-progestin oral contraceptive reported that they had not been warned about the potential interaction between the medications.[25] Surprisingly, surveys of neurologists and obstetrician-gynecologists also report that there is a low level of awareness about the interaction between AEDs and hormonal contraceptives.[26] When providing contraceptive counseling for WWE, prioritize the use of a copper or levonorgestrel IUD. When providing preconception counseling for WWE, educate the patient about the high teratogenicity of valproate and the lower risk of malformations associated with the use of lamotrigine, levetiracetam, and oxcarbazepine. ●

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Minimally invasive surgery for cervical cancer: Is surgeon volume a factor?

Could surgeon volume account for some of the findings of the LACC trial (which indicated better outcomes for open versus minimally invasive hysterectomy for early-stage cervical cancer)? New data say probably not.

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The role of minimally invasive surgery for early-stage cervical cancer has been the subject of heated debate since the presentation of the results of the Laparoscopic Approach to Cervical Cancer (LACC) Trial at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer in 2018. This was an international, randomized, phase 3 trial comparing minimally invasive radical hysterectomy (MH) to open radical hysterectomy (OH) in the treatment of early-stage cervical cancer. The trial was closed early by the study's Data and Safety Monitoring Committee due to an imbalance of deaths between the groups, with a higher rate in the minimally invasive arm. The final results, which were largely unexpected by the medical community, showed that the disease-free survival (DFS) at 4.5 years was 86.0% in the MH arm and 96.5% in the OH arm, which was a larger difference than their noninferiority cutoff of -7.2 percentage points.[1] Results of an epidemiologic study, which used data from the Surveillance, Epidemiology, and End Results (SEER) program and the National Cancer Database, also were presented at this meeting, and they reinforced the findings of the LACC trial.[2]

The combined results have caused significant concern and confusion from the medical community regarding the clinical implication that minimally invasive surgery may be an unacceptable approach for radical hysterectomy in cervical cancer. Prior to this study, retrospective data supported similar outcomes between the two approaches.[3] Additionally, robotic surgery has made radical hysterectomy an option for those with a higher body mass index, as an open radical hysterectomy can be technically challenging in larger patients and result in a higher rate of adverse outcomes.

LACC trial questioned by US surgeons

Many in the United States have questioned the design and conclusions of the LACC trial. This trial was conducted primarily outside of North America and utilized conventional laparoscopic surgery 85% of the time as opposed to robotic surgery. Additionally, the found difference in DFS between MH and OH may have been driven more by the superior performance of the OH group (compared with historical data) than the poorly performing MH group.[4] Other criticisms have touched on the low number of overall survival events, the low bar for surgeon volume or skill assessment, and the inability to make conclusions regarding "low-risk" lesions (<2 cm, no lymphovascular space invasion, <1 cm depth of invasion).

Were requirements for surgical skill adequate? Regarding surgeon skill, the LACC trial required documentation of the perioperative outcomes from 10 laparoscopic or robotic radical hysterectomies, as well as 2 unedited videos of each surgeon participating in the study to verify their technique, which some have considered inadequate to sufficiently vet a surgeon's ability. Additionally, 14 of the 33 centers enrolled in the study accrued 71% of the patients, and concerns about the surgeon volume of the remaining 19 centers have been raised. Finally, there has been discussion about whether the variance

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in surgical approach can even be adequately assessed in a trial of this nature, as surgical skill is not a binary variable that is easily amenable to randomization. Unlike other trials, which have clear exposure and control arms, no 2 surgeries are exactly alike, and surgical technique is highly variable between surgeons, institutions, and countries.

New data evaluate for surgeon volume

In an effort to address the concerns regarding surgical approach and expertise, the recently published study by Cusimano and colleagues uses population-based data from Ontario for all women undergoing radical hysterectomy for cervical cancer over a 10-year period from 2006 through 2016.[5] The primary outcome was all-cause death, but the study also sought to address whether surgeon volume has an impact on recurrence rates for patients undergoing MH versus OH. To measure this impact the authors stratified surgeon characteristics by technique-specific volume and cervical cancer volume, splitting these volumes at the 50% percentile for low- and high-volume surgeons. They defined technique-specific volume as the number of simple and radical hysterectomies performed in the prior year using the selected approach (MH or OH). Cervical cancer volume was calculated as the number of hysterectomies of any type for cervical cancer in the previous 2 years. The technique-specific volume variable was subsequently re-categorized into tertiles, examined as a continuous variable, and analyzed at the 50th percentile for each year of the study.

Death and recurrence rates better in the OH group. The final cohort included 958 women that were relatively evenly split between MH and OH procedures. Results from their analysis show no difference in terms of all-cause death, cervical cancer–specific death, or recurrence. However, all 3 of these parameters were significantly different in favor of the OH group in women with Stage IB disease, which comprised over half of the overall cohort. Importantly, neither technique-specific volume nor cervical cancer volume had an effect on death or recurrence in Stage IB patients in any of the investigators' analyses.

Important limitations. There are several limitations to this study that have to be taken into account before drawing any conclusions. Pathologic data were obtained from the database and did not include some important details about the tumor specimens (including specifying subgroups of Stage IA and IB disease, tumor size, presence of lymphovascular space invasion, and depth of stromal invasion). All of these details have been shown to be important prognostic variables in early-stage cervical cancer. Additionally, the MH group included a predominantly laparoscopic approach with only 10% of cases performed robotically, which again brings into question the generalizability of the data.

However, despite some of these shortcomings, the study authors do make a compelling argument that surgeon volume alone does not seem to play a significant role in cancer outcomes after MH.

With surgical approaches hard to compare, turn to careful patient counseling

Definitive assessment of the impact of surgical skill and experience on cervical cancer outcomes is probably an impossible task, as even a perfectly designed trial cannot entirely account for the intricacies of a complex surgical procedure. Variations in tumor characteristics and patient anatomy that affect operative decision making are not likely to be reflected when a patient's outcome is plugged into a database. As a result, some surgeons and departments have turned to reporting personal or institutional recurrence rates for MH, which they believe may be a better representation of a patient's risk in their hands. Meanwhile, many surgeons and groups have stopped performing MH altogether, largely due to the results of the LACC trial. Irrespective of final surgical route, it is important that the risks and benefits of both minimally invasive and open approaches be adequately discussed with patients so that they can make informed decisions regarding their own medical care. ●

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iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Cohort 1		Cohort 2	
	Injectafer (N=244)	Oral Iron (N=251)	Injectafer (N=245)	IV SC[a] (N=237)
Baseline	10.6 (1.0)	10.6 (1.0)	9.1 (1.6)	9.0 (1.5)
Highest Value	12.2 (1.1)	11.4 (1.2)	12.0 (1.2)	11.2 (1.3)
Change (from baseline to highest value)	1.6 (1.2)	0.8 (0.8)	2.9 (1.6)	2.2 (1.3)
p-value	0.001		0.001	

SD=standard deviation; [a]: Intravenous iron per standard of care

Increases from baseline in mean ferritin (264.2 ± 224.2 ng/mL in Cohort 1 and 218.2 ± 211.4 ng/mL in Cohort 2), and transferrin saturation (13 ± 16% in Cohort 1 and 20 ± 15% in Cohort 2) were observed at Day 35 in Injectafer-treated patients.

14.2 Trial 2: Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease

Trial 2: REPAIR-IDA, Randomized Evaluation of efficacy and safety of Ferric carboxymaltose in Patients with iron deficiency Anemia and Impaired Renal function, (NCT00981045) was a randomized, open-label, controlled clinical study in patients with non-dialysis dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) $\leq$ 11.5 g/dL, ferritin $\leq$ 100 ng/mL or ferritin $\leq$ 300 ng/mL when transferrin saturation (TSAT) $\leq$ 30%. Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 101); 64% were female; 54% were Caucasian, 26% were African American, 18% Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

Table 3. Mean Change in Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Injectafer (N=1249)	Venofer (N=1244)
Baseline	10.3 (0.8)	10.3 (0.8)
Highest Value	11.4 (1.2)	11.3 (1.1)
Change (from baseline to highest value)	1.1 (1.0)	0.9 (0.92)
Treatment Difference (95% CI)	0.21 (0.13, 0.28)	

Increases from baseline in mean ferritin (734.7 ± 337.8 ng/mL), and transferrin saturation (30 ± 17%) were observed prior to Day 56 in Injectafer-treated patients.

17 PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*].

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Conservative to invasive approaches are available for treating women with fecal incontinence, but how do they stack up in terms of efficacy and safety? Two experts review recent evidence on first- and second-line treatments, a vaginal bowel control system, and a sacral neuromodulation device.

Fecal incontinence (FI), also known as accidental bowel leakage, is the involuntary loss of feces, which includes both liquid and solid stool as defined by the International Continence Society (ICS) and the International Urogynecological Association (IUGA).[1,2] Fecal incontinence is common, occurring in 7% to 25% of community-dwelling women, and it increases with age.[2-6] The condition is rarely addressed, with only 30% of women seeking care.[6-8] This is due to patient embarrassment and the lack of a reliable screening tool. However, FI affects quality of life and mental health, and the associated economic burden likely will rise given the increased prevalence of FI among older women.[2,4,7,9]

Fecal incontinence occurs due to poor stool consistency, anal and pelvic muscle weakness, reduced rectal compliance, reduced or increased rectal sensation, or bowel inflammation or dysfunction. Many conditions can cause FI (**TABLE 1**, page 24).[5,10,11] It is therefore important to elicit a full medical history with a focus on specific bowel symptoms, such as stool consistency type (**TABLE 2**, page 26),[12] FI frequency, and duration of symptoms, as well as to perform a complete examination to identify any readily reversible or malignant causes. A colonoscopy is recommended for individuals who meet screening criteria or present with a change in bowel symptoms, such as diarrhea, bleeding, or obstruction.[13,14]

Fecal incontinence treatments include a range of approaches categorized from conservative, or first-line therapy, to fourth-line surgical managements (**FIGURE 1**, page 26).[1,10,13,14]

In this Update, we review the results of 3 well-designed trials that enrolled women with frequent nonneurogenic FI.

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Common first- and second-line treatments produce equivalent improvements in FI symptoms at 6 months

Jelovsek JE, Markland AD, Whitehead WE, et al; National Institute of Child Health and Human Development Pelvic Floor Disorders Network. Controlling faecal incontinence in women by performing anal exercises with biofeedback or loperamide: a randomized clinical trial. Lancet Gastroenterol Hepatol. 2019;4:698-710.

In a multicenter, randomized trial of first- and second-line treatments for FI, Jelovsek and colleagues evaluated the efficacy of oral placebo, loperamide, pelvic floor physical therapy (PFPT) with biofeedback using anorectal manometry, or combination therapy over a 24-week period.

Four treatments compared

Three hundred women with FI occurring monthly for 3 months were included in the trial. Women were excluded if they had a stool classification of type 1 or type 7 on the Bristol Stool Scale, inflammatory bowel disease (IBD), history of rectovaginal fistula or cloacal defect, rectal prolapse, prior bowel diversion, fecal impaction, neurologic disorder leading to incontinence, use of loperamide or diphenoxylate within the last 30 days, childbirth within the last 3 months, need for antiretroviral drugs, hepatic impairment, or chronic abdominal pain without diarrhea.

Baseline characteristics and symptoms severity were similar among participants. The average age of the women was 63 years, with 79% white and 85% postmenopausal. Participants had a mean (SD) of 1.6 (1.8) leaks per day.

Participants were randomly assigned in a 0.5:1:1:1 fashion to receive oral placebo, loperamide, oral placebo with PFPT/biofeedback, or loperamide with PFPT/biofeedback. All participants received a standardized educational pamphlet that outlined dietary and behavioral recommendations.

Women assigned to PFPT/biofeedback received 6 sessions every other week. Loperamide was started at a dosage of 2 mg per day with the possibility of dose maintenance, escalation, reduction, or discontinuation.

TABLE 1 Etiologies of fecal incontinence[5,10,11]

Gastrointestinal	Anatomic	Congenital	Neurologic	Risk factors
Myopathy (scleroderma)	Obstetric injury	Imperforate anus	Central nervous system	Smoking
Colitis or proctitis	Surgical (fistulotomy, hemorrhoidectomy, sphincterotomy)	Spina bifida	Dementia	Obesity
Constipation	Bowel resection	Myelomeningocele	Stroke	Older age
Rectal prolapse	Rectocele		Sciatica	Physical disability
Radiation			Multiple sclerosis	
Inflammatory bowel disease			Peripheral neuropathy (eg, diabetic)	
Irritable bowel syndrome			Neoplasm	
Prior cholecystectomy			Spinal cord lesions	

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TABLE 2 Stool consistency classification by type according to the Bristol Stool Scale[12]

Type	Description
1	Separate hard lumps, like nuts (hard to pass)
2	Sausage-shaped but lumpy
3	Like a sausage but with cracks on the surface
4	Like a sausage or snake, smooth and soft
5	Soft blobs with clear-cut edges
6	Fluffy pieces with ragged edges, a mushy stool
7	Watery, no solid pieces; entirely liquid

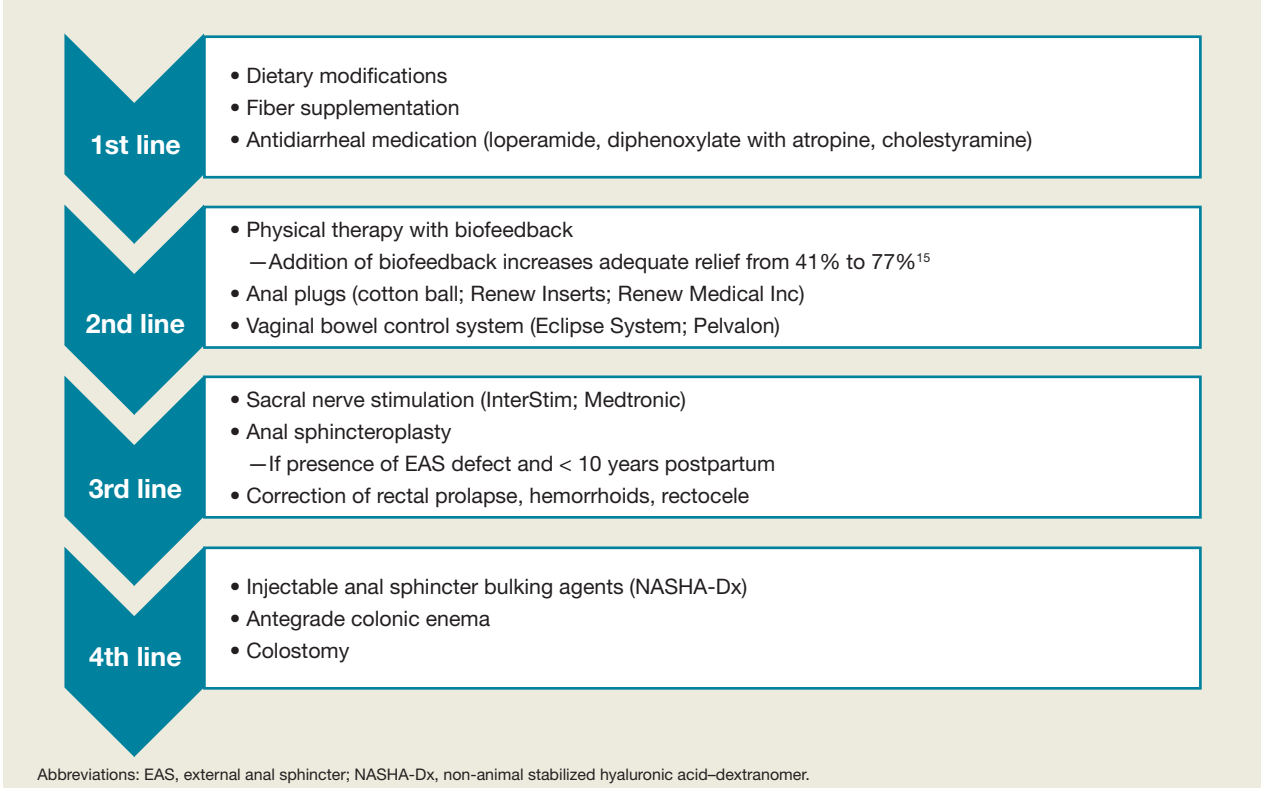
Study outcomes. The primary outcome was a change from baseline to 24 weeks in the Vaizey FI symptom severity score, which assesses fecal frequency, urgency, and use of pads and medications. Secondary outcomes included assessment of a 7-day bowel diary and other quality-of-life measures. Data at 24 weeks were available for 89% of the women.

All treatment groups experienced improved FI symptoms

Based on changes in Vaizey scores after 24 weeks of treatment, women in all treatment groups had similar improvement in symptoms severity. However, those who received loperamide and PFPT/biofeedback had decreased pad changes per week and more accident-free days compared with women treated with placebo and biofeedback. Quality of life at 24 weeks was not statistically different between treatment groups as improvement was seen in all groups, including those who received oral placebo and patient education.

Adverse events. The proportion of gastrointestinal adverse effects was similar between treatment groups, ranging from 45% to 63%. Constipation was the most common adverse event overall and was more common in those taking loperamide,

FIGURE 1 Treatment algorithm for fecal incontinence: Summary of society recommendations[1,10,13,14]



Abbreviations: EAS, external anal sphincter; NASHA-Dx, non-animal stabilized hyaluronic acid–dextranomer.

occurring in 51% of the loperamide plus PFPT/biofeedback group, 38% of those who received loperamide alone, 23% of the biofeedback with placebo group, and 12% of the placebo-alone group.

Strengths and limitations. Strengths of this study include its multisite, large sample size, low dropout rate, and sufficiently powered design to compare various combinations of first- and second-line therapies in women with a mean baseline FI of 1.6 leaks per day. Another strength is the robustness of the PFPT/biofeedback sessions that used anorectal manometry. This may, however, limit the study's external validity given that clinical use of this device is likely rare. Additionally, the population was comprised largely of postmenopausal and white women, which may make the findings less generalizable to other populations.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Women who suffer from frequent FI may require both loperamide and PFPT/biofeedback if they want to increase the likelihood of accident-free days and use of fewer pads. Should they note increased constipation or are not amenable to scheduled PFPT sessions, formalized education about dietary modifications, according to this study, will provide improvement in symptom severity.

Novel vaginal bowel control system is effective, durable over 12 months for FI treatment

FAST TRACK

The bowel control device is a silicone-coated vaginal insert with a detachable pump and balloon that deflects the rectovaginal septum posteriorly, thus impeding stool passage in the rectum

Richter HE, Dunivan G, Brown HW, et al. A 12-month clinical durability of effectiveness and safety evaluation of a vaginal bowel control system for the nonsurgical treatment of fecal incontinence. Female Pelvic Med Reconstr Surg. 2019;25:113-119.

Richter and colleagues characterized clinical success, effect on quality of life, and durability over 12 months of a novel vaginal bowel control device (Eclipse System; Pelvalon) for FI in a prospective cohort study. The device is a silicone-coated vaginal insert with a detachable pump and balloon that deflects the rectovaginal septum posteriorly, thus impeding the passage of stool in the rectum (**FIGURE 2,** page 28).

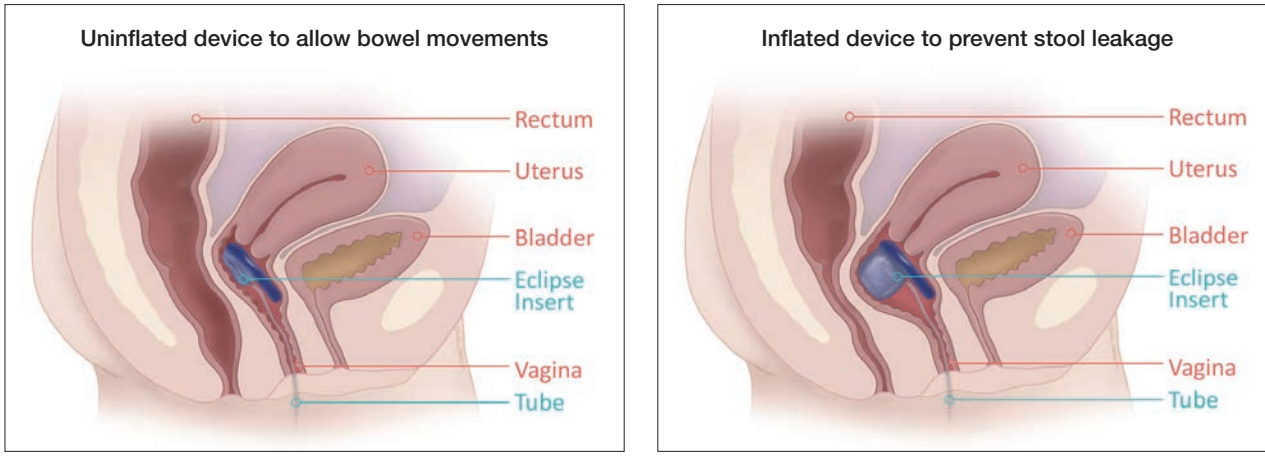
Study eligibility criteria and treatment protocol

Women were eligible for the study if they had 4 or more episodes of fecal soiling on a 2-week bowel diary and had FI for at least 6 months. Participants were excluded if they had prolapse outside the hymen, rectovaginal fistula, IBD, congenital anorectal malformation, urinary or colorectal infection, chronic pelvic or anorectal pain, pregnancy or planning pregnancy in the next 5 months, unmanaged chronic watery diarrhea, presence of an open wound or tear in the vagina, significant urogenital atrophy, or any psychiatric or neurologic disorder that would hinder the ability to participate.

Participants successfully fitted with the device (3 attempts were allowed) were entered into the study's run-in phase. Those who were successfully fitted and had a 50% or greater reduction in FI continued into the treatment phase with 12 months of follow-up.

Of the 137 women eligible for device fitting, 62% were successfully fitted. The 73 (86%) women who had a 50% or greater reduction in FI during the run-in period comprised the intent-to-treat study population. On average, these women were 61.3 years of age, with 70% white and 82% postmenopausal. At baseline, they had

FIGURE 2 The Eclipse System (Pelvalon) vaginal insert for bowel control



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FAST TRACK

With the bowel control device, complete continence was achieved in 46% of participants at 12 months, and major FI episodes decreased from 5.0 at baseline to 0.5 at 12 months

a mean of 14.1 episodes of FI over 2 weeks. (Prior to enrollment, 97.3% of women attempted self-management strategies, 17.8% to 23% failed conservative therapy, and 7.8% to 13.7% failed surgical therapy.) The follow-up rate at 12 months was 74%.

Study outcomes. The primary outcome was treatment success, defined as proportion of subjects with a 50% or greater reduction in FI episodes at 3 months; this outcome also was evaluated at 6 and 12 months. Secondary outcomes were the number of FI episodes and quality-of-life measures at 3, 6, and 12 months.

Treatment success, patient satisfaction high

In the treatment phase, women had sustained improvements in symptom severity and quality-of-life measures over 12 months. Treatment success was 73% at 3 months, 71% at 6 months, and 70% at 12 months. Complete continence was achieved in 46% of participants at 12 months, and major FI episodes (requiring immediate change of undergarments) decreased from 5.0 at baseline to 0.5 at 12 months. Quality-of-life measures were improved at 3 months, and improvement was sustained over 12 months. Satisfaction was 94% at 12 months.

Adverse events. No serious device-related adverse events occurred. Mild device-related adverse events were experienced by 45% of women during the fitting process and by 38% during treatment period. These included vaginal wall injury such as hyperemia and erosion; vaginal or pelvic discomfort; vaginal infection; constipation; and lower urinary tract issues such as urinary tract infection, urinary incontinence, and voiding dysfunction. No adverse events led to treatment discontinuation.

Strengths and limitations. Strengths of this study include that it was conducted at multiple clinical sites, had a large sample size, and had a 1-year follow-up period in a population with daily FI. A limitation was that only women who had a 50% or greater reduction in FI episodes during the run-in period were followed for 12 months; however, this was 86% of the original cohort. The use of a comparative group using other devices, such as anal plugs, would have strengthened this study.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The Eclipse intravaginal bowel control device (approved by the US Food and Drug Administration in 2015) provided a sustained 50% or greater reduction in FI episodes in more than 70% of women wearing the device for 1 year, with high patient satisfaction. Thus, for women who fail conservative treatment methods for FI, clinicians should consider referring them to a urogynecologist or specialist who is knowledgeable in fitting this vaginal bowel control device.

Sacral neuromodulation for FI is effective long-term

Hull T, Giese C, Wexner SD, et al; for the SNS Study Group. Long-term durability of sacral nerve stimulation therapy for chronic fecal incontinence. Dis Colon Rectum. 2013;56:234-245.

In this multicenter, prospective cohort study, Hull and colleagues evaluated the 5-year efficacy of sacral neuromodulation (SNM), also known as sacral nerve stimulation, for treatment of FI. This study followed an earlier investigation by Wexner and colleagues, which reported that 83% of 120 patients treated with SNM had a 50% or greater improvement in FI episodes at 12 months.[16]

Details of the study

The investigators enrolled 133 participants (92% female) who had more than 2 episodes of FI per week for longer than 6 months (12 months after vaginal delivery). Participants were excluded if they had congenital anorectal malformations, prior rectal surgery within the past 12 months (or 24 months if due to cancer), defects greater than 120° of the external anal sphincter (EAS), IBD, unmanaged chronic watery diarrhea, stool consistency type 6 or type 7 on the Bristol Stool Scale, sequela of pelvic radiation, active anal abscess or fistula, pregnancy, or planned pregnancy.

Eligible participants underwent a 2-stage procedure with the InterStim bowel control device (Medtronic). If participants experienced a 50% or greater reduction in incontinence episodes with a wearable external SNM device in the test stimulation (stage 1), they received the chronic SNM implant device (stage 2).

Participants who underwent device implantation were followed at 1, 3, and 6 months and annually for 5 years or until they exited the study. Bowel diaries and quality of life assessments were completed at baseline and at follow-up.

The primary outcome was therapeutic success, defined as 50% or greater improvement in FI episodes per week.

A total of 120 participants (90%) underwent implantation of the chronic lead and neuromodulator, and 76 (63%) were followed for 5 years. Baseline characteristics available in the initial study of 133 participants showed that the mean age was 60.5 years; 25% had undergone a prior anal sphincteroplasty; and 16.5% and 10.5% had EAS or internal anal sphincter (IAS) defects, respectively, on endoanal ultrasonography.[16]

Therapeutic success was high at 5 years

At the 5-year follow-up, 89% (64/72) of participants met therapeutic success, with a reduction in weekly FI episodes from 9.1 at baseline to 1.7 at 5 years. The number of incontinence pads required decreased, and more participants wore no pads at 5 years. In the intention-to-treat analysis, carrying forward the baseline FI rate in participants who lacked follow-up data, the therapeutic success rate was 69%. Quality-of-life measures improved at 5 years, both statistically and by minimal clinical difference.

Adverse events. Sixty-eight percent of participants experienced device-related adverse events, including implant site pain, change in sensation of stimulation, change in efficacy, implant site infection, or neurostimulator battery depletion (neurostimulator use commonly expires after 3 to 5 years). Of these events, 80% were successfully treated with medications, reprogramming, or no intervention. The 5-year probability of device revision or replacement was 24.4%, and the 5-year probability of device explant was 19.0%.

Strengths and limitations. Overall, this study was a well-designed, multicenter trial with long-term follow-up that showed significant improvement in FI with the use of

FAST TRACK

Device-related adverse events occurred in 68% of participants; 80% of these events were successfully treated with medications, reprogramming, or no intervention

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Sacral neuromodulation is an excellent therapy for women with daily FI who have failed noninvasive options and desire to proceed to a more durable, long-lasting device therapy. Although adverse events may occur, they are mild and most often resolve with device reprogramming.

SNM. Its strengths include the enrollment of postmenopausal women who had current defects in EAS and/or IAS on endoanal ultrasonography and 25% who had a prior sphincteroplasty. The findings therefore are relevant to the gynecologic population in whom anal sphincteroplasty would not be recommended. The study also accounted for dropouts and reported the adjusted success rate of 69% at 5 years in that group.

The lack of a control arm to rule out the placebo effect is a limitation of this study, although randomized trials comparing the effect of SNM "on" versus "off" showed greater improvement with the device "on."[17]

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Targeting US maternal mortality: ACOG's recent strides and future action

How the Preventing Maternal Deaths Act of 2018, newly introduced ACOG-supported bills, and ACOG partnerships have and intend to make a difference in US rates of maternal mortality

Lucia DiVenere, MA

Real progress was achieved in 2018 in the effort to reduce the US maternal mortality rate, the highest of any developed nation and where women of color are 3 to 4 times more likely than others to die of childbirth-related causes. Importantly, the United States is the only nation other than Afghanistan and Sudan where the rate is rising.[1]

In May 2019, the Centers for Disease Control and Prevention (CDC) published a Vital Signs document focused on preventable maternal deaths.[2] It affirmed that about 60% of the 700 pregnancy-related deaths that occur annually in the United States are preventable, and it provided important information on when and why these deaths occur.

Among the CDC findings, about:

- one-third of deaths (31%) occurred **during pregnancy** (before delivery)
- one-third (36%) occurred **at delivery or in the week after**
- one-third (33%) occurred **1 week to 1 year postpartum**.

In addition, the CDC highlighted that:

- Heart disease and stroke caused more than 1 in 3 deaths (34%). Infections and severe bleeding were other leading causes of death.
- Black and American Indian/Alaska Native women were about 3 times as likely to die from a pregnancy-related cause as white women.

The American College of Obstetricians and Gynecologists (ACOG), under the leadership of President Lisa Hollier, MD, MPH (2018–2019), fully embraced the challenge and responsibility of meaningfully improving health care for every mom. In this article, I review some of the critical steps taken in 2018 and preview ACOG's continued commitment for 2019 and beyond.

Efforts succeed: Bills are now laws of the land

ACOG and our partner organizations, including the Society for Maternal-Fetal Medicine and the March of Dimes, have long recognized the value of state-based maternal mortality review committees (MMRCs) in slowing and reversing the rate of maternal mortality. An MMRC brings together local experts to examine the causes of maternal deaths—not to find fault, but to find ways to prevent future deaths. With the right framework and support, MMRCs already are providing us with data and driving policy recommendations.

CONTINUED ON PAGE 32

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The author reports no financial relationships relevant to this article.

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Supporting MMRCs in all states. With this in mind, ACOG helped pass and push to enactment HR 1318, the Preventing Maternal Deaths Act of 2018 (Public Law No. 115-344), a bipartisan bill designed to help develop and provide support for MMRCs in every state. The bill was introduced in the US House of Representatives by Rep. Jaime Herrera Beutler (R-WA) and Rep. Diana DeGette (D-CO) and in the US Senate by Sen. Heidi Heitkamp (D-ND) and Sen. Shelley Moore Capito (R-WV). ACOG Fellow and US Rep. Michael Burgess, MD (R-TX), also was instrumental in the bill's success. The CDC is actively working toward implementation of this law, and grantees are expected to be announced by the end of September.

In addition, ACOG worked with Congress to secure $50 million in federal funding to reduce maternal mortality, allocated thusly:

- $12 million to support state MMRCs
- $3 million to support the Alliance for Innovation on Maternal Health
- $23 million for State Maternal Health Innovation Program grants
- $12 million to address maternal mortality in the Healthy Start program.

As these federal congressional initiatives worked their way into law, the states actively supported MMRCs as well. As of this writing, only 3 states—North Dakota, South Dakota, and Wyoming—have not yet developed an MMRC.[3]

Filling the gaps in ObGyn care. Another key ACOG-sponsored bill signed into law will help bring more ObGyns into shortage areas. Sponsored by Rep. Burgess, Rep. Anna Eshoo (D-CA), and Rep. Lucille Roybal-Allard (D-CA) and by Sen. Tammy Baldwin (D-WI) and Sen. Lisa Murkowski (R-AK), the Improving Access to Maternity Care Act (Public Law No. 115-320) requires the Department of Health and Human Services to identify maternity health professional target areas for use by the National Health Service Corps to bring ObGyns to where they are most needed.

Following up on that new law, ACOG currently is working closely with the American Academy of Family Physicians (AAFP) and the National Rural Health Association (NRHA) on the unique challenges women in rural areas face in accessing maternity and other women's health care services. In June, Dr. Hollier represented ACOG at the Rural Maternal Health forum, which was

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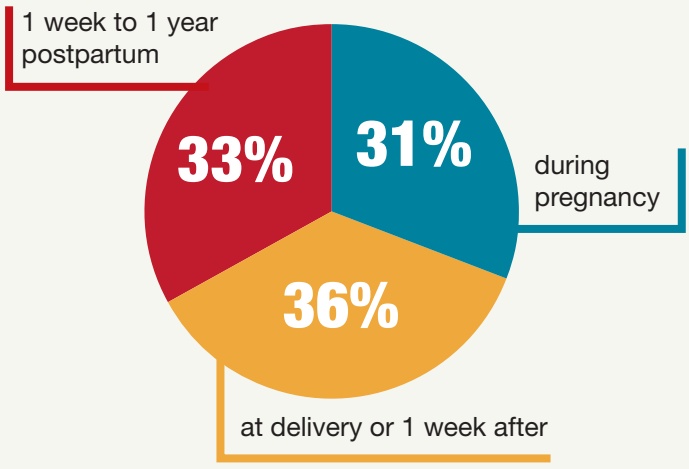
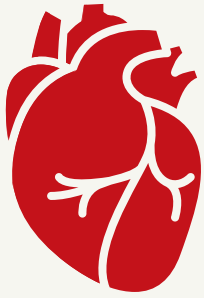
US maternal deaths, 2011-2015[2]





Heart disease and stroke caused more than

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convened by the Centers for Medicare and Medicaid and sponsored by ACOG, AAFP, and NRHA.[4] We are pursuing policies designed to increase the number of ObGyns and other physicians who choose to train in rural areas and increase the clinical use of telehealth to help connect rural physicians and patients with subspecialists in urban areas.

Projects in the works

Congress is ready to do more. Already, 5 ACOG-supported bills have been introduced, including bills that extend women's Medicaid coverage to 12 months postpartum (consistent with coverage for babies), support state perinatal quality collaboratives, and more. This interest is augmented by the work of the recently formed congressional Black Maternal Health Caucus, focused on reducing racial disparities in health care. In July, ACOG joined 12 members of Congress in a caucus summit to partner with these important congressional allies.

ACOG is expanding support for these legislative efforts through our work with another important ally, the American Medical Association (AMA). ACOG's delegation to the 2019 Annual Meeting of the AMA House of Delegates in June scored important policy wins, including AMA support for Medicaid coverage for women 12 months postpartum and improving access to care in rural communities.

There is momentum on Capitol Hill to take action on these important issues, and ACOG's priority is to ensure that any legislative package complements the important work many ObGyns are already doing to improve maternal health outcomes. ACOG has an important seat at the table and will continue to advocate each and every day for your practices and your patients as Congress deliberates legislative action.

Your voice matters

Encourage your representatives in the House and the Senate to support ACOG-endorsed legislation and be sure they know the importance of ensuring access to women's health care in your community. Get involved in advocacy; start by visiting the ACOG advocacy web page (www.acog.org/advocacy). Also note that members of Congress are back in their home states during seasonal breaks and many hold town halls and constituent meetings. The health of moms and babies is always an important issue, and you are the expert.

ACOG's commitment to ensuring healthy moms and babies, and ensuring that our members can continue providing high-quality care, runs through everything we do.

FAST TRACK

ACOG's priority is to ensure that any legislative package complements the important work many ObGyns are already doing to improve maternal health outcomes

Acknowledgments

The author thanks ACOG former Vice President for Health Policy Barbara Levy, MD, ACOG Senior Director Jeanne Mahoney, and ACOG Federal Affairs Director Rachel Tetlow for their helpful review and comments.

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Native tissue repair of POP: Surgical techniques to improve outcomes

Without mesh, it is imperative that gynecologic surgeons optimize their surgical technique to minimize failures and maximize patients' quality of life. Here, the Mayo Clinic's approach to transvaginal native tissue repair.

John B. Gebhart, MD, MS

> "Take pride in your surgical work. Do it in such a way that you would be willing to sign your name to it… the operation was performed by me."
> —Raymond A. Lee, MD

The US Food and Drug Administration (FDA) recently ordered companies to cease selling transvaginal mesh intended for pelvic organ prolapse (POP) repair (but not for the treatment of stress urinary incontinence [SUI] or for abdominal sacrocolpopexy).[1,2] The FDA is also requiring companies preparing premarket approval applications for mesh products for the treatment of transvaginal POP to continue safety and efficacy follow-up in existing section 522 postmarket surveillance studies.[3]

It is, therefore, incumbent upon gynecologic surgeons to understand the surgical options that remain and perfect their surgical approach to POP to optimize patient outcomes. POP may be performed transvaginally or transabdominally, with each approach offering its own set of risks and benefits. The ability to perform both effectively allows the surgeon to tailor the approach to the condition and circumstances encountered. It is also important to realize that "cures" are elusive in POP surgery. While we can frequently alleviate patient symptoms and improve quality of life, a lifelong "cure" is an unrealistic goal for most prolapse procedures.

This article focuses on transvaginal native tissue repair,[4] specifically the Mayo approach.

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The author reports no financial relationships relevant to this article.

Vaginal surgery fundamentals

Before we explore the details of the Mayo technique, let's review some basic principles of vaginal surgery. First, it is important to make a good clinical diagnosis so that you know which compartments (apex, anterior, or posterior) are involved. Although single compartment defects exist, multicompartment defects are far more common. Failing to recognize all compartment defects often results in incomplete repair, which can mean recurrent prolapse and additional interventions.

Second, exposure is critical when performing surgery by any route. You must be able to see your surgical field completely in order to properly execute your surgical

IN THIS ARTICLE

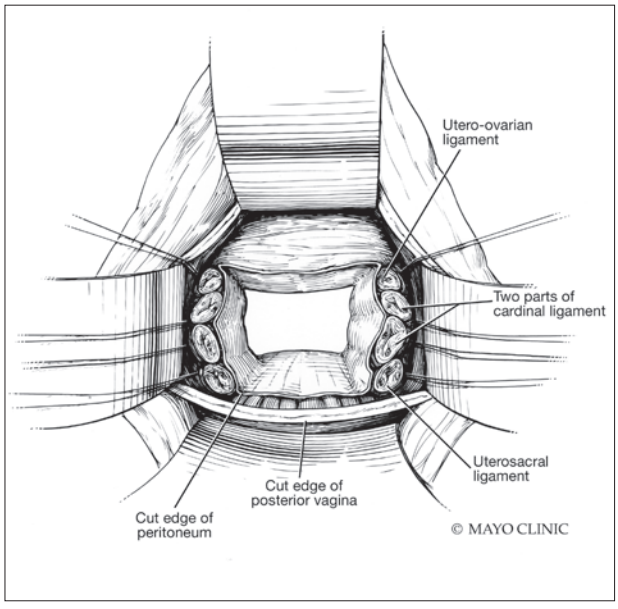

FIGURE 1 The open vaginal cuff after a completed vaginal hysterectomy is similar in appearance to that seen with a posthysterectomy vaginal vault prolapse.

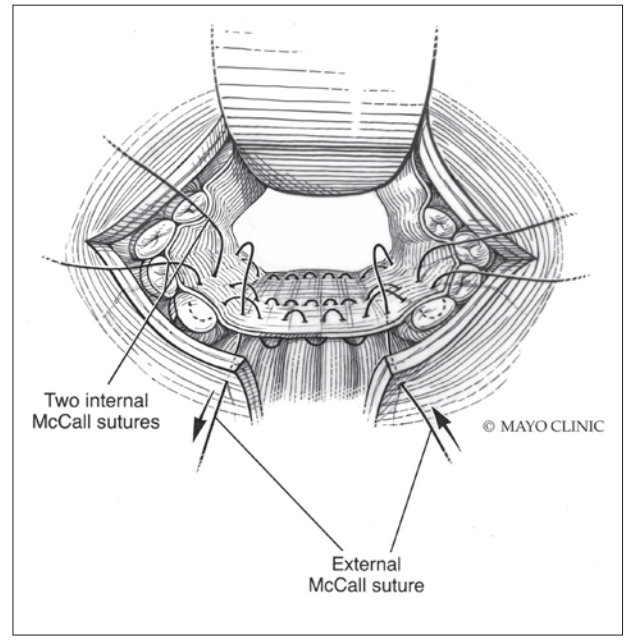

FIGURE 2 Internal and external uterosacral McCall sutures are shown.

approach. Table height, lighting, and retraction are all important to surgical success.

Lastly, it is important to know how to effectively execute your intended procedure. Native tissue repair is often criticized for having a high failure rate. It makes sense that mesh augmentation offers greater durability of a repair, but an effective native tissue repair will also effectively treat the majority of patients. An ineffective repair does not benefit the patient and contributes to high failure rates.

Vaginal apex repairs

Data from the OPTIMAL trial suggest that uterosacral ligament suspension and sacrospinous ligament fixation are equally effective in treating apical prolapse.[5] Our preference is a McCall culdoplasty (uterosacral ligament plication). It allows direct visualization (internally or externally) to place apical support stitches and plicates the ligaments in the midline of the vaginal cuff to help prevent enterocele protrusion. DeLancey has described the levels of support in the female pelvis and places importance on apical support.[6] Keep in mind that anterior and posterior compartment prolapse is often accompanied by apical prolapse. Therefore, treating the apex is critical for overall success.

External vs internal McCall sutures: My technique. Envision the open vaginal cuff after completing a vaginal hysterectomy or after opening the vaginal cuff for a posthysterectomy vaginal vault prolapse (**FIGURE 1**). External (suture placed through the vaginal cuff epithelium into the peritoneal cavity, incorporating the uterosacral ligaments and intervening peritoneum, and ultimately brought back out through the posterior cuff and tied) or internal (suture placed in the intraperitoneal space, incorporating the uterosacral ligaments and intervening

Take-home points

- Mesh slings for urinary incontinence and mesh use in sacrocolpopexy have not been banned by the FDA.
- Apical support is helpful to all other compartment support.
- Fixing the fascial defect between the base of the bladder and the apex will improve your anterior compartment outcomes.
- Monitor vaginal caliber throughout your posterior compartment repair.

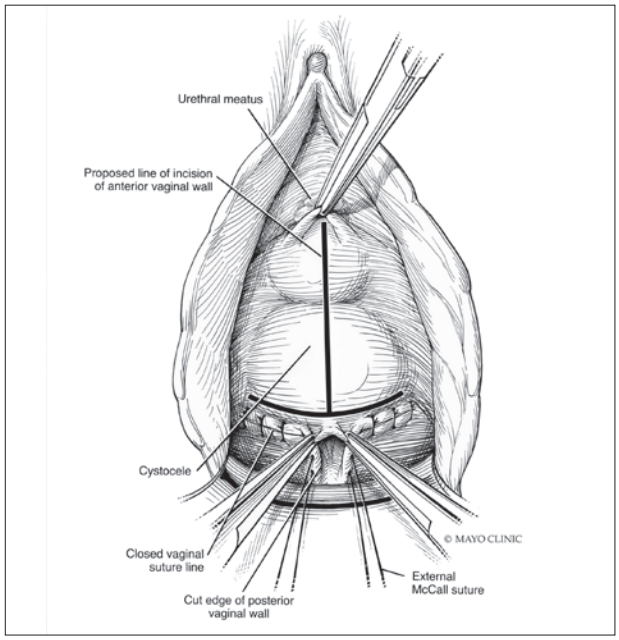

FIGURE 3 The black, upside down 'T' notes the 2 most common sites of fascial breaks. The vertical site is created by the surgeon, whereas the horizontal portion at the base is the cause of most cystoceles.

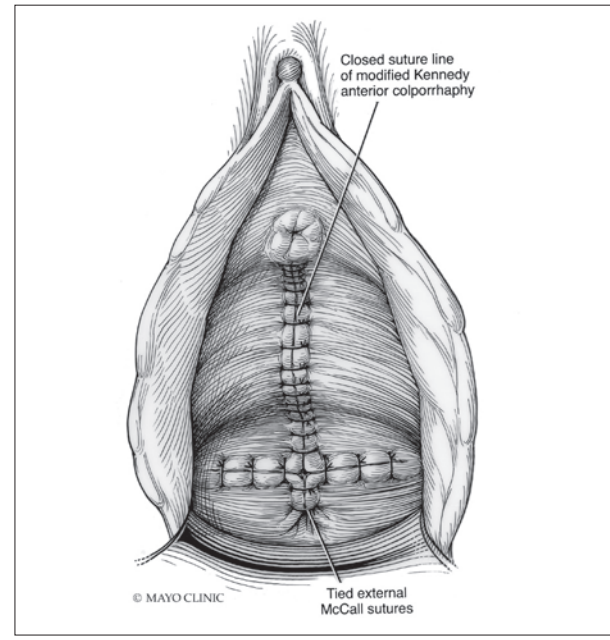

FIGURE 4 The completion of the anterior and apical repair. The fascia beneath the epithelium has been plicated in a similar manner as shown. The tied external McCall sutures exit just beneath the posterior vaginal cuff.

peritoneum, and tied internally) McCall sutures can be utilized (**FIGURE 2**). I prefer a combination of both. I use 0-polyglactin for external sutures, as the sutures will ultimately dissolve and not remain in the vaginal cavity. I usually place at least 2 external sutures with the lowest suture on the vaginal cuff being the deepest uterosacral stitch. Each subsequent suture is placed closer to the vaginal cuff and closer to the ends of the ligamentous stumps, starting deepest and working back toward the cuff with each stitch. I place 1 or 2 internal sutures (delayed absorbable or permanent) between my 2 external sutures. Because these sutures will be tied internally and located in the intraperitoneal space, permanent sutures may be used.

Avoiding ureteral injury: Tips for cystoscopy. A known risk of performing uterosacral ligament stitches is kinking or injury to the ureter. Therefore, cystoscopy is mandatory when performing this procedure. I tie one suture at a time starting with the internal sutures. I then perform cystoscopy after each suture tying. If I do not get ureteral spill after tying the suture, I remove and replace the suture and repeat cystoscopy until normal bilateral ureteral spill is achieved.

Key points for uterosacral ligament suspension. Achieving apical support at this point gives me the ability to build my anterior and posterior repair procedures off of this support. It is critical when performing uterosacral ligament suspension that you define the space between the ureter and rectum on each side. (Elevation of the cardinal pedicle and medial retraction of the rectum facilitate this.) The ligament runs down toward the sacrum when the patient is supine. You must follow that trajectory to be successful and avoid injury. One must also be careful not to be too deep on the ligament, as plication at that level may cause defecatory dysfunction.

Anterior compartment repairs

The anterior compartment seems the most susceptible to forces within the pelvis and is a common site of prolapse. Many theories exist as to what causes a cystocele—distension, displacement, detachment, etc. While paravaginal defects exist, I believe that most

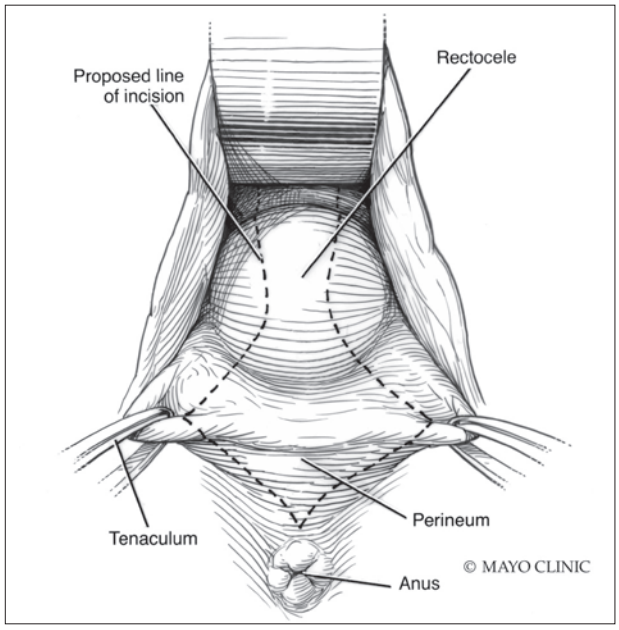

FIGURE 5 The proposed incision for the start of the posterior repair. The wider the wedge, the greater the risk of narrowing and excessive perineal buildup.

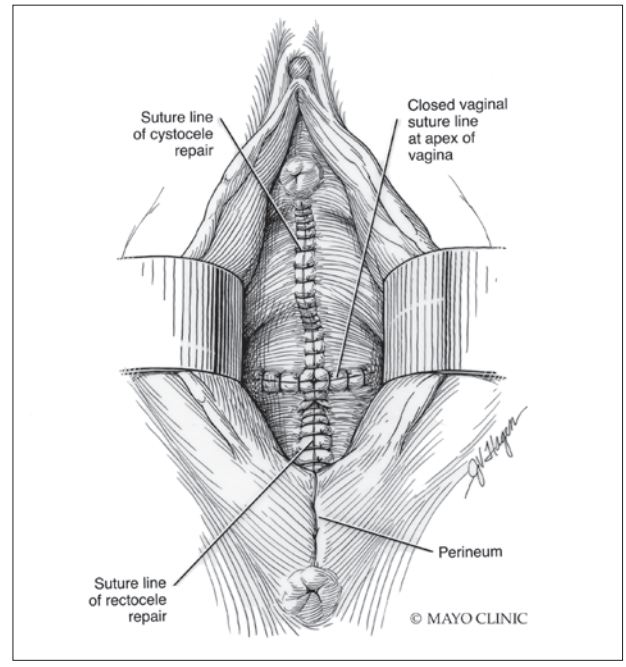

FIGURE 6 The completed transvaginal repair of all compartments.

FAST TRACK

When closing the midline fascial defect, avoid hernia by ensuring reunification of the anterior and apical fascia

cystoceles arise horizontally at the base of the bladder as the anterior endopelvic fascia detaches from the apex or cervix. The tissue then attenuates as the hernia progresses.

For surgical success: Make certain your repair addresses re-establishing continuity of the anterior endopelvic fascia with the fascia and ligaments at the vaginal apex; it will increase your success in treating anterior compartment prolapse.

We prefer to mobilize the epithelium in the midline from the vaginal apex to the midurethra (if performing a midurethral sling, we stop short of the bladder neck and perform a separate suburethral incision). When incising the epithelium in the midline, the underlying fascia is also split in the midline, creating a midline defect. Once the epithelium is split and mobilized laterally off the underlying fascia, we can begin reconstruction.

The midline fascial defect that was just created is closed with a running 2-0 polyglactin from just beneath the bladder neck down to and including the fascia and uterosacral ligaments at the apex. This is accomplished in an upside down 'T' orientation (**FIGURE 3,** page 37). It is critical that the fascia is reunited at the base or you will leave the patient with a hernia.

For surgical success: To check intraoperatively that the fascia is reunited at the base, try to place an index finger between the base of the cystocele repair and the apex. If you can insert your finger, that is where the hernia still exists. If you meet resistance with your finger, you are palpating reunification of the anterior and apical fascia.

Technique for Kelly-Kennedy bladder neck plication. If the patient has mild incontinence that does not require a sling procedure, we now complete the second portion of the anterior repair starting with a Kelly-Kennedy bladder neck plication. Utilizing interrupted 1-0 polyglactin suture, vertical bites are taken periurethrally, starting at the midurethra and then the bladder neck. This nicely supports the urethra and proximal bladder neck and is very helpful for mild incontinence or for prophylactic benefit. Then starting beneath the bladder neck, the fascia is plicated again in the midline,

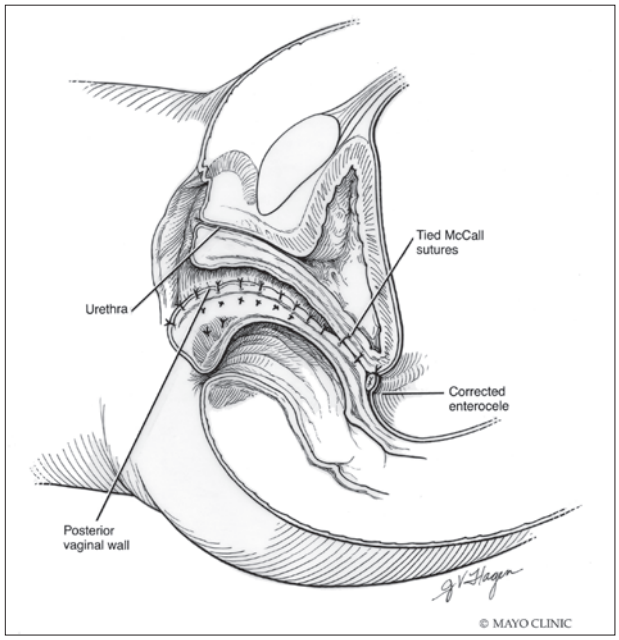

FIGURE 7 With the patient supine, a lateral view shows the posterior orientation of the vaginal axis after a completed repair.

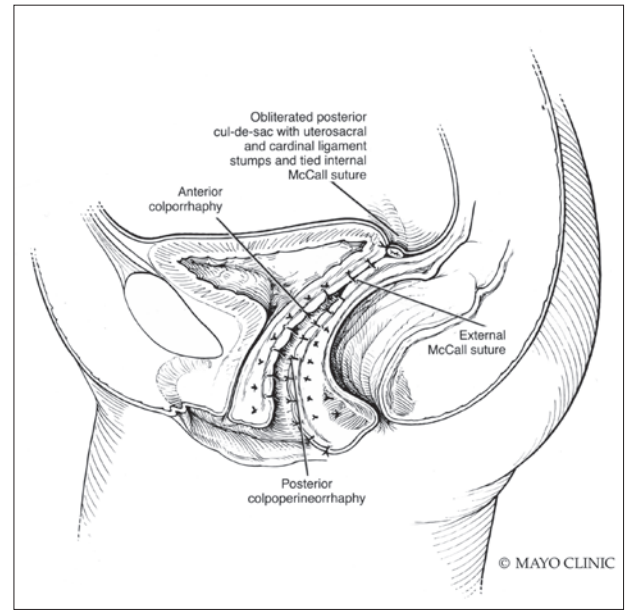

FIGURE 8 With the patient upright, a lateral view shows that posterior orientation of the apex and repair allows abdominal forces to compress the repair against the pelvic floor.

reinforcing the suture line of the inverse 'T' with 2-0 polyglactin. The redundant epithelium is trimmed and reapproximated with interrupted 2-0 polyglactin (**FIGURE 4**, page 37). We tend to be more aggressive by adding the Kelly-Kennedy plication, which can lead to temporary voiding delay. We offer placement of a suprapubic catheter at the time of surgery or self-intermittent catherization.

Lastly, given that we have just dissected and then plicated the tissues beneath the bladder, I like to perform cystoscopy to be certain the bladder has not been violated. It is also important not to over-plicate the anterior fascia so that the sutures shear through the fascia and weaken the support or narrow the vaginal lumen.

Posterior compartment repairs

Like with the anterior compartment, opinions differ as to the site of posterior compartment prolapse. Midline, lateral, distal, and site-specific defects and surgical approaches have been described. Research suggests that there is no benefit to the use of mesh in the posterior compartment.[7] It is very important to recognize that over-plication of the posterior compartment can lead to narrowing/stricture and dyspareunia. Therefore, monitor vaginal caliber throughout repair of the posterior compartment.

Although we believe that a midline defect in the endopelvic fascia is primarily responsible for rectoceles, we also appreciate that the fascia must be reconstructed all the way to the perineal body and that narrowing the genital hiatus is very important and often underappreciated (**FIGURE 5**). Thus, perineal reconstruction is universally performed. I will emphasize again that reconstruction must be performed while also monitoring vaginal caliber. If it is too tight with the patient under anesthesia, it will be too tight when the patient recovers. Avoidance is the best option. If the patient does not desire a functional vagina (eg, an elderly patient), then narrowing is a desired goal.

Perineal reconstruction technique and tips for success

A retractor at 12 o'clock to support the apex and anterior wall can be helpful for visualization in the posterior compartment. We start

FAST TRACK

If the patient desires a functional vagina, avoid stricture and dyspareunia by monitoring vaginal caliber throughout posterior compartment repair

ON THE WEB

Don't miss 3 related videos from Dr. Gebhart, demonstrating:
Apical suspension, anterior repair, and posterior repair
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FAST TRACK

Native tissue repair of POP offers a nonmesh option for patients; invest in learning effective techniques

with a v-shaped incision on the perineum. The width is determined by how much you want to build up the perineum and narrow the vagina (the wider the incision, the more building up of the perineal body and vaginal narrowing). A strip of epithelium is then mobilized in the midline (be careful not to excise too much). This dissection is carried all the way up the midline to just short of the tied apical suspension sutures at the posterior vaginal apex. The posterior dissection tends to be the most vascular in my experience.

Utilize cautery to obtain hemostasis along your dissection margins while protecting the underlying rectum. We have not found it necessary to dissect the posterior epithelium off the underlying fascia (that is an option at this point, however, if you feel more comfortable doing this). With an index finger in the vagina, compressing the rectum posteriorly, interrupted 1-0 polyglactin suture is placed through the epithelium and underlying fascia (avoiding the rectum) on one side, then the other, and then tied. The next sutures are placed utilizing the same technique, and the caliber of the vagina is noted with the placement of each suture (**if it is too tight, then remove and replace the suture and recheck**). It is important to realize you want to plicate the fascia in the midline and not perform an aggressive levatorplasty that could lead to muscle pain. Additionally, each suture should get the same purchase of tissue on each side, and the spacing of each suture should be uniform, like rungs on a ladder. Ultimately, the repair is carried down to the hymenal ring. At this point, the perineal reconstruction is performed, plicating the perineal body in the midline with deeper horizontal sutures and then closing the perineal skin with interrupted or subcuticular sutures (**FIGURE 6**, page 38). Completion of these repairs should orient the vagina toward the hollow of the sacrum (**FIGURE 7**, page 39), allowing downward forces to compress the vaginal supports posteriorly onto the pelvic floor instead of forcing it out the vaginal lumen (**FIGURE 8**, page 39).

Our patients generally stay in the hospital overnight, and we place a vaginal pack to provide topical pressure throughout the vagina overnight. We tell patients no lifting more than 15 lb and no intercourse for 6 weeks. While we do not tend to use hydrodissection in our repairs, it is a perfectly acceptable option.

Commit to knowledge of native tissue techniques

Given the recent FDA ban on the sale of transvaginal mesh for POP and the public's negative perception of mesh (based often on misleading information in the media), it is incumbent upon gynecologic surgeons to invest in learning or relearning effective native tissue techniques for the transvaginal treatment of POP. While not perfect, they offer an effective nonmesh treatment option for many of our patients. ●

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BREAK THIS PRACTICE HABIT

The case for outpatient cervical ripening for IOL at term for low-risk pregnancies

These authors, who share their protocols, have been performing outpatient cervical ripening at their institutions for several years. Should outpatient ripening be the standard of care for low-risk pregnancies?

Robyn Lamar, MD, MPH; Biftu Mengesha, MD, MAS; and Sarah Little, MD, MPH

CASE 1 Induction at 39 weeks in a healthy nulliparous woman

A healthy 35-year-old woman (G1P0) at 39 weeks 0 days and with an uncomplicated pregnancy presents to your office for a routine prenatal visit. She inquires about scheduling an induction of labor, noting that she read a news story about induction at 39 weeks and that it might lower her chance of having a cesarean delivery (CD).

You perform a cervical exam—she is 1 cm dilated, 3 cm long, -2 station, posterior, and firm. You sweep her membranes after obtaining verbal consent. After describing the induction process, you explain that she might be hospitalized for several days before the birth given the need for cervical ripening. "You mean I need to stay in the hospital for the entire process?" she asks incredulously.

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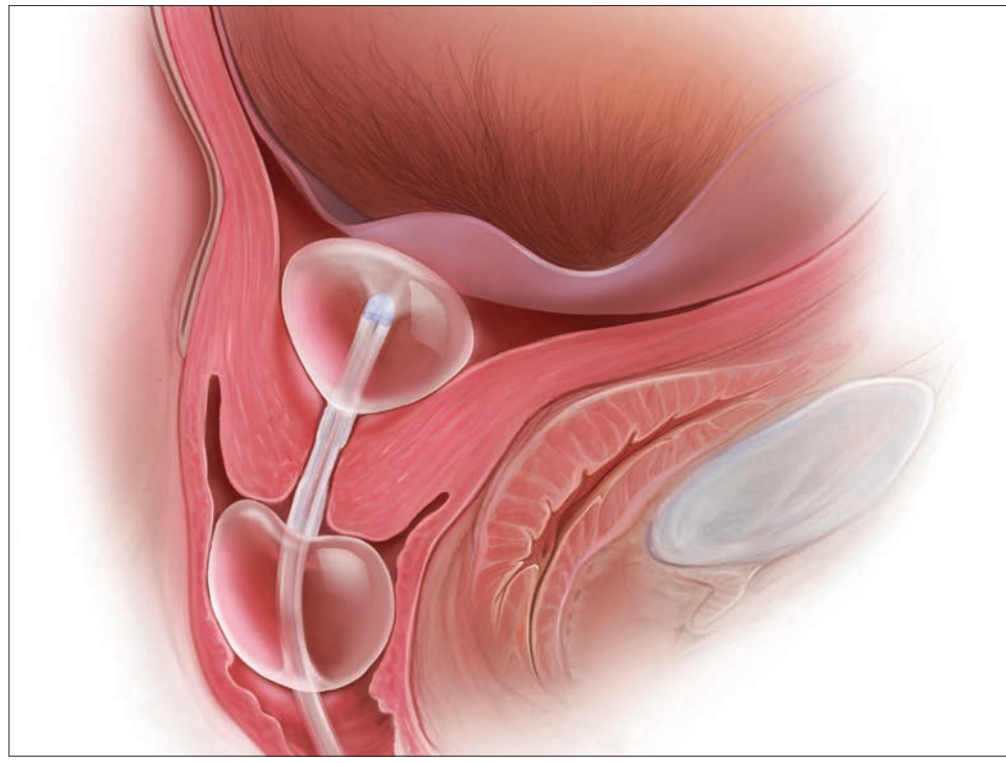
The authors report no financial relationships relevant to this article.

Over the past 20 years, the percentage of patients undergoing induction of labor (IOL) has increased from 10% to 25%.[1] This percentage likely will rise over time, particularly in the wake of a recent randomized controlled trial suggesting potential maternal benefits, such as reduced CD rate, for nulliparas induced at 39 weeks compared with expectant management.[2] Although there have not been any changes to guidelines for timing of IOL from such professional societies such as the American College of Obstetricians and Gynecologists (ACOG) or the Society for Maternal-Fetal Medicine, key considerations of rising IOL volume include patient experience, labor and delivery (L&D) units' capacity and resources, and associated health care costs.

An essential part of successful induction involves patience. Induction can be a lengthy process, particularly for nulliparas with unripe cervices. Cervical ripening is a necessary component of successful labor induction, whether achieved mechanically or pharmacologically with synthetic prostaglandins, and it has been shown to lower the chance of CD.[3,4] However, achieving a ripe cervix is often the lengthiest part of an induction, and not uncommonly consumes 12 to 24 hours or more of inpatient time. Investigators have sought ways to make this process

IN THIS ARTICLE



Mechanical cervical ripening prior to induction of labor at term in low-risk pregnancies is performed on an inpatient and outpatient basis in many hospitals across the United States. Cervical ripening also can be achieved in low-risk patients through pharmacologic methods.

FAST TRACK

Complication rates are low for inpatient mechanical cervical ripening; complication rates for outpatient ripening are low as well, although data are limited

more expeditious. For example, the FOR-MOMI trial demonstrated that the induction-to-delivery time was several hours shorter when cervical ripening combined mechanical and pharmacologic approaches (Foley balloon plus misoprostol), compared with either method alone, without any increase in maternal or fetal complication rates.[5]

Better yet, what if admission to the L&D unit for IOL at term could be deferred until the cervix is ripe? A number of hospitals in the United States have successfully introduced outpatient cervical ripening, and several small observational and randomized controlled trials have reported good results in terms of safety, efficacy and time saved, and patient experience. Here, we will make the case that outpatient cervical ripening should be the standard of care for low-risk pregnancies.

Mechanical cervical ripening

Safety

Although data are limited on the safety, the authors of an ACOG Practice Bulletin suggest that, based on the available evidence of mechanical ripening in an inpatient setting, it is also appropriate in the outpatient setting.[6] Unlike cervical ripening using prostaglandins, mechanical ripening is not associated with tachysystole, fetal intolerance of labor, or meconium staining.[3] A cohort study of nearly 2,000 low-risk patients who underwent Foley catheter placement for cervical ripening using an outpatient protocol but monitored overnight as inpatients and evaluated for adverse outcomes found no CD for fetal distress, vaginal bleeding, placental abruption, or intrapartum stillbirth.[7] The authors posited that, given this safety profile in the inpatient setting, that mechanical cervical ripening with a Foley catheter would be appropriate for outpatient use in low-risk populations. Other systematic reviews have been reassuring as well, with exceedingly low complication rates during inpatient mechanical cervical ripening.[8] These data advocate for the evaluation of cervical ripening in the outpatient setting.

The evidence for outpatient mechanical ripening, although again limited, also has

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

demonstrated safety. There does not appear to be an increased rate of maternal or neonatal complications, including infectious morbidity, postpartum hemorrhage, CD, operative vaginal delivery, or fetal distress.[9-12]

Efficacy and length-of-stay

Efficacy also generally has been shown to be similar when mechanical methods are used in the inpatient and outpatient settings. Small randomized trials of outpatient versus inpatient Foley catheter ripening have shown decreased length of stay (by 10 to 13 hours) and similar or less oxytocin use in the outpatient groups, as well as similar Bishop scores after cervical ripening and no difference in maternal or fetal outcomes.[9,11,13,14]

One major concern with increasing IOL prevalence is the availability of hospital resources and the associated health care costs, given the known increased length of inpatient stay due to cervical ripening time. Admission to an L&D unit is resource intensive; the costs are similar to admission to an intensive care unit in many hospitals given its level of acuity and high nurse/patient ratio. However, given the safety of outpatient mechanical cervical ripening described above, we argue that routinely admitting low-risk patients for mechanical ripening constitutes a suboptimal use of costly resources.

Indeed, data suggest significant inpatient time savings if cervical ripening can be accomplished prior to admission. A cost-effectiveness analysis in the Netherlands demonstrated a nearly 1,000-euro decrease in cost per induction when Foley catheter induction was done on an outpatient basis.[15] Interestingly, a recent trial confined to multiparas found no differences in hospital time when comparing outpatient ripening with Foley balloon alone with inpatient ripening with Foley balloon plus simultaneous oxytocin.[10] This certainly merits further study, but it may be that the largest time- and cost-savings are among nulliparas.

Patient preferences

Relatively few studies specifically have addressed patient experiences with outpatient versus inpatient mechanical cervical ripening. Outpatient cervical ripening may provide patients with the benefits of being in the comfort of their own homes with their preferred support persons, increased mobility, more bodily autonomy, and satisfaction with their birthing process.

In a pilot trial involving 48 women, inpatient was compared with outpatient cervical ripening using a Foley balloon. Those in the outpatient group reported getting more rest, feeling less isolated, and having enough privacy. However, participants in both groups were equally satisfied and equally likely to recommend their method of induction to others.[11] Another study comparing outpatient versus inpatient Foley balloon cervical ripening found that 85% of patients who underwent outpatient ripening were satisfied with the induction method; however, no query or comparison was done with the inpatient group.[12] A trial comparing outpatient mechanical cervical ripening with inpatient misoprostol found that outpatient participants reported several hours more sleep and less pain.[16] And in a discrete choice experiment of British gravidas, participants favored the option of outpatient cervical ripening, even if it meant an extra 1.4 trips to the hospital and over an hour of extra travel time.[17]

While these preliminary findings provide some insight that patients may prefer an outpatient approach to cervical ripening, more studies are needed to fully evaluate patient desires.

Our approach to mechanical cervical ripening

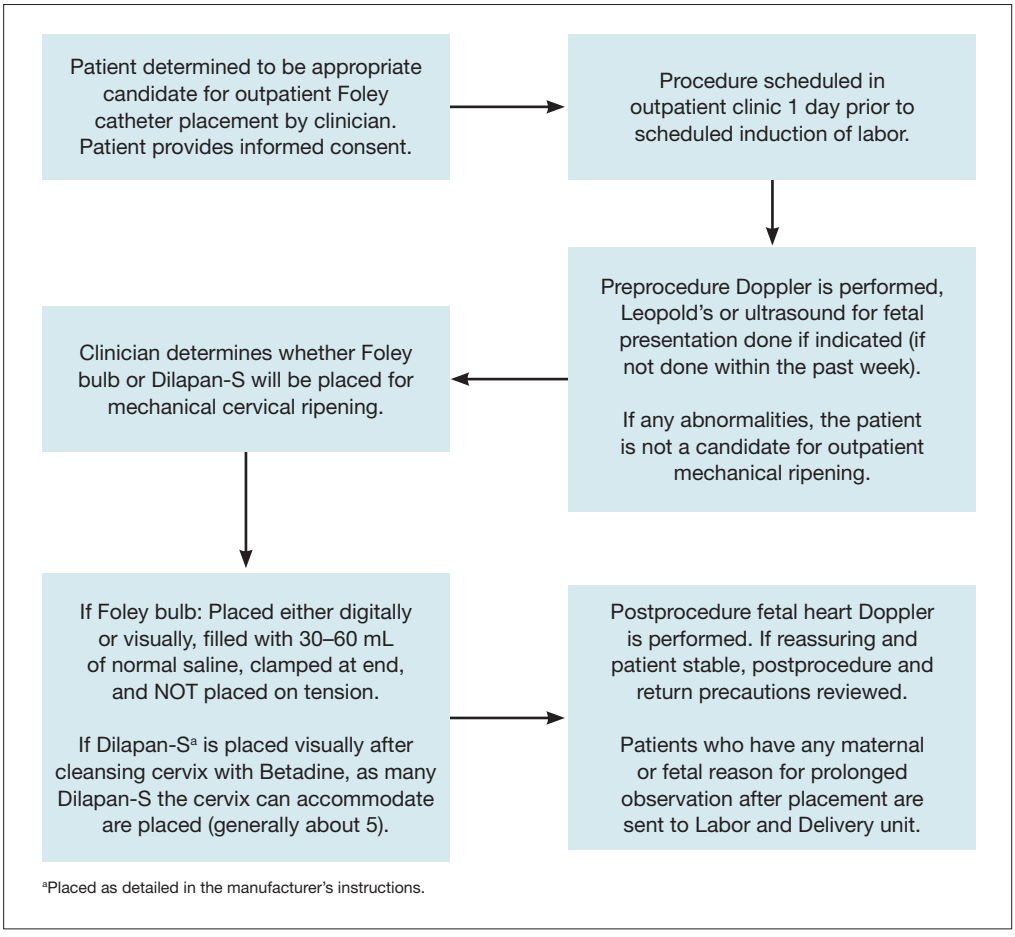
Most patients undergoing scheduled IOL are reasonable candidates for outpatient cervical ripening based on safety and efficacy. By definition, scheduling in advance implies that the provider has determined that outpatient management is reasonable until that date, and the plan for outpatient ripening need not prolong this period.

FIGURES 1 (page 44) and **2** (page 46) show protocols for our 2 hospital centers, which regularly allow for outpatient mechanical

FAST TRACK

Small trials of outpatient vs inpatient Foley catheter ripening have shown decreased length of stay and similar or less oxytocin use for the outpatient groups, as well as similar Bishop scores after ripening and no difference in maternal or neonatal outcomes

FIGURE 1 Hospital 1 outpatient mechanical cervical ripening protocol



[a]Placed as detailed in the manufacturer's instructions.

FAST TRACK

Ideal candidates for outpatient mechanical cervical ripening include patients undergoing elective or routine prolonged gestation inductions or inductions for well-controlled, stable chronic hypertension or gestational diabetes

cervical ripening. In the process of protocol development, we identified absolute and relative contraindications to determine appropriate candidates. We exclude women who require inpatient management of medical or obstetric conditions (for example, women with severe preeclampsia or any condition requiring continuous fetal monitoring). We also do not routinely recommend outpatient cervical ripening to patients who do not have the necessary social conditions to make this process as safe as possible (including stable housing, reliable transportation, and a support person), although this occurs with some exceptions depending on individual patient situations.

Some examples of ideal candidates for outpatient mechanical cervical ripening include those undergoing elective or routine prolonged gestation inductions, or inductions for well-controlled, stable conditions (chronic hypertension and gestational diabetes). At one center, after thorough counseling and assessment, outpatient cervical ripening is also offered to patients with mild risk factors, including twins, prior low transverse CD, stable preeclampsia without severe features, isolated oligohydramnios with otherwise reassuring fetal status, and other similar conditions.

After mechanical cervical ripening placement (either Foley catheter or mechanical dilators), the clinician completes a postprocedure safety checklist and detailed procedure documentation, including number and type of foreign bodies placed. If there

CONTINUED ON PAGE 45

2019

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Mark D. Walters, MD
Cleveland Clinic

Faculty

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University of Michigan

Michael S. Baggish, MD
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Andrew I. Brill, MD
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- 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

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)**
Sawsan As-Sanie, MD, MPH

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**
Sawsan As-Sanie, MD, MPH

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

10:30 AM **Break**

10:45 AM **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!

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

Dr. Neil Baum is the author of *The Complete Business Guide to a Successful Medical Practice* and *3-Stages of a Physician's Career*

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

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

Sawsan As-Sanie, MD, MPH
Director
Minimally Invasive Gyn Surgery and Chronic Pelvic Pain
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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
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Amanda Nickles Fader, MD
Associate Professor and Director
Kelly Gynecologic Oncology Service
Director of Minimally Invasive Surgery
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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

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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** Also open to non-attendees	$395	$495
■ **Best Buy!** 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 44

are any concerns regarding maternal or fetal well-being, the patient is sent to L&D for evaluation. If the procedure was tolerated well, the patient is discharged home, after a reactive postprocedure nonstress test is done, with detailed instructions for self-care, as well as with a list of symptoms that warrant prompt evaluation prior to scheduled induction time. In a large California hospital group following a similar protocol, only about 5% of women presented in labor before their scheduled induction.[18]

CASE 2 Cervical ripening for labor preparation in low-risk pregnancy

A 32-year-old woman (G1P0) with an uncomplicated pregnancy at 40 weeks and 3 days presents to your office for a routine prenatal visit. Her vital signs are normal, and her fetus is vertex with an estimated fetal weight of 7.5 lb by Leopald's maneuvers. You perform a cervical exam and find that her cervix is closed, long, and posterior.

You discuss with her your recommendation for induction of labor by 41 weeks, and she agrees. You also discuss the need for cervical ripening and recommend misoprostol given her closed cervix. You explain that several doses may be needed to get her cervix ready for labor, and she asks, "Do I have to stay in the hospital that whole time?"

Pharmacologic cervical ripening

Efficacy

There are multiple pharmacologic agents that can be used for ripening an unfavorable cervix. The main agents used in the United States are prostaglandins, either PGE1 (oral or vaginal misoprostol) or PGE2 in a gel or sustained-release vaginal insert (dinoprostone).

Outpatient misoprostol to avoid labor induction. Many studies have looked at outpatient misoprostol use as a "prophylactic measure" (to prevent the need for labor induction). For example, Gaffaney and colleagues showed that administering outpatient oral misoprostol (100 µg every 24 hours for up to 3 doses) after 40 weeks' gestation to women with an unfavorable cervix significantly decreased the time to delivery by a day and a half.[19] Similarly, PonMalar and colleagues demonstrated that administering 25 µg of vaginal misoprostol in a single dose as an outpatient after stripping the membranes significantly reduced time to delivery by 2 days.[20] And Stitely and colleagues found a significant reduction in the need for labor induction with the use of outpatient vaginal misoprostol. They administered up to 2 doses of misoprostol 25 µg vaginally every 24 hours for the 48 hours prior to a scheduled postdates induction and found a large reduction in the need for labor induction (11% vs 85%; $P<.01$).[21]

Multiple protocols and regimens have been studied but, overall, the findings suggest that administering outpatient misoprostol may shorten the time interval to spontaneous labor and decrease the need for a formal labor induction.[19-23]

Inpatient compared with outpatient prostaglandin use. These trials of "prophylactic" misoprostol generally have compared outpatient administration of misoprostol with placebo. Prostaglandins are one of the most common methods of inpatient cervical ripening, so what about comparisons of inpatient cervical ripening with outpatient prostaglandin administration? There are a handful of studies that make this comparison.

Chang and colleagues looked retrospectively at inpatient and outpatient misoprostol and found that outpatient administration saved 3 to 5 hours on labor and delivery.[24] Biem and colleagues randomly assigned women to either inpatient cervical ripening with PGE2 intravaginal inserts or 1 hour of inpatient monitoring after PGE2 administration and then outpatient discharge until the onset of labor or for a nonstress test at 12 hours. They found that those who underwent outpatient ripening spent 8 hours less on labor and delivery and were more highly satisfied with the initial 12 hours of labor induction experience (56% vs 39%; $P<.01$).[25]

The largest randomized controlled trial conducted to study outpatient prostaglandin

FAST TRACK

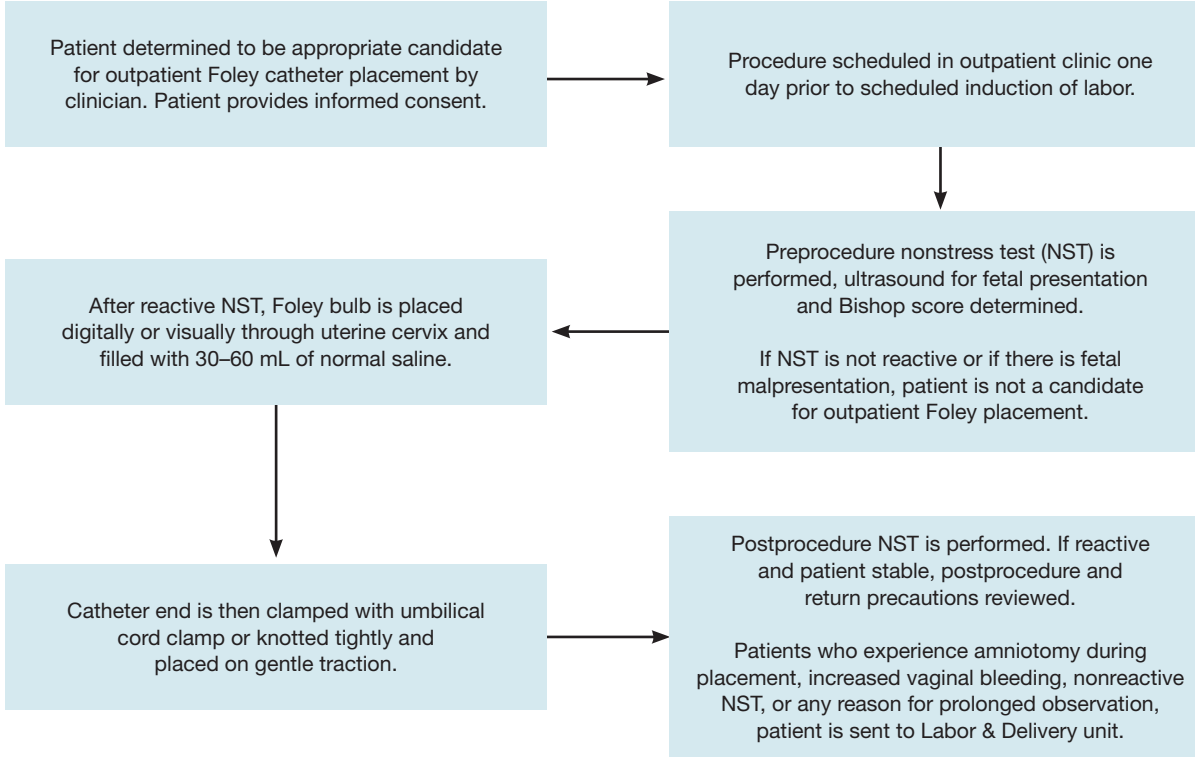
Administering outpatient misoprostol may shorten the time to spontaneous labor and decrease the need for formal labor induction

use was the OPRA study (involving 827 women). Investigators compared inpatient to outpatient PGE2 intravaginal gel.[26] The primary outcome was total oxytocin administration, which was not different between groups. The study was underpowered, however, as 50% of women labored spontaneously postrandomization. But in the outpatient arm,

FIGURE 2 Hospital 2 outpatient mechanical cervical ripening protocol

Absolute contraindications	Relative contraindications[a]
• Any contraindication to vaginal delivery • Nonreactive nonstress test • Biophysical profile score ≤6 • High-risk, uncontrolled medical or obstetric conditions (eg, preeclampsia with severe features) • Known or suspected placental abruption or active vaginal bleeding • Preterm gestation • Rupture of membranes • Fetal growth restriction • Fluid disorders (oligohydramnios or polyhydramnios) • Fetal anomalies requiring immediate and aggressive resuscitation • Patient unable to verbalize understanding of care plan or instructions for self-care	• Unreliable patient phone access • Unreliable patient transportation • Patient who has demonstrated difficulty attending prenatal appointments • Previous uterine scar (eg, previous cesarean delivery) • Intrahepatic cholestasis of pregnancy • Bishop score ≥6

[a]After thorough counseling and/or development of contingency plans for conditions listed, patients who meet these criteria may be appropriate candidates for outpatient mechanical cervical ripening as deemed by the clinician.



less than half of the women required additional inpatient ripening, and nearly 40% returned in spontaneous labor, suggesting that outpatient prostaglandin administration may indeed save women a significant amount of time on labor and delivery.

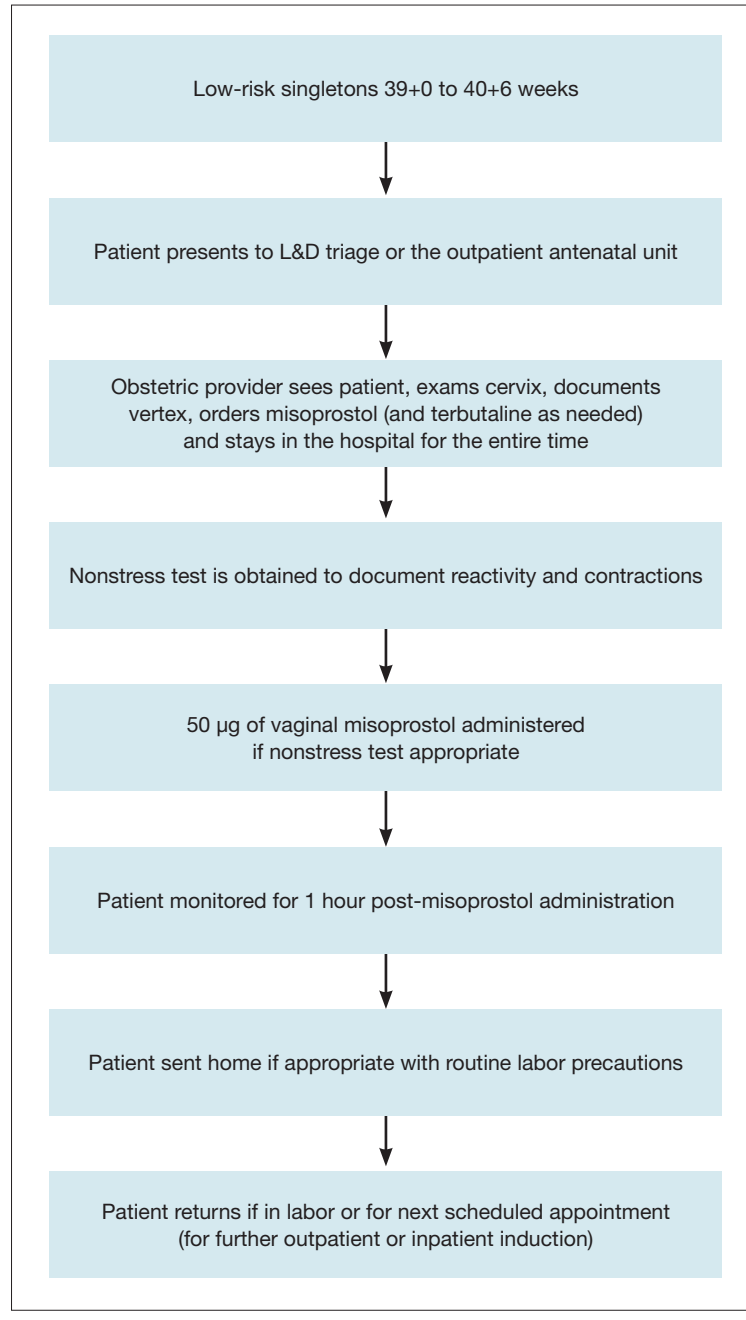
Safety

The safety of outpatient administration of prostaglandins is the biggest concern, especially since, when prostaglandins are compared to outpatient Foley catheter use, Foleys are overall associated with less tachysystole, fetal intolerance, and meconium-stained fluid.[3] Foley catheter use for cervical ripening may not be an appropriate choice for all patients, however. For instance, our case patient has a closed cervix, which could make Foley insertion uncomfortable or even impossible. Misoprostol use also offers the potential for flexibility in cervical ripening protocols as patients need not return for Foley balloon removal and indeed labor induction need not take place immediately after administration of misoprostol.

Patients also may prefer outpatient cervical ripening with misoprostol over a Foley. There are some data to suggest that women, overall, have a preference toward prostaglandins; in the PROBAAT-II trial, which compared inpatient oral misoprostol to Foley catheter for cervical ripening, 12% of women in the Foley arm would have preferred another method of induction (vs 6% in the misoprostol arm; $P = .02$).[27] This preference may be magnified in an outpatient setting.

But, again, is outpatient administration of prostaglandins safe? The published trials thus far have not reported an increase in out-of-hospital deliveries or adverse fetal outcomes. However, studies have been of limited size to see more rare outcomes. Unfortunately, an adequately powered study to demonstrate safety is likely never to be accomplished, given that if used responsibly (in low-risk patients with adequate monitoring after administration) the incidence of adverse fetal outcomes during the at-home portion of cervical ripening is likely to be very low. With responsible use, outpatient administration of prostaglandins should be safe. Women are monitored after misoprostol administration and are not sent home if there are any concerns for fetal distress or if frequent contractions continue. Misoprostol reaches maximum blood concentration 30 minutes after oral administration and

FIGURE 3 Example outpatient misoprostol protocol



70 to 80 minutes after vaginal administration.[28] After this time, if contractions start to intensify it is likely that misoprostol has triggered spontaneous labor. In this setting, women are routinely allowed to spontaneously labor at home. One may even argue that outpatient misoprostol could lead to improved safety, as women essentially have a contraction stress test prior to spontaneous labor, and misoprostol administration as an outpatient, as opposed to as an inpatient, may allow for longer time intervals between doses, which could prevent dose stacking.

Our approach to pharmacologic cervical ripening

Our hospital has been conducting outpatient cervical ripening using vaginal misoprostol for more than 15 years without any known adverse safety concerns (**FIGURE 3**, page 47). Women with a low-risk, singleton pregnancy between 39+0 and 40+6 weeks are potential candidates for outpatient ripening. The majority of outpatient inductions are done electively without any medical indication. Women with stable, minor risk factors (such as diet-controlled gestational diabetes) also may be candidates at their clinician's discretion. Patients are monitored either in our L&D triage area or in our outpatient antenatal unit; both units are in the same building. One clinician offers outpatient misoprostol in the office, across the street from L&D. We allow for clinician flexibility after administration. Some clinicians do 1 or 2 doses of outpatient cervical ripening in a day prior to a scheduled inpatient induction the next day. Some do multiple daily doses over the course of a week.

Conclusion

While the data continue to be limited, we strongly believe there is sufficient quality evidence from a safety and efficacy perspective to support implementation and evaluation of outpatient cervical ripening protocols for low-risk pregnancies. In the setting of renewed commitments to reducing suboptimal health care costs and utilization as well as increasing patient satisfaction and control in their birthing experiences, we posit it is the responsibility of obstetricians, L&D leadership, and health care institutions to explore the implementation of outpatient cervical ripening for appropriate candidates in their settings. ●

FAST TRACK

At our institution, outpatient cervical ripening using vaginal misoprostol for low-risk pregnancies at 39+0 to 40+6 weeks has been an option for more than 15 years without known adverse safety concerns

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Would routine use of tranexamic acid for PPH be cost-effective in the United States?

Yes. A decision-tree analysis incorporated US-specific hemorrhage-related cost and probability data with tranexamic acid (TXA) outcome data from the international WOMAN trial. The study results indicate that routine use of TXA for postpartum hemorrhage (PPH) in the United States would be cost saving from both the health system and societal perspectives, particularly when TXA is administered within 3 hours of delivery.

Sudhof LS, Shainker SA, Einerson BD. Tranexamic acid in the routine treatment of postpartum hemorrhage in the United States: a cost-effectiveness analysis. Am J Obstet Gynecol. Published online June 18, 2019. doi.org/10.1016/j.ajog.2019.06.030.

EXPERT COMMENTARY

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Postpartum hemorrhage is a leading cause of morbidity and mortality in the United States. The World Maternal Antifibrinolytic (WOMAN) trial showed that the use of TXA, an antifibrinolytic agent, for PPH decreases hemorrhage-related mortality and laparotomy. Routine use of TXA for PPH has demonstrated cost-effectiveness in low-resource countries, where hemorrhage-related mortality rates are higher than in the United States. This study aimed to determine if routine use of TXA for PPH in the United States also is cost-effective.

The authors report no financial relationships relevant to this article.

Details of the study

Sudhof and colleagues conducted a decision-tree analysis to compare the cost-effectiveness of 3 strategies regarding routine use of TXA for PPH in the United States: no TXA, TXA given at any time, and TXA given within 3 hours of delivery.

Health care system perspective. In the primary analysis, the 3 strategies were evaluated from the perspective of the health care system. Outcomes included cost, number of laparotomies, and maternal deaths from delivery until 6 weeks postpartum. Rates of hemorrhage and related complications, as well as cost assumptions, were derived from multiple US-based studies. The relative risk reduction in death and laparotomy with TXA in the United States was assumed to be similar to that found in the WOMAN trial (19% and 36%, respectively).

FAST TRACK

Three strategies for PPH were analyzed for cost-effectiveness in the United States: no TXA, TXA given at any time, and TXA given within 3 hours of delivery

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Routine use of TXA for PPH, particularly within 3 hours of delivery, is likely cost-effective in the United States. Consideration should be given to including TXA in institutional hemorrhage protocols.

REBECCA F. HAMM, MD, AND ADI HIRSHBERG, MD

Societal perspective. In the secondary analysis, the 3 TXA strategies were evaluated from the societal perspective, comparing quality-adjusted life-years (QALYs) and cost per QALY. For both the primary and secondary analyses, sensitivity analyses were performed across a range of values for each input.

Main findings. Tranexamic acid use would be cost saving if the relative risk reduction for maternal death with TXA was greater than approximately 5%, which is significantly lower than that seen in the WOMAN trial (19%). The primary analysis demonstrated that—assuming a 3% rate of PPH—giving TXA to women with PPH would save $11.3 million, prevent 334 laparotomies, and avert 9 maternal deaths annually in the United States. This cost saving nearly tripled if TXA was administered within 3 hours of delivery, with 5 additional maternal deaths prevented.

Secondary analysis incorporating QALYs also showed TXA use to be cost-effective. These findings held through various sensitivity analyses.

Study strengths and limitations

This study is novel in its critical objective to determine the cost-effectiveness of routine use of TXA for PPH in the United States. Robust modeling using Monte Carlo estimation and a variety of sensitivity analyses add reliability to the authors' findings.

This work is limited, however, by the assumptions put into the authors' models. For example, outcome data regarding effectiveness of TXA was taken from the WOMAN trial, which was not performed within the United States. In addition, it is difficult to quantify in dollars an event as profound as a maternal death. The authors recognize that they likely underestimate the "cost" of a maternal death, but that this underestimation would only increase the cost-effectiveness of TXA.

Finally, it is important to take into account that such economic analyses are helpful to inform institutional guidelines and hemorrhage protocols, but that patient-specific decision-making should be individualized based on the clinical scenario at hand. ●

INDEX OF ADVERTISERS

*Demographic advertisement

The case for outpatient cervical ripening for IOL at term for low-risk pregnancies

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Rx Only

This Brief Summary does not include all the information needed to use SOLOSEC™ safely and effectively. See full Prescribing Information for SOLOSEC.

SOLOSEC (secnidazole) 2g oral granules

Single oral dose

Initial U.S. approval: 2017

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

The safety data described below reflect exposure to 589 patients, of whom 518 received a 2g dose of SOLOSEC. SOLOSEC was evaluated in 3 clinical trials of patients diagnosed with bacterial vaginosis: 2 placebo-controlled trials (Trial 1 n=215, Trial 2 n=189) and 1 uncontrolled safety trial (Trial 3 n=321).

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

Most Common Adverse Reactions

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

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

Adverse Reaction	SOLOSEC N=197 n (%)	Placebo N=136 n (%)
Vulvovaginal candidiasis	19 (9.6)	4 (2.9)
Headache	7 (3.6)	2 (1.5)
Nausea	7 (3.6)	1 (0.7)
Diarrhea	5 (2.5)	1 (0.7)
Abdominal pain	4 (2.0)	2 (1.5)
Vulvovaginal pruritus	4 (2.0)	2 (1.5)

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

Postmarketing Experience. The following adverse reactions have been reported during use of other formulations of secnidazole 2g outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Reported adverse reactions were nausea, dysgeusia, abdominal pain, headache, and vomiting.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nitroimidazoles, which have similar chemical structures to secnidazole, have been associated with tumors affecting the liver, lungs, mammary, and lymphatic tissues in animals after lifetime exposures. It is unclear if these positive tumor findings in lifetime rodent studies of these nitroimidazoles indicate a risk to patients taking a single dose of secnidazole to treat bacterial vaginosis.

Secnidazole was positive in the bacterial reverse mutation assay, but was negative for the rat micronucleus test and mouse lymphoma test.

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

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Manufactured for and Distributed by:
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Based on 7179660 Issued 10/2017

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A full course of BV treatment in one oral dose[1]

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INDICATION

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

SELECT IMPORTANT SAFETY INFORMATION

- SOLOSEC is contraindicated in patients with a history of hypersensitivity to secnidazole, other ingredients of the formulation, or other nitroimidazole derivatives.
- Vulvo-vaginal candidiasis may develop with SOLOSEC and require treatment with an antifungal agent.
- Potential risk of carcinogenicity in patients taking single-dose of SOLOSEC to treat bacterial vaginosis is unclear. Chronic use should be avoided.
- SOLOSEC is a single-dose therapy for oral use. The entire contents of SOLOSEC packet should be sprinkled onto applesauce, yogurt or pudding and consumed once within 30 minutes without chewing or crunching the granules. SOLOSEC is not intended to be dissolved in any liquid.
- In clinical studies, the most common adverse events occurring in (≥2%) of patients receiving SOLOSEC 2g oral granules were vulvovaginal candidiasis (9.6%), headache (3.6%), nausea (3.6%), dysgeusia (3.4%), vomiting (2.5%), diarrhea (2.5%), abdominal pain (2.0%), and vulvovaginal pruritus (2.0%).

Please see Brief Summary of Prescribing Information on adjacent page.

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

References: 1. SOLOSEC [prescribing information]. Baltimore, MD: Lupin Pharmaceuticals, Inc; 2017.
2. Broumas AG, Basara LA. Potential patient preference for 3-day treatment of bacterial vaginosis: responses to new suppository form of clindamycin. *Adv Ther*. 2000;17(3):159-166

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