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OBG MANAGEMENT

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Arnold Advincula's Video Series
Excision of abdominal wall endometriosis

What's in store for ObGyn reimbursement
ACOG's Donna Tyler; Barbara Levy, MD

Managing breast pain

Including whether or not to order imaging

Laila Samiian, MD

One or two uterotonics for reducing postpartum blood loss?
Robert L. Barbieri, MD

Immediate delivery vs expectant management for women with late preterm mild hypertension

Surgical Technique
Gastrointestinal endometriosis

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

- Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials.
- ORILISSA users had a higher incidence of depression and mood changes compared to placebo and ORILISSA users with a history of suicidality or depression had an increased incidence of depression. Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits. Patients with new or worsening depression, anxiety, or other mood changes should be referred to a mental health professional, as appropriate.
- Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORILISSA if such events occur.

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

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

Proven relief of moderate to severe pain associated with endometriosis

Dysmenorrhea
Non-menstrual Pelvic Pain

150 mg QD

Dysmenorrhea
Non-menstrual Pelvic Pain
Dyspareunia

200 mg BID

Tablets and packages pictured are not actual size.

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

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

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

These are not all the possible side effects of ORILISSA.

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

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

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

Orilissa®
elagolix tablets 150 mg 200 mg

ORILISSA™ (elagolix) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Important Dosing Information

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

Table 1. Recommended Dosage and Duration of Use

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

Hepatic Impairment

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

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

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

Missed Dose

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

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

CONTRAINDICATIONS

ORILISSA is contraindicated in women:

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials. ORILISSA subjects had a higher incidence of depression and mood changes compared to placebo, and ORILISSA subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history *[see Adverse Reactions]*. Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits *[see Adverse Reactions]*. Patients with new or worsening depression, anxiety or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORILISSA if such events occur.

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

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

Clinical Trials Experience

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

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

Serious Adverse Events

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

Adverse Reactions Leading to Study Discontinuation

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

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

Common Adverse Reactions:

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

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

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

Less Common Adverse Reactions:

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

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

Bone Loss

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

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

In Study EM-1, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was -0.9% (95% CI: -1.3, -0.4) with ORILISSA 150 mg once daily and -3.1% (95% CI: -3.6, -2.6) with ORILISSA 200 mg twice daily (Table 3). The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was 2% with ORILISSA 150 mg once daily, 7% with ORILISSA 200 mg twice daily and < 1% with placebo. In the blinded extension Study EM-3, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 8% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

In Study EM-2, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was -1.3% (95% CI: -1.8, -0.8) with ORILISSA 150 mg once daily and -3.0% (95% CI: -3.5, -2.6) with ORILISSA 200 mg twice daily (Table 3). The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was < 1% with ORILISSA 150 mg once daily, 6% with ORILISSA 200 mg twice daily and 0% with placebo. In the blinded extension Study EM-4, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 2% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

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

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

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

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

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

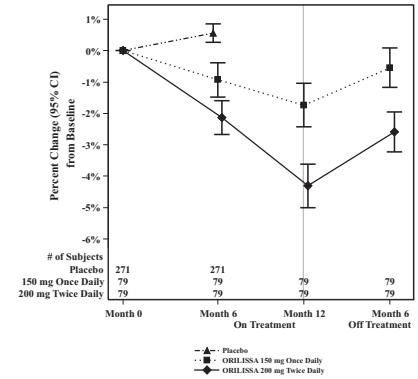
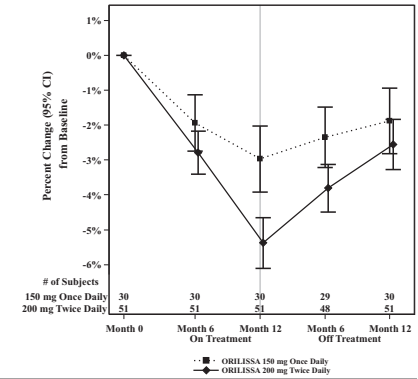


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

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

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

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

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

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

Hepatic Transaminase Elevations

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

Changes in Lipid Parameters

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

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

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

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

Hypersensitivity Reactions

In Studies EM-1 and EM-2, non-serious hypersensitivity reactions including rash occurred in 5.8% of ORILISSA treated-subjects and 6.1% of placebo-treated subjects. These events led to study drug discontinuation in 0.4% of ORILISSA-treated subjects and 0.5% of placebo-treated subjects.

Endometrial Effects

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

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

Effects on menstrual bleeding patterns

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

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

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

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

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

After 6 months of therapy with ORILISSA 150 mg once daily, resumption of menses after stopping treatment was reported by 59%, 87% and 95% of women within 1, 2, and 6 months, respectively. After 6 months of therapy with ORILISSA 200 mg twice daily, resumption of menses after stopping treatment was reported by 60%, 88%, and 97% of women within 1, 2, and 6 months, respectively.

After 12 months of therapy with ORILISSA 150 mg once daily resumption of menses after stopping treatment was reported by 77%, 95% and 98% of women within 1, 2, and 6 months respectively. After 12 months of therapy with ORILISSA 200 mg twice daily resumption of menses after stopping treatment was reported by 55%, 91% and 96% of women within 1, 2, and 6 months respectively.

DRUG INTERACTIONS

Potential for ORILISSA to Affect Other Drugs

Elagolix is a weak to moderate inducer of cytochrome P450 (CYP) 3A. Co-administration with ORILISSA may decrease plasma concentrations of drugs that are substrates of CYP3A.

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

Potential for Other Drugs to Affect ORILISSA

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

Concomitant use of ORILISSA 200 mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and strong CYP3A inhibitors to 6 months.

Co-administration of ORILISSA with drugs that induce CYP3A may decrease elagolix plasma concentrations.

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

Drug Interactions - Examples and Clinical Management

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

Table 7. Established Drug Interactions Based on Drug Interaction Trials

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

The limited human data with the use of ORILISSA in pregnant women are insufficient to determine whether there is a risk for major birth defects or miscarriage. Although two cases of congenital malformations were reported in clinical trials with ORILISSA, no pattern was identified and miscarriages were reported at a similar incidence across treatment groups *(see Data).*

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

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

Data

Human Data

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

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

Animal Data

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

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

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

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

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

Lactation

Risk Summary

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

Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Renal Impairment

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

Hepatic Impairment

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) that administered elagolix by the dietary route revealed no increase in tumors in mice at up to 19-fold the MRHD based on AUC. In the rat, there was an increase in thyroid (male and female) and liver (males only) tumors at the high dose (12 to 13-fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans.

Elagolix was not genotoxic or mutagenic in a battery of tests, including the *in vitro* bacterial reverse mutation assay, the *in vitro* mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, and the *in vivo* mouse micronucleus assay.

In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/day in female rats is approximately 5-fold. However, because elagolix has low affinity for the GnRH receptor in the rat *[see Use in Specific Populations]*, and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

PATIENT COUNSELING INFORMATION

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

- Advise patients on contraceptive options, not to get pregnant while using ORILISSA, to be mindful that menstrual changes could reflect pregnancy and to discontinue ORILISSA if pregnancy occurs *[see Contraindications and Warnings and Precautions]*.
- Inform patients that estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA.
- Inform patients about the risk of bone loss. Advise adequate intake of calcium and vitamin D *[see Warnings and Precautions]*.
- Advise patients to seek immediate medical attention for suicidal ideation and behavior. Instruct patients with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention *[see Warnings and Precautions]*.
- Counsel patients on signs and symptoms of liver injury *[see Warnings and Precautions]*.
- Instruct patients who miss a dose of ORILISSA to take the missed dose on the same day as soon as she remembers and then resume the regular dosing schedule:
  - 150 mg once daily: no more than 1 tablet each day should be taken.
  - 200 mg twice daily: no more than 2 tablets each day should be taken.
- Instruct patients to dispose of unused medication via a take-back option if available or to otherwise follow FDA instructions for disposing of medication in the household trash, www.fda.gov/drugdisposal, and not to flush down the toilet.

Manufactured by
AbbVie Inc.
North Chicago, IL 60064

Ref: 03-B671 Revised: July, 2018

206-1956816 **MASTER**

US-ORIL-190087

abbvie

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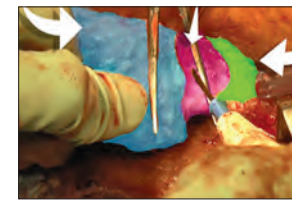

Abdominal wall endometriosis **C3**

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Only **Paragard® IUD**, with 1 hormone-free active ingredient (copper), delivers the **strongest combination of benefits for the widest range of women**[1,2*]

The Paragard Promise:

- Proven >99% efficacy
- 100% hormone free
- Pregnancy prevention for up to 10 years
- Immediately reversible whenever she decides

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

Indication

Paragard is intended for intrauterine contraception for up to 10 years.

Important Safety Information

- Paragard must not be used by women who have acute pelvic inflammatory disease (PID); have had a postpregnancy or postabortion uterine infection in the past 3 months; have cancer of the uterus or cervix; have an infection of the cervix; have an allergy to any component; or have Wilson's disease.
- If a woman misses her period, she must be promptly evaluated for pregnancy.
- Possible serious complications that have been associated with intrauterine contraceptives are PID, embedment, perforation of the uterus, and expulsion.
- Paragard must not be used by women who are pregnant as this can be life threatening and may result in loss of pregnancy or infertility.
- The most common side effects of Paragard are bleeding and spotting; for most women, these typically subside after 2 to 3 months.
- **Paragard does not protect against HIV or other sexually transmitted infections (STI).**

Please see the following page for a brief summary of full Prescribing Information.

Over 6 million Paragard units distributed[3]

Paragard® T380A
intrauterine copper contraceptive

simple, honest pregnancy prevention™

CooperSurgical

References: 1. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use; 2017. **2.** Kaneshiro B, Aeby T. Long-term safety, efficacy, and patient acceptability of the intrauterine Copper T-380A contraceptive device. *Int J Womens Health*. 2010;2:211-220. **3.** Data on file, March 2018. CooperSurgical, Inc.

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR
ParaGard® T 380A Intrauterine Copper Contraceptive

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ParaGard® is indicated for intrauterine contraception for up to 10 years. The pregnancy rate in clinical studies has been less than 1 pregnancy per 100 women each year.

CONTRAINDICATIONS

ParaGard® should not be placed when one or more of the following conditions exist:

1. Pregnancy or suspicion of pregnancy
2. Abnormalities of the uterus resulting in distortion of the uterine cavity
3. Acute pelvic inflammatory disease, or current behavior suggesting a high risk for pelvic inflammatory disease
4. Postpartum endometritis or postabortal endometritis in the past 3 months
5. Known or suspected uterine or cervical malignancy
6. Genital bleeding of unknown etiology
7. Mucopurulent cervicitis
8. Wilson's disease
9. Allergy to any component of ParaGard®
10. A previously placed IUD that has not been removed

WARNINGS

1. Intrauterine Pregnancy

If intrauterine pregnancy occurs with ParaGard® in place and the string is visible, ParaGard® should be removed because of the risk of spontaneous abortion, premature delivery, sepsis, septic shock, and, rarely, death. Removal may be followed by pregnancy loss.

If the string is not visible, and the woman decides to continue her pregnancy, check if the ParaGard® is in her uterus (for example, by ultrasound). If ParaGard® is in her uterus, warn her that there is an increased risk of spontaneous abortion and sepsis, septic shock, and rarely, death. In addition, the risk of premature labor and delivery is increased.

Human data about risk of birth defects from copper exposure are limited. However, studies have not detected a pattern of abnormalities, and published reports do not suggest a risk that is higher than the baseline risk for birth defects.

2. Ectopic Pregnancy

Women who become pregnant while using ParaGard® should be evaluated for ectopic pregnancy. A pregnancy that occurs with ParaGard® in place is more likely to be ectopic than a pregnancy in the general population. However, because ParaGard® prevents most pregnancies, women who use ParaGard® have a lower risk of an ectopic pregnancy than sexually active women who do not use any contraception.

3. Pelvic Infection

Although pelvic inflammatory disease (PID) in women using IUDs is uncommon, IUDs may be associated with an increased relative risk of PID compared to other forms of contraception and to no contraception. The highest incidence of PID occurs within 20 days following insertion. Therefore, the visit following the first post-insertion menstrual period is an opportunity to assess the patient for infection, as well as to check that the IUD is in place. Since pelvic infection is most frequently associated with sexually transmitted organisms, IUDs are not recommended for women at high risk for sexual infection. Prophylactic antibiotics at the time of insertion do not appear to lower the incidence of PID.

PID can have serious consequences, such as tubal damage (leading to ectopic pregnancy or infertility), hysterectomy, sepsis, and, rarely, death. It is therefore important to promptly assess and treat any woman who develops signs or symptoms of PID. Guidelines for treatment of PID are available from the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia at www.cdc.gov or 1-800-311-3435. Antibiotics are the mainstay of therapy. Most healthcare professionals also remove the IUD.

The significance of actinomyces-like organisms on Papanicolaou smear in an asymptomatic IUD user is unknown, and so this finding alone does not always require IUD removal and treatment. However, because pelvic actinomycosis is a serious infection, a woman who has *symptoms* of pelvic infection possibly due to actinomyces should be treated and have her IUD removed.

4. Immunocompromise

Women with AIDS should not have IUDs inserted unless they are clinically stable on antiretroviral therapy. Limited data suggest that asymptomatic women infected with human immunodeficiency virus may use intrauterine devices. Little is known about the use of IUDs in women who have illnesses causing serious immunocompromise. Therefore these women should be carefully monitored for infection if they choose to use an IUD. The risk of pregnancy should be weighed against the theoretical risk of infection.

5. Embedment

Partial penetration or embedment of ParaGard® in the myometrium can make removal difficult. In some cases, surgical removal may be necessary.

6. Perforation

Partial or total perforation of the uterine wall or cervix may occur rarely during placement, although it may not be detected until later. Spontaneous migration has also been reported. If perforation does occur, remove ParaGard® promptly, since the copper can lead to intraperitoneal adhesions. Intestinal penetration, intestinal obstruction, and/or damage to adjacent organs may result if an IUD is left in the peritoneal cavity. Pre-operative imaging followed by laparoscopy or laparotomy is often required to remove an IUD from the peritoneal cavity.

7. Expulsion

Expulsion can occur, usually during the menses and usually in the first few months after insertion. There is an increased risk of expulsion in the nulliparous patient. If unnoticed, an unintended pregnancy could occur.

8. Wilson's Disease

Theoretically, ParaGard® can exacerbate Wilson's disease, a rare genetic disease affecting copper excretion.

PRECAUTIONS

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

1. Information for patients

Before inserting ParaGard® discuss the Patient Package Insert with the patient, and give her time to read the information. Discuss any questions she may have concerning ParaGard® as well as other methods of contraception. Instruct her to promptly report symptoms of infection, pregnancy, or missing strings.

2. Insertion precautions, continuing care, and removal.

3. Vaginal bleeding

In the 2 largest clinical trials with ParaGard®, menstrual changes were the most common medical reason for discontinuation of ParaGard®. Discontinuation rates for pain and bleeding combined are highest in the first year of use and diminish thereafter. The percentage of women who discontinued ParaGard® because of bleeding problems or pain during these studies ranged from 11.9% in the first year to 2.2 % in year 9. Women complaining of heavy vaginal bleeding should be evaluated and treated, and may need to discontinue ParaGard®.

4. Vasovagal reactions, including fainting

Some women have vasovagal reactions immediately after insertion. Hence, patients should remain supine until feeling well and should be cautious when getting up.

5. Expulsion following placement after a birth or abortion

ParaGard® has been placed immediately after delivery, although risk of expulsion may be higher than when ParaGard® is placed at times unrelated to delivery. However, unless done immediately postpartum, insertion should be delayed to the second postpartum month because insertion during the first postpartum month (except for immediately after delivery) has been associated with increased risk of perforation.

ParaGard® can be placed immediately after abortion, although immediate placement has a slightly higher risk of expulsion than placement at other times. Placement after second trimester abortion is associated with a higher risk of expulsion than placement after the first trimester abortion.

6. Magnetic resonance imaging (MRI)

Limited data suggest that MRI at the level of 1.5 Tesla is acceptable in women using ParaGard®. One study examined the effect of MRI on the CU-7® Intrauterine Copper Contraceptive and Lippes Loop™ intrauterine devices. Neither device moved under the influence of the magnetic field or heated during the spin-echo sequences usually employed for pelvic imaging. An in vitro study did not detect movement or temperature change when ParaGard® was subjected to MRI.

7. Medical diathermy

Theoretically, medical (non-surgical) diathermy (short-wave and microwave heat therapy) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. However, a small study of eight women did not detect a significant elevation of intrauterine temperature when diathermy was performed in the presence of a copper IUD.

8. Pregnancy

ParaGard® is contraindicated during pregnancy.

9. Nursing mothers

Nursing mothers may use ParaGard®. No difference has been detected in concentration of copper in human milk before and after insertion of copper IUDs. The literature is conflicting, but limited data suggest that there may be an increased risk of perforation and expulsion if a woman is lactating.

10. Pediatric use

ParaGard® is not indicated before menarche. Safety and efficacy have been established in women over 16 years old.

ADVERSE REACTIONS

The most serious adverse events associated with intrauterine contraception are discussed in **WARNINGS** and **PRECAUTIONS**. These include:

Intrauterine pregnancy	Pelvic infection
Septic abortion	Perforation
Ectopic pregnancy	Embedment

The following adverse events have also been observed. These are listed alphabetically and not by order of frequency or severity.

Anemia	Menstrual flow, prolonged
Backache	Menstrual spotting
Dysmenorrhea	Pain and cramping
Dyspareunia	Urticarial allergic skin reaction
Expulsion, complete or partial	Vaginitis
Leukorrhea	

CooperSurgical

CooperSurgical, Inc
95 Corporate Drive
Trumbull, CT 06611

This brief summary is based on the ParaGard full prescribing information dated September 2014.

PAR-41287 01/18

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SIVAN VAINER, MD, AND MEGAN L. EVANS, MD, MPH

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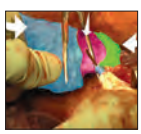

Excision of abdominal wall endometriosis
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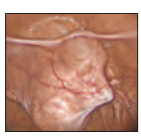

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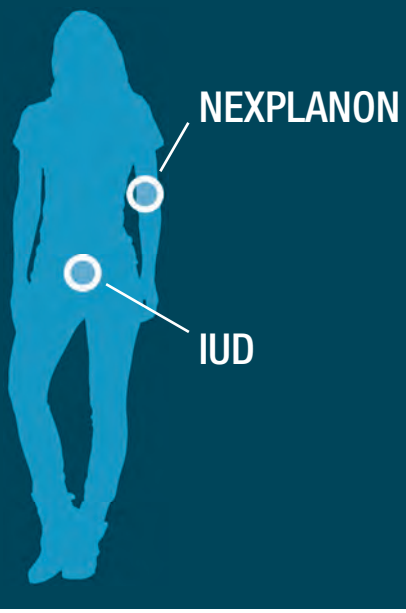

Help your patients understand both of their LARC location options[1]

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

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

Complications of insertion and removal

- NEXPLANON should be inserted subdermally and be palpable after insertion. Palpate immediately after insertion to ensure proper placement. Undetected failure to insert the implant may lead to unintended pregnancy. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.
- Insertion and removal-related complications may include pain, paresthesias, bleeding, hematoma, scarring, or infection. If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. Implant removal may be difficult or impossible if the implant is not inserted correctly, inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. If at any time the implant cannot be palpated, it should be localized and removal is recommended.
- There have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Endovascular or surgical procedures may be needed for removal.

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

US-XPL-00236 03/19

NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

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

>99% effective†

Reversible if her plans change

Placed subdermally just under the skin in the inner upper arm

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

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

(Actual implant shown; actual implant is 4 cm)

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

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

MERCK

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

The efficacy of NEXPLANON does not depend on daily, weekly or monthly administration. All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON. A single NEXPLANON implant is inserted subdermally just under the skin at the inner side of the non-dominant upper arm. The insertion site is overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult or impossible *[see Dosage and Administration and Warnings and Precautions]*. NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

- Known or suspected pregnancy
- Current or past history of thrombosis or thromboembolic disorders
- Liver tumors, benign or malignant, or active liver disease
- Undiagnosed abnormal genital bleeding
- Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past
- Allergic reaction to any of the components of NEXPLANON *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

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

Complications of Insertion and Removal

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

If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To help reduce the risk of neural or vascular injury, NEXPLANON should be inserted subdermally just under the skin at the inner side of the non-dominant upper arm overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. Deep insertions of NEXPLANON have been associated with paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, encased in fibrous tissue, or has migrated.

There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion. There also have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal.

If at any time the implant cannot be palpated, it should be localized and removal is recommended.

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

Changes in Menstrual Bleeding Patterns

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

In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding pattern were the most common reason for stopping treatment (11.1%). Irregular bleeding (10.8%) was the single most common reason women stopped treatment, while amenorrhea (0.3%) was cited less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

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

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

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

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

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

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

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

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

Ectopic Pregnancies

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

Thrombotic and Other Vascular Events

The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of venous and arterial thromboembolism be carefully assessed. There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using etonogestrel implants. NEXPLANON should be removed in the event of a thrombosis.

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

Ovarian Cysts

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

Carcinoma of the Breast and Reproductive Organs

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

Liver Disease

Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove NEXPLANON if jaundice develops. Hepatic adenomas are associated with combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON. The progestin in NEXPLANON may be poorly metabolized in women with liver impairment. Use of NEXPLANON in women with active liver disease or liver cancer is contraindicated *[see Contraindications]*.

Weight Gain

In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for having the non-radiopaque etonogestrel implant removed.

Elevated Blood Pressure

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

Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among combination hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

Carbohydrate and Lipid Metabolic Effects

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

Depressed Mood

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

Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

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

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

***In Situ* Broken or Bent Implant**
There have been reports of broken or bent implants while in the patient's arm. Based on *in vitro* data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety *[see Dosage and Administration]*.

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

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

ADVERSE REACTIONS
In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant]) (11.1% of women).
Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

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

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

*Includes "frequent", "heavy", "prolonged", "spotting", and other patterns of bleeding irregularity.
† Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.
‡ Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

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

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

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

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%), and swelling (0.7%) were reported.

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

Substances increasing the plasma concentrations of HCs: Co-administration of certain HCs and strong or moderate CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase the serum concentrations of progestins, including etonogestrel.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of progestin have been noted in cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine, efavirenz] or increase [e.g., etravirene]). These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral and anti-retroviral concomitant medications to identify potential interactions.

Effects of Hormonal Contraceptives on Other Drugs
Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, cyclosporine) or decrease (for example, lamotrigine). Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant *[see Contraindications]*. Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 781 times the anticipated human dose (60 µg/day). NEXPLANON should be removed if maintaining a pregnancy.

Lactation
Risk Summary
Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers.This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

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

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

Hepatic Impairment
No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated *[see Contraindications]*.

Overweight Women
The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

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

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

PATIENT COUNSELING INFORMATION *See FDA-Approved Patient Labeling*.
- Counsel women about the insertion and removal procedure of the NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.
- Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.
- Counsel women that NEXPLANON does not protect against HIV infection (AIDS) or other STDs.
- Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA.

For more detailed information, please read the Prescribing Information.
USPI-MK8415-IPTX-1810r020
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MERCK

AVOIDING OBSTETRIC COMPLICATIONS

One versus two uterotonics: Which is better for minimizing postpartum blood loss?

A Cochrane network meta-analysis concluded that the two highest-ranked interventions for reducing the rate of postpartum blood loss ≥ 500 mL were misoprostol plus oxytocin and ergonovine plus oxytocin. However, administering two agents significantly increases the rate of adverse effects.

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Excessive postpartum bleeding is a major cause of maternal morbidity and mortality. Worldwide, obstetric hemorrhage is the most common cause of maternal death.[1,2] Medications reported to reduce postpartum bleeding include oxytocin, misoprostol, ergonovine, methylergonovine, carboprost, and tranexamic acid. A recent Cochrane network meta-analysis of 196 trials, including 135,559 women, distilled in 1,361 pages of analysis, reported on the medications associated with the greatest reduction in postpartum bleeding.[3] Surprisingly, for preventing blood loss ≥ 500 mL, misoprostol plus oxytocin and ergonovine plus oxytocin were the highest ranked interventions. This evidence is summarized here.

Misoprostol plus oxytocin

After newborn delivery, active management of the third stage of labor, including uterotonic administration, is strongly recommended because it will reduce postpartum blood loss, decreasing the rate of postpartum hemorrhage (PPH).[4] Both oxytocin and misoprostol are effective uterotonics. However, the combination of oxytocin plus misoprostol appears to be more effective than oxytocin alone in reducing the frequency of postpartum blood loss greater than 500 mL.[3] To understand the clinical efficacy and adverse effects (AEs) of combined oxytocin plus misoprostol a meta-analysis was performed for both vaginal and cesarean deliveries (CDs).

Efficacy and AEs during vaginal delivery. In the meta-analysis, about 6,000 vaginal deliveries were analyzed, with no significant differences for misoprostol plus oxytocin versus oxytocin alone found for the following outcomes: maternal death, intensive care unit admissions, and rate of blood loss ≥ 1,000 mL (1.7% for both uterotonics vs 2.2% for oxytocin alone).[3] Misoprostol plus oxytocin was *significantly superior* to oxytocin alone for the following outcomes: reduced risk of blood transfusion (0.95% vs 2.5%), reduced risk of blood loss ≥ 500 mL (5.9% vs 8.0%), reduced risk of requiring an additional uterotonic (3.6% vs 5.8%), and a smaller decrease in hemoglobin concentration from pre- to postdelivery (-0.89 g/L).[3]

In my opinion, the difference in hemoglobin concentration, although statistically significant, is not of clinical significance. However, compared with oxytocin alone, misoprostol plus oxytocin caused significantly more nausea (2.4% vs 0.66%), vomiting (3.1% vs 0.86%), and fever (21% vs 3.9%).[3] A weakness of this meta-analysis is that the trials used a wide range of misoprostol dosages (200 to 600 µg) and multiple routes of administration, including sublingual (under the tongue), buccal, and rectal. This makes it impossible to identify a best misoprostol dosage and administration route.

Efficacy and AEs during CD. In the same meta-analysis about 2,000 CDs were analyzed, with no significant difference for misoprostol plus oxytocin versus oxytocin alone for the

CONTINUED ON PAGE 17

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

Solosec™ (secnidazole) is the first and only bacterial vaginosis (BV) treatment designed to deliver a complete course of therapy in just one oral dose[1,2]

To learn how Solosec may make it easy for patients to complete treatment, visit **solosechcp.com/journal.**

ONE PACKET.
ONE DOSE.
ONE TIME.

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

PP-SOL-0096

solosec™
secnidazole
2g Oral Granules

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:
Lupin Pharmaceuticals, Inc.
Baltimore, MD 21202

Based on 7179660 Issued 10/2017

LUPIN PHARMACEUTICALS, INC.

NP-SOL-0004

CONTINUED FROM PAGE 14

Pharmacokinetic properties of common uterotonics used to reduce postpartum bleeding

	Half-life	Storage		
Oxytocin	1 to 6 minutes	Cold storage	With intravenous bolus or infusion, onset of action is achieved within 1 minute. Duration of action is 1 hour.	With intramuscular injection the onset of action is within 5 minutes. The duration of action is 2 to 3 hours.
Misoprostol	20 to 40 minutes	Stable at ambient temperature	Peak concentration is reached at approximately 15, 30, and 60 minutes with oral, sublingual, and buccal administration, respectively.[1]	Peak concentration is reached at 60 minutes with vaginal and rectal administration.[2]
Ergonovine (ergonovine)	30 to 120 minutes	Cold storage	With intramuscular administration, onset of action is 2 to 5 minutes and duration of action is up to 3 hours.	Contraindicated in women with hypertension.
Methylergonovine (Methergine)	1.5 to 13 hours	Cold storage	With intramuscular administration, onset of action is 2 to 5 minutes and duration of action is up to 3 hours.	Contraindicated in women with hypertension.
Carboprost (Hemabate) 15-methyl prostaglandin F2 alpha	8 minutes	Cold storage	After intramuscular injection peak plasma concentration is reached in 30 minutes.	
Carbetocin (not available in the United States)	40 minutes	Stable at ambient temperature	After intravenous bolus administration over 1 minute (recommended route), sustained contraction for 6 minutes and rhythmic contractions for 60 minutes.	After intramuscular injection, sustained contraction for 11 minutes and rhythmic contractions for 120 minutes.

Data provided by Lexicomp, except where noted.

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following outcomes: maternal death, intensive care unit admissions, and PPH ≥ 1,000 mL blood loss (6.2% vs 6.5%).[3] Misoprostol plus oxytocin was *significantly superior* to oxytocin alone for the following outcomes: reduced risk of blood transfusion (2.6% vs 5.4%), reduced risk of blood loss ≥ 500 mL (32% vs 47%), reduced risk of requiring an additional uterotonic (14% vs 28%), and a smaller decrease in hemoglobin concentration from before to after delivery (-4.0 g/L).[3] In my opinion, the statistically significant difference in hemoglobin concentration is not clinically significant. However, compared with oxytocin alone, misoprostol plus oxytocin caused significantly more nausea (12% vs 6.1%), vomiting (8.1% vs 5.4%), shivering (13% vs 7%), and fever (7.7% vs 4.0%).[3]

Ergonovine plus oxytocin

Ergonovine is an ergot derivative that causes uterine contractions and has been shown to effectively reduce blood loss at delivery. In the United States a methyl-derivative of ergonovine, methylergonovine, is widely available. In a meta-analysis with mostly vaginal deliveries, there were no significant differences for ergonovine plus oxytocin versus oxytocin alone for the following outcomes: death, intensive care unit admission, rate of blood loss ≥ 1,000 mL (2.0% vs 2.7%), blood transfusion, administration of an additional uterotonic, change in hemoglobin from pre- to postdelivery, nausea, hypertension, shivering, and fever.[3] However, ergonovine plus oxytocin, compared with oxytocin alone, resulted in a significantly reduced rate of blood loss ≥ 500 mL (8.3% vs 10.2%) and an increased rate of vomiting (8.1% vs 1.6%).[3] In these trials women with a blood pressure ≥ 150/100 mm Hg were generally excluded from receiving ergonovine because of its hypertensive effect.

Clinical practice options

Given the Cochrane meta-analysis results, ObGyns have two approaches for optimizing PPH reduction.

Option 1: Use a single uterotonic to reduce postpartum blood loss. If excess bleeding occurs, rapidly administer a second uterotonic agent. Currently, monotherapy with intravenous or intramuscular oxytocin is the standard for reducing postpartum blood loss.[5,6] Advantages of this approach compared with dual

agent therapy include simplification of care and minimization of AEs. However, oxytocin monotherapy for minimizing postpartum bleeding may be suboptimal. In the largest trial ever performed (involving 29,645 women) when oxytocin was administered postpartum, the rates of estimated blood loss ≥ 500 mL and ≥ 1,000 mL were 9.1% and 1.45%, respectively.[5] Is 9% an optimal rate for blood loss ≥ 500 mL following a vaginal delivery? Or should we try to achieve a lower rate?

Given the "high" rate of blood loss ≥ 500 mL with oxytocin alone, it is important for clinicians using the one-uterotonic approach to promptly recognize patients who have excessive bleeding and **transition rapidly from prevention to treatment**. When PPH cases are reviewed, a common finding is that the clinicians did not timely recognize excess bleeding, delaying transition to treatment with additional uterotonics and other interventions. When routinely using oxytocin monotherapy, lowering the threshold for administering a second uterotonic (methylergonovine, carboprost, misoprostol, or tranexamic acid) may help decrease the frequency of excess postpartum blood loss.

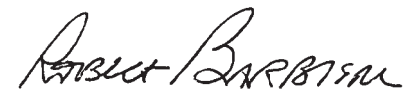
Option 2: Administer two uterotonics to reduce postpartum blood loss at all deliveries. Given the "high" rate of excess postpartum blood loss with oxytocin monotherapy, an alternative is to administer two uterotonics at all births or at births with a high risk of excess blood loss. As discussed, administering two uterotonics, **oxytocin plus misoprostol** or **oxytocin plus ergonovine**, has been reported to be more effective than oxytocin alone for reducing postpartum bleeding ≥ 500 mL.[3] In the Cochrane meta-analysis, per 1,000 women given oxytocin following a vaginal birth, 122 would have blood loss ≥ 500 mL, compared with 85 given **oxytocin plus misoprostol** or **oxytocin plus ergonovine**.[3]

Misoprostol is administered sublingually, buccally, or rectally, and methylergonovine is administered by intramuscular injection. Although dual uterotonic therapy is more effective than monotherapy, dual therapy is associated with more AEs. As noted, compared with oxytocin monotherapy, the combination of oxytocin plus misoprostol is associated with more nausea, vomiting, shivering, and fever. Oxytocin plus ergonovine is associated with a higher rate of vomiting than oxytocin monotherapy. In my practice I prefer using intramuscular methylergonovine as the second agent to avoid the high rate of fever associated with misoprostol.

For dual agent therapy, one approach is to administer misoprostol 200 µg or 400 µg through the buccal[7,8] or sublingual[9,10] routes. Higher dosages of misoprostol (600 µg to 800 µg) have been used[11,12] but are likely associated with higher rates of nausea, vomiting, shivering, and fever than the lower dosages. Methylergonovine 0.2 mg is administered intramuscularly.

The bottom line

PPH is a major cause of maternal morbidity, and in low-resource settings, mortality. Oxytocin is the standard for reducing postpartum blood loss, but rates of blood loss ≥ 500 mL are high following this monotherapy. To reduce postpartum blood loss beyond what is possible with oxytocin alone, clinicians can more rapidly transition to administering a second uterotonic when they suspect blood loss is becoming excessive or they can use two uterotonic agents with all births or in those at high risk for excess bleeding. If blood loss does become excessive, clinicians need to pivot rapidly from prevention with oxytocin to treatment with our entire therapeutic armamentarium. ●



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Dr. Barbieri reports no financial relationships relevant to this article.

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In women with late preterm mild hypertensive disorders, does immediate delivery versus expectant management differ in terms of neonatal neurodevelopmental outcomes?

Yes. For women with late preterm (34–37 weeks) mild hypertensive disorders in pregnancy, immediate delivery resulted in poorer neurodevelopmental outcomes in offspring at 2 years when compared with expectant management. In this follow-up study of 342 women enrolled in the HYPITAT-II trial, expectant management until clinical deterioration or term is reached maximized childhood outcomes at age 2.

FAST TRACK

Study investigators found more abnormal scores on the Ages and Stages Questionnaire for children whose mothers underwent immediate delivery (28% vs 18%)

Zwertbroek EF, Franssen MT, Broekhuijsen K, et al; HYPITAT-II Study Group. Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring of mild hypertensive disorders of pregnancy: 2-year outcomes of the HYPITAT-II trial. Am J Obstet Gynecol. doi:10.1016/j.ajog.2019.03.024.

EXPERT COMMENTARY

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In women with mild hypertensive disorders in the preterm period, the maternal benefits of delivery should be weighed against the consequences of preterm birth for the neonate. In a recent study, Zwertbroek and colleagues sought to evaluate the long-term neurodevelopmental effects of this decision on the offspring.

The authors report no financial relationships related to this article.

Details of the study

The authors conducted a follow-up study of the randomized, controlled Hypertension and Preeclampsia Intervention Trial At Term II (HYPITAT-II), in which 704 women diagnosed with late preterm (34–37 weeks) hypertensive disorders in pregnancy (gestational hypertension, chronic hypertension, or mild preeclampsia) were randomly assigned to immediate delivery or expectant management.

Expectant management consisted of close monitoring until 37 weeks or until an indication for delivery occurred, whichever came first. Children born to those mothers were eligible for this study (women enrolled during 2011–2015) when they reached 2 years of age; 342 children were included in this analysis. Of note, children from the expectant management group had been delivered at a more advanced gestational age (median,

37.0 vs 36.1 weeks; *P*<.001) than those in the immediate-delivery group.

Survey tools. Parents completed 2 response surveys, the Ages and Stages Questionnaire (ASQ) and the Child Behavior Checklist (CBCL), between 23 and 26 months' corrected age. The ASQ is designed to detect developmental delay, while the CBCL assesses behavioral and emotional problems. The primary outcome was an abnormal result on either screen.

Results. Based on 330 returned questionnaires, the authors found more abnormal ASQ scores (45 of 162 [28%] vs 27 of 148 [18%] children; *P* = .045) in the immediate-delivery group versus the expectant management group, most pronounced in the fine motor domain. They found no difference in the CBCL scores. The authors concluded that immediate delivery for women with late preterm mild hypertensive disorders in pregnancy increases the risk of developmental delay in the children.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

This follow-up study of the HYPITAT-II randomized, controlled trial demonstrates poorer neurodevelopmental outcomes in offspring of late preterm mild hypertensives who undergo immediate delivery. These data support current practice recommendations to expectantly manage women with late preterm mild hypertensive disease until 37 weeks or signs of clinical worsening, whichever comes first.

Study strengths and limitations

This study is unique as a planned follow-up to a randomized, controlled trial, allowing for 2-year outcomes to be assessed on children of enrolled women with mild hypertensive disorders in the late preterm period. The authors used validated surveys that are known to predict long-term neurodevelopmental outcomes.

This work has several limitations, however. Randomization was not truly maintained given the less than 50% response rate of original participants. Additionally, parents completed the surveys and provider confirmation of developmental concerns or diagnoses was not obtained. Further, assessments at 2 years of age may be too early to detect subtle differences, with evaluations at 5 years more predictive of long-term outcomes; the authors stated that these data already are being collected.

Finally, while these data importantly reinforce the conclusions of the parent HYPITAT-II trial, which support expectant management for mild hypertensive disorders in the late preterm period,[1] clinicians must always take care to individualize decisions in the face of worsening maternal disease. ●

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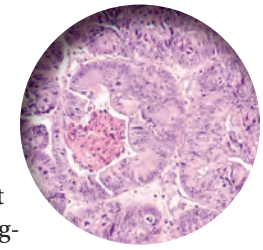
What is the risk of endometrial cancer in women with postmenopausal bleeding, and who should be evaluated? Plus, consensus guidance on managing GSM in breast cancer survivors and addressing depression in perimenopausal women.

Among peri- and postmenopausal women, abnormal bleeding, breast cancer, and mood disorders represent prevalent conditions. In this Update, we discuss data from a review that provides quantitative information on the likelihood of finding endometrial cancer among women with postmenopausal bleeding (PMB). We also summarize 2 recent consensus recommendations: One addresses the clinically important but controversial issue of the treatment of genitourinary syndrome of menopause (GSM) in breast cancer survivors, and the other provides guidance on the management of depression in perimenopausal women.

IN THIS ARTICLE

Endometrial cancer is associated with a high prevalence of PMB



Clarke MA, Long BJ, Del Mar Morillo A, et al. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. JAMA Intern Med. 2018;178:1210-1222.

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer among US women. In recent

years, the incidence of and mortality from endometrial cancer have increased.[1] Despite the high prevalence of endometrial cancer, population-based screening currently is not recommended.

PMB affects up to 10% of women and can be caused by endometrial atrophy, endometrial polyps, uterine leiomyoma, and malignancy. While it is well known that PMB is a common presenting symptom of endometrial cancer, we do not have good data to guide counseling patients with PMB on the likelihood that endometrial cancer is present. Similarly, estimates are lacking regarding what proportion of women with endometrial cancer will present with PMB.

To address these 2 issues, Clarke and colleagues conducted a comprehensive systematic review and meta-analysis of the prevalence of PMB among women with endometrial cancer (sensitivity) and the risk of endometrial cancer among women with PMB (positive predictive value). The authors included 129 studies—with 34,432 women with PMB and 6,358 with endometrial cancer—in their report.

Cancer prevalence varied with HT use, geographic location

The study findings demonstrated that the prevalence of PMB in women with endometrial cancer was 90% (95% confidence interval [CI], 84%–94%), and there was no significant difference in the occurrence of PMB by cancer stage. The risk of endometrial cancer in women with PMB ranged from 0% to 48%, yielding an overall pooled estimate of 9% (95% CI, 8%–11%). As an editorialist pointed out, the risk of endometrial cancer in women with PMB is similar to that of colorectal cancer in individuals with rectal bleeding (8%) and breast cancer in women with a palpable mass (10%), supporting current guidance that recommends evaluation of women with PMB.[2] Evaluating 100 women with PMB to diagnose 9 endometrial cancers does not seem excessive.

Interestingly, among women with PMB, the prevalence of endometrial cancer was significantly higher among women not using hormone therapy (HT) than among users of HT (12% and 7%, respectively). In 7 studies restricted to women with PMB and polyps (n = 2,801), the pooled risk of endometrial cancer was 3% (95% CI, 3%–4%). In an analysis stratified by geographic region, a striking difference was noted in the risk of endometrial cancer among women with PMB in North America (5%), Northern Europe (7%), and in Western Europe (13%). This finding may be explained by regional differences in the approach to evaluating PMB, cultural perceptions of PMB that can affect thresholds to present for care, and differences in risk factors between these populations.

The study had several limitations, including an inability to evaluate the number of years since menopause and the effects of body mass index. Additionally, the study did not address endometrial hyperplasia or endometrial intraepithelial neoplasia.

CONTINUED ON PAGE 24

WHAT THIS EVIDENCE MEANS FOR PRACTICE

PMB accounts for two-thirds of all gynecologic visits among perimenopausal and postmenopausal women.[3] This study revealed a 9% risk of endometrial cancer in patients experiencing PMB, which supports current practice guidelines to further evaluate and rule out endometrial cancer among all women presenting with PMB[4]; it also provides reassurance that targeting this high-risk group of women for early detection and prevention strategies will capture most cases of endometrial cancers. However, the relatively low positive predictive value of PMB emphasizes the need for additional triage tests with high specificity to improve management of PMB and minimize unnecessary biopsies in low-risk women.

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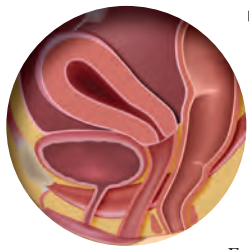

Treating GSM in breast cancer survivors: New guidance targets QoL and sexuality

Faubion SS, Larkin LC, Stuenkel CA, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. Menopause. 2018;25:596-608.

FAST TRACK

Management of GSM should be individualized based on shared decision-making involving the patient and her oncologist

More than 3 million breast cancer survivors reside in the United States. Accordingly, ObGyns see survivors on a frequent basis. For several reasons, genitourinary syndrome of menopause (also known as vulvovaginal atrophy) is particularly prevalent in women who have been treated for breast cancer. Chemotherapy, for example, often induces ovarian failure. For some premenopausal women, bilateral salpingo-oophorectomy may be performed or gonadotropin-releasing hormone agonists may be prescribed as part of breast cancer treatment. In postmenopausal survivors with hormone receptor–positive tumors, adjuvant aromatase inhibitor (AI) therapy may be used for up to 10 years. Treatment with AIs is associated with GSM symptoms.[5] Although vaginal estrogen is an effective treatment for GSM, package labeling for all estrogens, including vaginal estrogens, lists a personal history of breast cancer as a contraindication.

Given that there is little evidence addressing the safety of vaginal estrogen, other hormonal therapies, and nonprescription treatments for GSM in breast cancer survivors, many survivors with bothersome GSM symptoms are not appropriately treated.

Expert panel creates evidence-based guidance

Against this backdrop, The North American Menopause Society and the International Society for the Study of Women's Sexual Health convened a group comprised of menopause specialists (ObGyns, internists, and nurse practitioners), specialists in sexuality, medical oncologists specializing in breast cancer, and a psychologist to create evidence-based interdisciplinary consensus guidelines for enhancing quality of life and sexuality for breast cancer survivors with GSM.

Measures to help enhance quality of life and sexuality

The group's key recommendations for clinicians include:

- Sexual function and quality of life (QoL) should be assessed in all women with or at high risk for breast cancer.
- Management of GSM should be *individualized* based on shared decision-making involving the patient and her oncologist.
- Initial treatment options include:
  - —over-the-counter vaginal moisturizers used several times weekly on a regular basis
  - —lubricants used with intercourse
  - —vaginal dilator therapy
  - —pelvic floor physical therapy.
- Low-dose vaginal estrogen therapy may be appropriate for select women who have been treated for breast cancer:
  - —With use of vaginal estrogen, serum estradiol levels remain in the postmenopausal range.
  - —Based on limited data, use of vaginal estrogen is associated with a minimal risk for recurrence of breast cancer.
  - —Because their use is associated with the lowest serum estradiol levels, vaginal tablets, rings, or inserts may be preferable to creams.
  - —Decisions regarding use of vaginal estrogen in breast cancer survivors

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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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should involve the woman's oncologist. Appropriate candidates for off-label use of vaginal estrogen may be survivors:

- who are at relatively low risk for recurrence
- with hormone receptor–negative disease
- using tamoxifen rather than an AI
- who are particularly concerned about quality of life.

—Given that AIs prevent recurrence by lowering estrogen levels, oncologists may be reluctant to consider use of vaginal estrogen in survivors using adjuvant agents.

—With respect to use of vaginal estrogen, oncologists may be more comfortable with use in patients taking tamoxifen.

- Neither intravaginal dehydroepiandrosterone (DHEA; prasterone) nor the oral selective estrogen receptor modulator ospemifene has been studied in breast cancer survivors.

In women with metastatic disease, QoL, comfort, and sexual intimacy are key considerations when weighing potential therapies; optimal choices will vary with probability of long-term survival.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although more data addressing the safety of vaginal estrogen as well as prasterone and ospemifene in breast cancer survivors clearly are needed, these guidelines should help clinicians who care for breast cancer survivors with GSM.

Framework provided for managing depressive disorders in perimenopausal women

Maki PM, Kornstein SG, Joffe H, et al; Board of Trustees for The North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. Menopause. 2018;25:1069-1085.

Although perimenopausal women are more susceptible to the development of depressive symptoms and major depressive episodes (MDE), there is a lack of consensus regarding how to evaluate and treat depression in women during the menopausal transition and postmenopausal period.

Recently, an expert panel comprised of representatives from The North American Menopause Society and the National Network of Depression Centers Women and Mood Disorders Task Group developed clinical guidelines addressing epidemiology, clinical presentation, therapeutic effects of antidepressants, effects of HT, and efficacy of other therapies. Here we provide a summary of the expert panel's findings and guidelines.

Certain factors are associated with higher risk for depression

The perimenopause represents a time of increased risk for depressive symptoms and major depressive disorder (MDD), even in women with no prior history of depression. Several characteristics and health factors

are associated with the increased risk during the menopause transition. These include a prior history of MDD, current antidepressant use, anxiety, premenstrual depressive symptoms, African American race, high body mass index, younger age, social isolation, upsetting life events, and menopausal sleep disturbances.

Although data are inconclusive on whether surgical menopause increases or decreases the risk for developing depression compared with women who transition through menopause naturally, recent studies show an elevated risk of depression in women following hysterectomy with and without oophorectomy.[6,7]

Menopausal and depressive symptoms can overlap

Midlife depression presents with classic depressive symptoms that commonly occur in combination with menopausal symptoms, including vasomotor symptoms, sleep and sexual disturbances, and weight and energy changes. These menopausal symptoms can complicate, co-occur, and overlap with the clinical presentation of depression.

Conversely, depression may affect an individual's judgment of the degree of bother from menopausal somatic symptoms, thereby further magnifying the effect of symptoms on quality of life. The interrelationship between depressive symptoms and menopausal symptoms may pose a challenge when attempting to parse out contributing etiologies, relative contributions of each etiology, and the potential additive effects.

Diagnosis and treatment options

Diagnosis involves identifying the menopausal stage, assessing for co-existing psychiatric and menopause symptoms, appreciating the psychosocial factors common in midlife, and considering the differential diagnosis. Validated screening instruments can be helpful. Although a menopause-specific mood disorder scale does not yet exist, several general validated screening measures, such as the Patient Health Questionnaire-9, or PHQ-9, can be used for categorical determination of mood disorder diagnoses during the menopause transition.

Antidepressants, cognitive-behavioral therapy, and other psychotherapies are considered first-line treatments for perimenopausal major depressive episodes. Only desvenlafaxine has been studied in large randomized placebo-controlled trials and has proven efficacious for the treatment of MDD in perimenopausal and postmenopausal women.

A number of small open-label studies of other selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and mirtazapine to treat MDD in perimenopausal and postmenopausal women have demonstrated a positive effect on mood, and several SSRIs and SNRIs also have the added benefit of improving menopause-related symptoms.

In women with a history of MDD, a prior adequate response to a particular antidepressant should guide treatment selection when MDD recurs during the midlife years.

Although estrogen is not approved by the US Food and Drug Administration specifically for the treatment of mood disturbances, some evidence suggests that unopposed estrogen therapy has efficacy similar to that of antidepressant medications in treating depressive disorders in *perimenopausal women*,[8-11] but it is ineffective in

CONTINUED ON PAGE 53

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The findings from this expert review panel demonstrate that women in the perimenopausal transition are at increased risk for depressive symptoms, major depressive episodes, and major depressive disorder. The interrelationship between symptoms of depression and menopause can complicate, co-occur, overlap, and magnify one another. Clinicians treating perimenopausal women with depression that is unresponsive to conventional antidepressant therapy should consider concurrent use of estrogen-based hormone therapy or referring the patient to a clinician comfortable doing so.

FAST TRACK

SSRIs, SNRIs, and mirtazapine to treat MDD in peri- and postmenopausal women have been shown to have a positive effect on mood, and several SSRIs and SNRIs have the added benefit of improving menopause-related symptoms

ON THE WEB

at mdedge.com/obgyn
Drs. Kaunitz and McCullough provide key takeaways for 3 studies focusing on hormone therapy route of administration and treatment timing

What's in store for ObGyn reimbursement in the EHR age and beyond

ACOG intends to retain the physician lead in how ObGyns get paid for their work

Donna Tyler, and Barbara Levy, MD

In an effort to reduce burden on physicians and qualified health care professionals, the Centers for Medicare and Medicaid Services (CMS) has made changes to Evaluation and Management (E/M) documentation requirements and payment policies. Get ready for fairly extensive changes planned for CY 2021. Here we outline already-implemented and future changes and describe the commitment of the American College of Obstetricians and Gynecologists (ACOG) to ObGyn payment in its collaborations with CMS and the American Medical Association (AMA).

ILLUSTRATION: PAUL ZWOLAK FOR OBG MANAGEMENT

IN THIS ARTICLE

E/M services: CMS reduced documentation

Effective January 2019, the CMS made changes to the documentation requirements for E/M services to provide some common-sense relief for physicians facing excessive documentation requirements in their practices. Most physicians agree that modern medical practice, with the use of electronic health records (EHRs), is different now than in the mid-1990s, when the current E/M structures were developed and implemented. Streamlining documentation requirements reduces paperwork burden and some of the time-consuming duplicative work involved in medical practice today.

For instance, when relevant information is already contained in the medical record, it is not necessary to re-document a full medical history. Physicians will now be able to focus their documentation on the interval since the previous visit. Physicians should still review prior data, update as necessary, and indicate in the medical record that they have done so.

Also, for E/M office and outpatient visits for both new and established patients, physicians are no longer required to re-document information that has already been entered in the patient's record by practice staff or by the patient. If the patient's chief complaint and history already has been entered by ancillary staff or the beneficiary, the physician should simply indicate in the medical record that the information has been reviewed and verified.

For E/M visits furnished by teaching physicians, CMS has removed the requirement for potentially duplicative notations that

CONTINUED ON PAGE 33

Ms. Tyler is Director of Coding, American College of Obstetricians and Gynecologists (ACOG), Washington, DC.

Dr. Levy is Vice President for Health Policy at ACOG.

The authors report no financial relationships relevant to this article.

2019

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- Energy-Based Devices for Hysterectomy and Tissue Extraction Techniques **NEW!**
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SCIENTIFIC SESSION TOPICS INCLUDE:

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

PLUS, SPECIAL KEYNOTES

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

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

COURSE CHAIRS

Tommaso Falcone, MD
Cleveland Clinic London

Mickey M. Karram, MD
The Christ Hospital

SPECIAL KEYNOTE SPEAKER

Mark D. Walters, MD
Cleveland Clinic

Faculty

Sawsan As-Sanie, MD, MPH
University of Michigan

Michael S. Baggish, MD
St. Helena Hospital

Linda D. Bradley, MD
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Andrew I. Brill, MD
California Pacific Medical Center

Amanda Nickles Fader, MD
Johns Hopkins Hospital

John B. Gebhart, MD, MS
Mayo Clinic

Rosanne M. Kho, MD
Cleveland Clinic

Javier F. Magrina, MD
Mayo Clinic Phoenix

Beri M. Ridgeway, MD
Cleveland Clinic

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

PAGS AGENDA

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

WEDNESDAY, DECEMBER 11, 2019

PRE-CONFERENCE WORKSHOPS
(Optional, Separate fee required)

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

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

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

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

GENERAL SCIENTIFIC SESSIONS

THURSDAY, DECEMBER 12, 2019

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

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

PELVIC ANATOMY

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

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

INCONTINENCE AND PROLAPSE SURGERY

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

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

10:25 AM **Break/Exhibits**

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

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

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

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

1:10 PM **Lunch**

1:25 PM **Luncheon Symposium**

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

THURSDAY'S KEYNOTE LECTURE

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

BENIGN GYNECOLOGY

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

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

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

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

FRIDAY, DECEMBER 13, 2019

6:45 AM **Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

HYSTERECTOMY - TECHNIQUE

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

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

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

9:45 AM **Break /Exhibits**

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

11:00 AM **Tissue Extraction Techniques (Morcellation)**
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!

3.25 CME Credits Available

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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
- The 4 Pillars of a Successful Practice
- How to Improve the Efficiency, Productivity, and Profitability of Your Practice
- Online Reputation Management
- Why Market and Promote Your ObGyn Practice

3:30 PM **Break**

3:45 PM
- Using Social Media to Get to the Top of Google
- Numbers You Need to Know
- Moving from Volume to Value

5:00 PM **Q and A**

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

PAGS Scientific Faculty

Course Chairs

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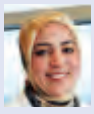
Chief of Staff
Chief Academic Officer
Medical Director
Cleveland Clinic London
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
London, UK

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



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

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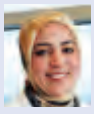

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CONTINUED FROM PAGE 32

may have been made previously in the medical records by residents or other members of the medical team.

Finally, CMS eliminated the requirement to document the medical necessity of a home visit in lieu of an office visit.

Outpatient coding changes for 2021

Outpatient coding for E/M will continue in its current form for the remainder of 2019 and 2020. However, in 2021, expect substantial changes to take effect. If the CMS rule is instituted, payment for E/M office and outpatient visits will be drastically "simplified." The current CMS plan for 2021 is to collapse payment for existing E/M Levels 2 through 4 to one payment level for new patients and one payment level for established patients, with optional add-on codes. Level 5 visits will continue at a separate payment level and with continuation of current documentation requirements.

In addition to collapsing the payment in E/M Levels 2, 3, and 4, CMS also will allow flexibility in how those E/M office and outpatient visits are documented. Specifically, documentation may be based on any of the following:

- current framework (1995 or 1997 guidelines)
- medical decision making (MDM)
- time.

When using MDM or the current 1995/1997 framework to document an office visit, Medicare will only require documentation to support a Level 2 E/M outpatient visit code for history, exam, and/or MDM. When time is used as the basis for coding the visit, physicians will document the medical necessity of the visit and that the billing practitioner personally spent the required amount of time face-to-face with the beneficiary.

CMS also has finalized the creation of new add-on codes that describe the additional resources inherent in visits for primary care and particular kinds of nonprocedural specialized medical care (and will not be restricted by physician specialty). These codes would only be reportable with E/M office and outpatient level 2 through 4 visits, and their use generally would not impose new documentation requirements. It is not clear which types of visits would support the use of these add-on codes at this time.

Finally, a new "extended visit" add-on code will be available for use only with E/M Level 2 through 4 visits to account for the additional resources required when spending extended time with a patient.

CMS believes these policies will allow physicians, and all who bill E/M codes, greater flexibility to exercise clinical judgment in their documentation, so that they can focus on what is clinically relevant and medically necessary for the beneficiary.

ACOG's voice in the process

ACOG strongly opposed several proposals that CMS made during the rule-making process that the agency decided not to finalize. These aspects of the proposal would have:

1. reduced payment by 50% for the least expensive procedure or visit when an E/M office or outpatient visit is furnished on the same day as a procedure by the same physician. These are separately identifiable E/M visits that normally would be reported with a modifier 25.
2. established separate coding and payment for podiatric E/M visits, or
3. standardized the allocation of practice expense relative value units (RVUs) for the codes that describe these services.

CMS has stated that they intend to engage in further discussions with the public and stakeholders to potentially further refine the policies for CY 2021.

AMA-CPT and RUC initiative

Although the AMA, ACOG, and physicians in general applauded the CMS initiative to reduce the administrative and documentation burden on providers, there was concern about the unintended consequences of the payment changes that are currently scheduled to take effect in 2021. To address these concerns, the AMA convened a work group of physician ex-

FAST TRACK

Payment for E/M outpatient and office visits will be drastically simplified in 2021, with E/M Levels 2 through 4 collapsing payment to one level for new patients and one level for established patients, with add-on codes optional

Summary of CPT Editorial Panel actions for office or other outpatient services, February 2019 (Effective Date January 1, 2021)

- CPT code 99201 to be deleted
- Revision of codes 99202–99215 as follows:
- removing history and examination as key components
  - (A) for selecting the level of service but requiring a medically appropriate history and or examination be performed in order to report codes 99202–99215
  - (B) making the basis for code selection on either the level of medical decision making (MDM) performed or the total time spent performing the service on the day of the encounter
  - (C) changing the definition of the time element associated with codes 99202–99215 from *typical face-to-face time* to *total time spent on the day of the encounter* and changing the amount of time associated with each code.
- Revision of the MDM elements associated with codes 99202–99215 as follows:
  - (i) revising "Number of Diagnoses or Management Options" to "Number and Complexity of Problems Addressed";
  - (ii) revising "Amount and/or Complexity of Data to be Reviewed" to "Amount and/or Complexity of Data to be Reviewed and Analyzed"; and
  - (iii) revising "Risk of Complications and/or Morbidity or Mortality" to "Risk of Complications and/or Morbidity or Mortality of Patient Management."
- Revision of the E/M guidelines by:
  - (A) restructuring the guidelines into three sections: "Guidelines Common to All E/M Services," "Guidelines for Hospital Observation, Hospital Inpatient, Consultations, Emergency Department, Nursing Facility, Domiciliary, Rest Home or Custodial Care and Home E/M Services," and "Guidelines for Office or Other Outpatient E/M Services" to distinguish the new reporting guidelines for the Office or Other Outpatient Services codes 99202–99215
  - (B) adding new guidelines that are applicable only to Office or Other Outpatient codes (99202–99215); adding a Summary of Guideline Differences table of the differences between the sets of guidelines
  - (C) revised existing E/M guidelines to ensure there is no conflicting information between the different sets of guidelines
  - (D) adding definitions of terms associated with the elements of MDM applicable to codes 99202–99215
  - (E) adding an MDM table that is applicable to codes 99202–99215
  - (F) defining total time associated with codes 99202–99215
  - (G) adding guidelines for reporting time when more than one individual performs distinct parts of an E/M service; revision of the MDM table in the Amount and/or Complexity of Data to be Reviewed and Analyzed column:
    - (1) inserted a dash (-) after the asterisk in the asterisk definition, "* - Each unique test, order, or document may be summed if multiple," to clarify this is the meaning of the asterisk and not an asterisked item itself
    - (2) for limited amount of data to be reviewed and analyzed (codes 99203/99213), the parenthetical regarding the number of categories for which requirements must be met was revised to state, "…categories of tests and documents, or independent historian(s)" rather than "categories within tests, documents, or independent historian(s)"
    - (3) removing the word "or" after each of the bulleted items for limited, moderate (codes 99202/99214), and high (99205/99215) amount and/or complexity of data to be reviewed and analyzed.

perts who are knowledgeable in the *Current Procedural Terminology* (CPT) code development and valuation processes. The charge to the E/M work group is to collaborate across the provider, payer, and coding communities to establish or revise the coding structure and guidelines for outpatient E/M services. The members formed a multispecialty work group representing primary care and surgical specialties and have experience in developing, defining, and valuing codes.

Dr. Barbara Levy, ACOG's Vice President of Health Policy, co-chaired this expert panel with geriatrician Dr. Peter Hollmann to develop comprehensive consensus-led changes to revise and modernize E/M codes. The work group followed 4 guiding principles to inform their E/M work:

1. to decrease the administrative burden of documentation and coding
2. to decrease the need for audits
3. to decrease unnecessary and redundant

documentation in the medical record that is not needed for patient care

4. to ensure that payment for E/M services is resource based. There is no direct goal for payment redistribution among specialties.

A primary concern expressed by physicians about the CMS proposal was that the collapse of payment for E/M visit across levels 2–4 might lead to a lack of appropriate care for more complex patients since the CMS rule does not provide payment based on the resources required to perform the work of the visit. No one believes that the work needed to care for someone with a sore throat or pink eye is equivalent to the work involved in diagnosing and managing depression, for example.

Beginning in August 2018, the work group met regularly to build consensus. The work group worked at an accelerated pace to develop and value codes that better fit the current medical workflows and meet patient needs.

The work group submitted a code change proposal for E/M codes to the CPT Editorial Panel for consideration during the February 2019 meeting. The next step was the code valuation process through the AMA/Specialty Society RVS Update Committee (RUC) process.

CMS has stated that the 2-year delay to 2021 in implementation of their original proposed changes is to allow time for the E/M code change proposals to move through the development and valuation process and subsequent review by the agency. To date, commercial payers and coders have been supportive of the AMA E/M work group proposals. Dr. Levy, Dr. Hollmann, and AMA staff are meeting with CMS and Department of Health and Human Services staff to provide clarity as they review the CPT proposals. ACOG supports the changes, which would simplify documentation for outpatient E/M codes while retaining differential payments. CMS is closely following the progress of the code changes through the CPT process and RUC code valuation process. We await further rulemaking by CMS in defining and valuing this important code set.

ACOG is at the helm, with a watchful eye

This is a challenging undertaking because E/M codes are used across specialties for office visits and outpatient care. The potential for unintended consequences for all services that include E/M, such as the global obstetrical services or 90-day global surgical services, is substantial. ACOG is intimately involved in this undertaking, watching the developments carefully to ensure that the interests of ObGyns and their patients are protected. ●

Modern surgical techniques for gastrointestinal endometriosis

Current operative techniques for extragenital endometriosis can provide excellent outcomes with less risk for postoperative complications

Camran Nezhat, MD; Megan Kennedy Burns, MD, MA; Michelle A. Wood, DO; and Ceana Nezhat, MD

IN THIS ARTICLE

About 10% of all reproductive-aged women and 35% to 50% of women with pelvic pain and infertility are affected by endometriosis.[1,2] The disease typically involves the reproductive tract organs, anterior and posterior cul-de-sacs, and uterosacral ligaments. However, disease outside of the reproductive tract occurs frequently and has been found on all organs except the spleen.[3]

The bowel is the most common site for extragenital endometriosis, affected in an estimated 3.8% to 37% of patients with known endometriosis.[4-7] Implants may be superficial, involving the bowel serosa and subserosa (**FIGURE 1**), or they can manifest as deeply infiltrating lesions involving the muscularis and mucosa (**FIGURE 2**, page 38). The rectosigmoid colon is the most common location for bowel endometriosis, followed by the rectum, ileum, appendix, and cecum[4,8] (**FIGURES 3, 4,** and **5,** pages 38-39). Case reports also have described endometrial implants on the stomach and transverse colon.[9] Although isolated bowel involvement has been recognized, most patients with bowel endometriosis have concurrent disease elsewhere.[2,4]

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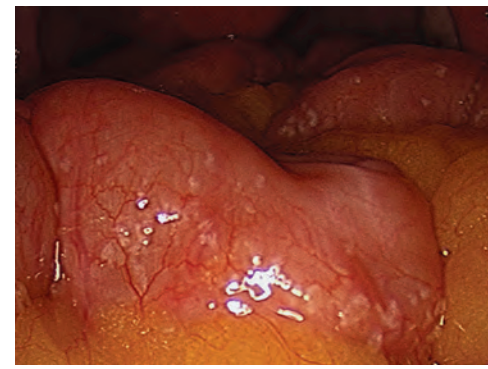
The authors report no financial relationships relevant to this article.

FIGURE 1 Diffuse serosal disease across the bowel



Historically, segmental resection was performed regardless of the anatomical location of the lesion.[10] Even today, many surgeons continue to routinely perform segmental bowel resection as a first-line surgical approach.[11] Unnecessary segmental resection, however, places patients at risk for short- and long-term postoperative morbidity, including the possibility of permanent ostomy. Modern surgical techniques, such as shaving excision and disc resection, have been performed to successfully treat bowel endometriosis with excellent long-term outcomes and fewer complications when compared with traditional segmental resection.[2,12-16]

In this article, we focus on the clinical indications and surgical techniques for video-laparoscopic management, but first we

CONTINUED ON PAGE 38

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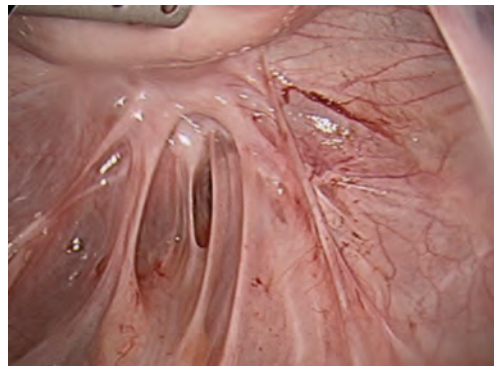
Modern surgical techniques for gastrointestinal endometriosis

CONTINUED FROM PAGE 36

FIGURE 2 Severe rectovaginal adhesions



describe the pathophysiology, clinical presentation, and diagnosis of bowel endometriosis.

Pathophysiology of bowel endometriosis

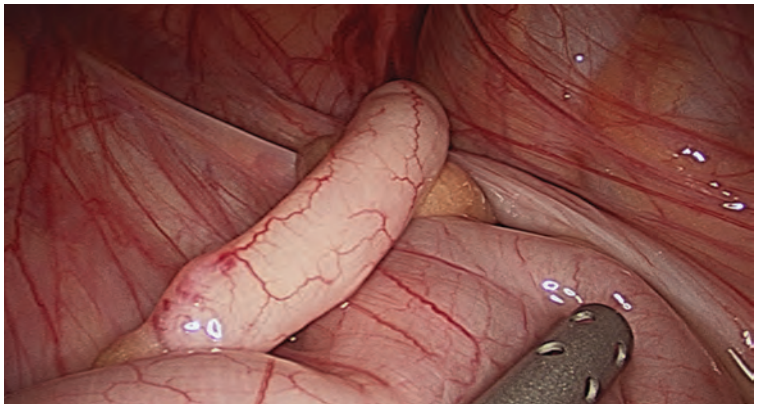
The pathogenesis of endometriosis remains unknown, as no single mechanism explains all clinical cases of the disease. The most popular proposed theory describes retrograde menstruation through the fallopian tubes.[17] Once inside the peritoneal cavity, endometrial cells attach to and invade healthy peritoneum, establishing a blood supply necessary for growth and survival.

In the case of bowel endometriosis, deposition of effluxed endometrial cells may lead to an inflammatory response that increases the risk of adhesion formation, leading to potential cul-de-sac obliteration. Lesions may originate as Allen-Masters peritoneal defects, developing into deeply infiltrative rectovaginal septum lesions. The anatomical shelter theory contributes to lesions within the pelvis, with the rectosigmoid colon blocking the cephalad flow of effluxed menstrual blood from the pelvis, thus leading to a preponderance of lesions in the pelvis and along the rectosigmoid colon.[2]

FAST TRACK

Because of its nonspecific symptoms, bowel endometriosis is often misdiagnosed and goes untreated for years

FIGURE 3 Appendiceal endometriosis



Clinical presentation and diagnosis

Women presenting with endometriosis of the bowel are typically of reproductive age and commonly report symptoms of dysmenorrhea, chronic pelvic pain, dyspareunia, and dyschezia. Some women also experience catamenial diarrhea, constipation, hematochezia, and bloating.[2] The differential diagnosis of these symptoms is broad and includes irritable bowel disease, ischemic colitis, inflammatory bowel disease, diverticulitis, pelvic inflammatory disease, and malignancy.

Because of its nonspecific symptoms, bowel endometriosis is often misdiagnosed and the disease goes untreated for years.[18] Therefore, it is imperative that clinicians maintain a high index of suspicion when evaluating reproductive-aged women with gastrointestinal symptoms and pelvic pain.

Physical examination can be helpful in making the diagnosis of endometriosis. During bimanual examination, findings such as a fixed, tender, or retroverted uterus, uterosacral ligament nodularity, or an enlarged adnexal mass representing an ovarian endometrioma may be appreciated. Rectovaginal exam can identify areas of tenderness and nodularity along the rectovaginal septum. Speculum exam may reveal a laterally displaced cervix or blue powder-burn lesions along the cervix or posterior fornix.[19] Rarely, endometriosis is found on the perineum within an episiotomy scar.[20]

Imaging studies can be used in conjunction with physical examination findings to aid in the diagnosis of endometriosis. Images also guide preoperative planning by characterizing lesions based on their size, location, and depth of invasion. Hudelist and colleagues

found transvaginal ultrasound (TVUS) to have an overall sensitivity of 71% to 98% and a specificity of 92% to 100%.[21] However, it was noted that the accuracy of the diagnosis was directly related to the experience of the sonographer, and lesions above the sigmoid colon were generally unable to be diagnosed. Other imaging modalities that have been reported to have high sensitivity and specificity for diagnosing bowel endometriosis include rectal water contrast TVUS,[22,23] rectal endoscopic sonography,[22] magnetic resonance imaging,[22] and barium enema.[24]

Medical management

Medical therapy for patients with endometriosis is utilized with the goal of suppressing ovulation, lowering circulating hormone levels, and inducing endometrial atrophy. Medications commonly employed include gonadotropin-releasing hormone agonists and antagonists, anabolic steriods such as danazol, combined oral contraceptive pills, progestins, and aromatase inhibitors.

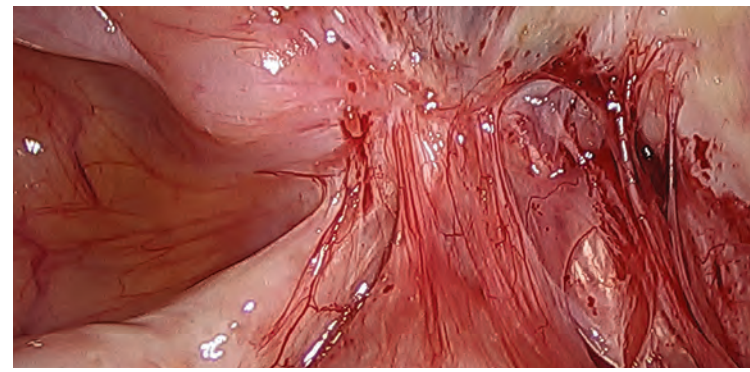
To date, no optimal hormonal regimen has been established for the treatment of bowel endometriosis. Vercellini and colleagues demonstrated that progestins with and without low-dose estrogen improved symptoms of dysmenorrhea and dyspareunia.[25] Ferrero and colleagues reported that 2.5 mg of norethindrone daily resulted in 53% of women with colorectal endometriosis reporting improved gastrointestinal symptoms.[26] However, by 12 months of follow-up, 33% of these patients had elected to undergo surgical management.

Gonadotropin-releasing hormone agonists, such as leuprolide acetate, also can be used to mitigate symptoms of bowel endometriosis or to decrease disease burden at the time of surgery, and they can be used with add-back norethindrone acetate. The use of these medications is limited by adverse effects, such as vasomotor symptoms and decreased bone mineral density when used for longer than 6 months.[2]

Medical therapy is commonly used for patients with mild to moderate symptoms and in those who are poor surgical candidates or decline surgical intervention. Medical therapy is especially useful when employed postoperatively to suppress the regrowth of microscopic ectopic endometrial tissue.

Patients must be counseled, however, that even with medical management, they may still require surgery in the future to control their symptoms and/or to preserve organ function.[2]

FIGURE 4 Severe rectosigmoid adhesions



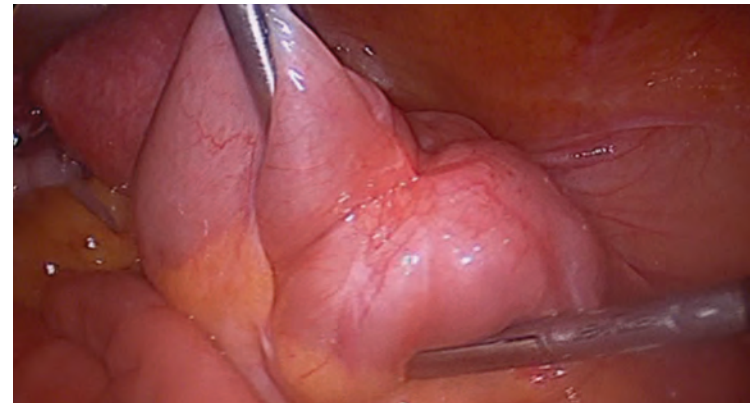
Surgical management

Surgical treatment for bowel endometriosis depends on the disease location, the size and depth of the lesion, the presence or absence of stricture, and the surgeon's level of expertise.[2,12,27-30] In our group, we advocate for video-laparoscopy, with or without robotic assistance. Minimally invasive surgery offers reduced blood loss, shorter recovery time, and fewer postoperative complications compared with laparotomy.[2,16,27,31-33] The conversion rate

FAST TRACK

To date, no optimal hormonal regimen has been established for the treatment of bowel endometriosis

FIGURE 5 Ileocecal endometriosis



Modern surgical techniques for gastrointestinal endometriosis

Key points

- The clinical presentation of bowel endometriosis is often nonspecific, with a broad differential diagnosis. Maintain a high index of suspicion when reproductive-aged women present for evaluation of dysmenorrhea, chronic pelvic pain, dyspareunia, bloating, dyschezia, or hematochezia.
- Symptomatic patients not desiring fertility, poor surgical candidates, and those declining surgical intervention may benefit from medical management. Patients who fail medical therapy, have severe symptoms, or experience infertility are candidates for surgical intervention.
- Surgical management involves shaving excision, disc resection, and segmental resection. Some surgeons advocate for aggressive segmental resection regardless of the endometriotic lesion's location. Based on our extensive experience, we prefer shaving excision for lesions below the sigmoid to avoid dissection into the retrorectal space and inadvertent injury to nerve tissue controlling bowel and bladder function.
- Following shaving excision, patients experience low complication rates[29,39,40] and favorable long-term outcomes.[15,40,56] For lesions above the sigmoid colon, including the small bowel, segmental resection or disc resection for smaller lesions are reasonable surgical approaches.

to laparotomy has been reported to be about 3% when performed by an experienced surgeon.[12]

Darai and colleagues conducted a randomized trial of 52 patients undergoing surgery for colorectal endometriosis via either laparoscopic or open colon resection.[33] Blood loss was significantly lower in the laparoscopy group (1.6 vs 2.7 mg/L, P <.05). No difference was noted in long-term outcomes. In a retrospective study of 436 cases, Ruffo and colleagues showed that those who underwent laparoscopic colorectal resection had higher postoperative pregnancy rates compared with those who had laparotomy (57.6% vs 23.1%, P <.035).[32]

The goal of surgical management of bowel endometriosis is to remove as many of the endometriotic lesions as possible while minimizing short- and long-term complications. Three surgical approaches have been described: shaving excision, disc resection, and segmental resection.[2]

Some surgeons prefer traditional segmental resection of the bowel regardless of the anatomical site, citing reduced disease recurrence with this approach; however, traditional segmental resection confers increased risk of complications. Increasingly, in an effort to reduce morbidity, more surgeons are advocating for the less aggressive methods of shaving excision and disc resection.

Aggressive resection at the level of the low rectum requires extensive surgical dissection of the retrorectal space, with the potential for inadvertent injury to surrounding neurovascular structures, such as the pelvic splanchnic nerves and superior and inferior hypogastric plexus.[29] Injury to these structures can lead to significant complications, including bowel stenosis, fistula formation, constipation, and urinary retention. Complete resection of other areas, such as the small bowel, do not carry the same risks and may have more significant benefit to the patient than less aggressive techniques.

Our group recommends carefully balancing the risks and benefits of aggressive surgical treatment for each individual and treating the patient with the appropriate technique. Regardless of technique, surgical treatment of bowel endometriosis can lead to long-term improvements in pain and infertility.[29,30,34,35]

Shaving excision

The most conservative approach to resection of bowel endometriosis is shaving excision; this involves removing endometriotic tissue layer-by-layer until healthy, underlying tissue is encountered.[2] With bowel endometriosis, the goal of shaving excision is to remove as much of the diseased tissue as possible while leaving behind the mucosal layer and a portion of the muscularis.[2,15,16,36-38] This is the most conservative of the 3 surgical techniques and is associated with the lowest complication rate.[2,14,15,36,37]

Our group reported on 185 women who underwent shaving excision for bowel endometriosis. At the time of surgery, 80 women had complete obliteration of the cul-de-sac (**FIGURE 6**). Of the study patients, 174 patients were available for follow-up, with 93% reporting moderate to complete pain relief.[15]

In a retrospective analysis of 3,298 surgeries for rectovaginal endometriosis in

which shaving excision was used on all but 1% of patients, Donnez and colleagues reported a very low complication rate, with 1 case of rectal perforation, 1 case of fecal peritonitis, and 3 cases of ureteral injury.[39]

Roman and colleagues described the use of shaving excision for rectal endometriosis using plasma energy (n = 54) and laparoscopic scissors (n = 68).[40] Only 4% of patients reported experiencing symptom recurrence, and the pregnancy rate was 65.4%, with 59% of those patients spontaneously conceiving. Two cases of rectal fistula were noted.

Disc resection

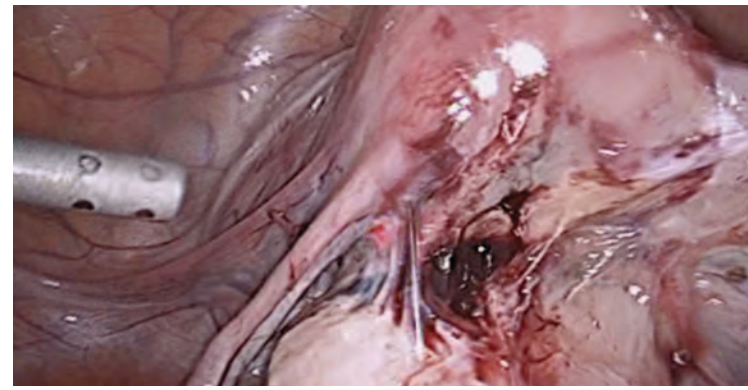
Laparoscopic disc excision has been described in the literature since the 1980s, and the technique involves the full-thickness removal of the diseased portion of the bowel, followed by closure of the remaining defect.[2,12-14,28,29,31,41-45] To be appropriate for this technique, a lesion should involve only a portion of the bowel wall and, preferably, less than one-half of the bowel circumference.[2,42] Disc excision results in excellent outcomes with fewer postoperative complications than segmental resection, but with more complications when compared to shaving excision.[2,12,13,29,45,46]

We reported on a series of 141 women with bowel endometriosis who underwent disc excision.[2] At 1-month follow-up, 87% of patients experienced an improvement in their symptoms. No cases required conversion to laparotomy or were complicated by rectovaginal fistula formation, ureteral injury, bowel perforation, or pelvic abscess.[2]

Segmental resection

The most aggressive surgical approach, segmental resection involves complete removal of a diseased portion of bowel, followed by side-to-side or end-to-end reanastomosis of the adjacent segments.[2] For this procedure, a multidisciplinary approach is recommended, with involvement of a colorectal surgeon or gynecologic oncologist trained in performing bowel resections. Segmental resection is indicated for lesions that are larger than 3 cm, circumferential, obstructive, or multifocal.

FIGURE 6 Complete obliteration of the cul-de-sac



Given the higher complication rate associated with this procedure and the good outcomes associated with less invasive techniques, we avoid segmental resection whenever possible, especially for lesions near the anal verge.[2]

Complications associated with surgical approach

In 2005, our group reported on a cohort of 178 women who underwent laparoscopic treatment of deeply infiltrative bowel endometriosis with shaving excision (n = 93), disc excision (n = 38), and segmental resection (n = 47).[34] The major complication rate was significantly higher for those undergoing segmental resection (12.5%, $P < .001$); only 7.7% of those who underwent disc resection experienced a major complication; and none were observed in the group treated with shaving excision.

In 2011, De Cicco and colleagues conducted a systematic review of 1,889 patients who underwent segmental bowel resection.[35] The major complication rate was 11%, with a leakage rate of 2.7%, fistula rate of 1.8%, major obstruction rate of 2.7%, and hemorrhage rate of 2.5%. Many of these complications, however, occurred in patients who had low rectal resections.

Regardless of surgical approach, the complication rate is related to the surgeon's ability to preserve the superior and inferior hypogastric plexuses and the sympathetic and parasympathetic nerve bundles. Nerve-sparing techniques should be used to

FAST TRACK

Given the higher complication rate associated with segmental resection and the good outcomes with less invasive techniques, we avoid segmental resection whenever possible, especially for lesions near the anal verge

decrease the incidence of postoperative bowel, bladder, and sexual function complications.[2] (See "Innervation of the pelvic organs" in the online version of this article.)

Our group's preferences

In our practice, we emphasize that the choice of surgical technique depends on the location, size, and depth of the lesion, as well as the extent of bowel wall circumferential invasion.[2]

We categorize lesions by their anatomic location: those above the sigmoid colon, on the sigmoid colon, on the rectosigmoid colon, and on the rectum. For lesions above the sigmoid colon, segmental or disc resection is appropriate.[2] We recommend segmental resection for multifocal lesions, lesions larger than 3 cm, or for lesions involving more than one-third of the bowel lumen.[37,44,45,47] Disc resection is appropriate for lesions smaller than 3 cm even if the bowel lumen is involved.[44,45,48] If endometriosis is encountered in any location along the bowel, appendectomy can be performed even without visible disease, due to a high incidence of occult disease of the appendix.[49,50]

When lesions involve the sigmoid colon, we prefer utilizing shaving excision when possible to limit dissection of the retrorectal space and pelvic sidewall nerves.[2] Segmental resection at or below the sigmoid colon has been associated with postoperative surgical site leakage[51] and long-term bowel and bladder dysfunction with risk of permanent colostomy.[52,53] For lesions smaller than 3 cm or involving less than one-third of the bowel lumen, disc resection can be performed. Segmental resection is required if multifocal disease or obstruction are present, if lesions are larger than 3 cm, or if more than one-third of the bowel lumen is involved.

For lesions along the rectosigmoid colon, we prefer utilizing shaving excision when possible.[2] Disc excision can be performed utilizing a transanal approach, being mindful to minimize dissection of the retroperitoneal space and pelvic sidewall nerves.[48] Segmental resection is avoided even with lesions larger than 3 cm, unless prior surgery has failed. Approaches for segmental resection can utilize laparoscopy or the natural orifices of the rectum or vagina.[31,51]

For lesions on the rectum, we strongly advise shaving excision.[2] Evidence fails to show that the benefits of segmental resection outweigh the risks when compared to conservative techniques at the rectum.[30,39,54] There is evidence indicating that aggressive surgery 5 to 8 cm from the anal verge is predictive of postoperative complications.[55] In our group, we use shaving excision to remove as much disease as possible without compromising the integrity of the bowel wall or surrounding neurovascular structures. We err on the side of caution, leaving some of the disease on the rectum to avoid rectal perforation, and plan for postoperative hormonal suppression in these patients.

For patients desiring fertility, successful pregnancy is often achieved using the shaving technique.[41]

FAST TRACK

For lesions on the rectum, we err on the side of caution and leave some disease on the rectum to avoid rectal perforation; we plan for postoperative hormonal suppression in these patients

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What to do when a patient presents with breast pain

Most breast pain is due to hormonal and fibrocystic changes, with conservative measures and patient reassurance prioritized. Here, types of breast pain, when imaging and referral are required, and management strategies.

Laila Samiian, MD

IN THIS ARTICLE

Breast pain is one of the most common breast-related patient complaints and is found to affect at least 50% of the female population.[1] Most cases are self-limiting and are related to hormonal and normal fibrocystic changes. The median age of onset of symptoms is 36 years, with most women experiencing pain for 5 to 12 years.[2] Because the cause of breast pain is not always clear, its presence can produce anxiety in patients and physicians over the possibility of underlying malignancy. Although breast cancer is not associated with breast pain, many patients presenting with pain are referred for diagnostic imaging (usually with negative results). The majority of women with mastalgia and normal clinical examination findings can be reassured with education about the many benign causes of breast pain.

What are causes of breast pain without an imaging abnormality?

Hormones. Mastalgia can be focal or generalized and is mostly due to hormonal changes. Elevated estrogen can stimulate the growth of breast tissue, which is known as epithelial hyperplasia.[3] Fluctuations in hormone levels can occur in perimenopausal women in their forties and can result in new symptoms of breast pain.[4] Sometimes starting a new contraceptive medication or hormone replacement therapy can exacerbate the pain. Switching brands or medications may help. Another cause of mastalgia may be elevated prolactin levels, with hypothalamic-pituitary dysfunction.[5,6]

Diet. There is evidence to link a high-fat diet with breast pain. The pain has been shown to improve when lipid intake is reduced and high- and low-density lipoprotein cholesterol levels are normalized. As estrogen is a steroid hormone that can be synthesized from lipids and fatty acids, elevated lipid metabolism can increase estrogen levels and exacerbate breast pain symptoms.[7,8] Essential fatty acids, such as evening primrose oil and vitamin E, have been used to treat mastalgia because they reduce inflammation in fatty breast tissue through the prostaglandin pathway.[9,10]

Caffeine. Methylxanthines can be found in coffee, tea, and chocolate and can aggravate mastalgia by enhancing the cyclin adenosine monophosphate (cAMP) pathway. This pathway stimulates cellular proliferation and fibrocystic changes which in turn can exacerbate breast pain.[11]

Smoking. In my clinical practice I have clearly noted a higher incidence of breast

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The majority (95%) of breast pain is caused by benign hormonal and fibrocystic changes, which can be managed conservatively, with no breast imaging necessary. Conservative measures include reassurance and education, supportive bra, and diet and lifestyle modification. Topical vitamins and analgesics and oral therapies are second- and third-line treatment options.

pain in patients who smoke. The pain tends to improve significantly when the patient quits or even cuts back on smoking. The exact reasons for smoking's effects on breast pain are not well known; however, they are thought to be related to acceleration of the cAMP pathway.

Large breast size. Very large breasts will strain and weaken the suspensory ligaments, leading to pain and discomfort. It has been shown that wearing a supportive sports bra during episodes of breast pain is effective.

Types of breast pain

Cyclical

Women with fibrocystic breasts tend to experience more breast pain. Breast sensitivity can be localized to the upper outer quadrants or to the nipple and sub-areolar area. It also can be generalized. The pain tends to peak with ovulation, improve with menses, and to recur every few weeks. Patients who have had partial hysterectomy (with ovaries in situ) or endometrial ablation will be unable to correlate their symptoms to menstruation. Therefore, women are encouraged to keep a diary or calendar of their symptoms to detect any correlation with their ovarian cycle. Such correlation is reassuring.

Noncyclical

Noncyclical breast pain is not associated with the menstrual cycle and can be unilateral or bilateral. Providers should perform a good history of patients presenting with noncyclical

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

breast pain, to include character, onset, duration, location, radiation, alleviating, and aggravating factors. A physical examination may elicit point tenderness at the chest by pushing the breast tissue off of the chest wall while the patient is in supine position and pressing directly over the ribs. Lack of tenderness on palpation of the breast parenchyma, but pain on the chest wall, points to a musculoskeletal etiology. Chest wall pain may be related to muscle spasm or muscle strain, trauma, rib fracture, or costochondritis (Tietze syndrome). Finally, based on history of review of systems and physical examination, referred pain from biliary or cardiac etiology should be considered.

Should I order breast imaging for my patient with breast pain and a normal clinical breast exam?

Breast pain is not associated with breast cancer. Most breast cancers do not hurt; they present as firm, painless masses. However, when a woman notices pain in her breast, her first concern is breast cancer. This concern is re-enforced by the medical provider whose first impulse is to order diagnostic imaging. Yet less than 3% of breast cancers are associated with breast pain.

There have been multiple published retrospective and prospective radiologic studies about the utility of breast imaging in women with breast pain without a palpable mass. All of the studies have demonstrated that breast imaging with mammography and ultrasonography in these patients yields mostly negative or benign findings. The incidence of breast cancer during imaging work-up in women with breast pain and no clinical abnormality is only 0.4% to 1.8%.[1-3] Some patients may develop future subsequent breast cancer in the symptomatic breast. But this is considered incidental and possibly related to increased cell turnover related to fibrocystic changes. Breast imaging for evaluation of breast pain only provides reassurance to the physician. The patient's reassurance will come from a medical explanation for the symptoms and advice on symptom management from the provider.

Researchers from MD Anderson Cancer Center reported imaging findings and cost analysis for 799 patients presenting with breast pain from 3 large network community-based breast imaging centers in 2014. Breast ultrasound was the initial imaging modality for women younger than age 30. Digital mammography (sometimes with tomosynthesis) was used for those older than age 30 that had not had a mammogram in the last 6 months. Breast magnetic resonance imaging was performed only when ordered by the referring physician. Most of the patients presented for diagnostic imaging, and 95% had negative findings and 5% had a benign finding. Only 1 patient was found to have an incidental cancer in the contralateral breast, which was detected by tomosynthesis. The cost of breast imaging was $87,322 in younger women and $152,732 in women older than age 40, representing overutilization of health care resources and no association between breast pain and breast cancer.[4]

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When breast pain occurs with skin changes

Skin changes usually have an underlying pathology. Infectious processes, such as infected epidermal inclusion cyst, hidradenitis of the cleavage and inframammary crease, or breast abscess will present with pain and induration with an acute onset of 5 to 10 days. Large pendulous breasts may develop yeast infection at the inframammary crease. Chronic infectious irritation can lead to hyperpigmentation of that area. Eczema or contact dermatitis frequently can affect the areola and become confused with Paget disease (ductal carcinoma in situ of the nipple). With Paget, the excoriation always starts at the nipple and can then spread to the areola. However, with dermatitis, the rash begins on the peri-areolar skin, without affecting the nipple itself.

When breast pain occurs with nipple discharge

Breast pain with nipple discharge usually is bilateral and more common in patients with significant fibrocystic changes who smoke. If the nipple discharge is bilateral, serous and nonbloody, and multiduct, it is considered benign and physiologic. Physiologic nipple discharge can be multifactorial and hormonal. It may be related to thyroid disorders or medications such as antidepressants, selective serotonin reuptake inhibitors (SSRIs), mood stabilizers, or antipsychotics. The only nipple discharge that is considered pathologic is unilateral spontaneous bloody discharge for which diagnostic imaging and breast surgeon referral is indicated. Women should be discouraged

from self-expressing their nipples, as 80% will experience serous nipple discharge upon manual self-expression.

Management of mastalgia

Appropriate breast pain management begins with a good history and physical examination. The decision to perform imaging should depend on clinical exam findings and not on symptoms of breast pain. If there is a palpable mass, then breast imaging and possible biopsy is appropriate. However, if clinical exam is normal, there is no indication for breast imaging in low-risk women under the age of 40 whose only symptom is breast pain. Women older than age 40 can undergo diagnostic imaging, if they have not had a negative screening mammogram in the past year.

Breast pain with abnormal clinical exam

In the patient who is younger than age 30 with a palpable mass. For this patient order targeted breast ultrasound (US) (**FIGURE 1,** page 48). If results are negative, repeat the clinical examination 1 week after menses. If the mass is persistent, refer the patient to a breast surgeon. If diagnostic imaging results are negative, consider breast MRI, especially if there is a strong family history of breast cancer.

In the patient who is aged 30 and older with a palpable mass. For this patient, bilateral diagnostic mammogram and US are in order. The testing is best performed 1 week after menses to reduce false-positive findings. If imaging is negative and the patient still has a clinically suspicious finding or mass, refer her to a breast surgeon and consider breast MRI. At this point if there is a persistent firm dominant mass, a biopsy is indicated as part of the triple test. If the mass resolves with menses, the patient can be reassured that the cause is most likely benign, with clinical examination repeated in 3 months.

Breast pain and normal clinical exam

When women who report breast pain have normal clinical examination findings (and have a negative screening mammogram in the past 12 months if older than age 40), there

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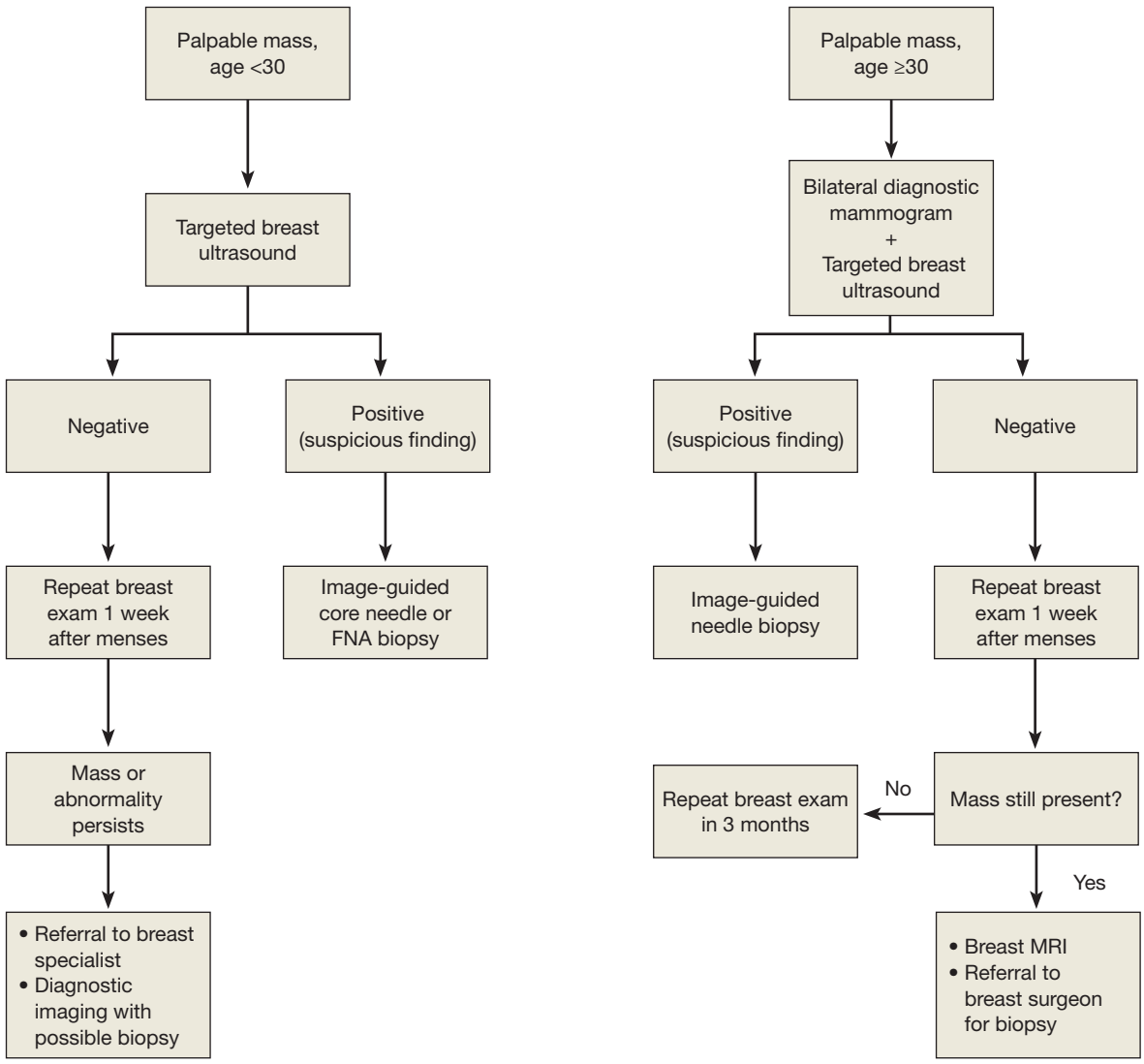
are several management strategies you can offer (**FIGURE 2,** page 50).

Reassurance and education. The majority of women with breast pain can be managed with reassurance and education, which are often sufficient to reduce their anxieties.

Supportive bra. The most effective intervention is to wear and sleep in a well-fitted supportive sports bra for 4 to 12 weeks. In a nonrandomized single-center trial of danazol versus sports bra, 85% of women reported relief of their breast pain with bra alone (vs 58% with danazol).[12] A supportive bra is the first-line management of mastalgia (Level II evidence).

Symptom diary/calendar. Many women do

FIGURE 1 Treatment algorithm for breast pain with abnormal clinical exam and palpable mass



Abbreviations: FNA, fine needle aspiration; MRI, magnetic resonance imaging.

not know whether or not their symptoms correspond to their ovarian cycle or are related to hormonal fluctuations. Therefore, it is reassuring and informative for them to keep a calendar or a diary of their symptoms to determine whether their symptoms occur or are exacerbated in a cyclical pattern.

Diet and lifestyle modification. Women should avoid caffeine (especially when having pain). Studies on methylxanthines have demonstrated some symptom relief with reducing caffeine intake.[11,13] One cup of coffee or tea per day most likely will not make a difference. However, if a woman is drinking large quantities of caffeinated beverages throughout the day, it will very likely improve her breast pain if she cuts back. This is especially true during the times of exacerbated pain prior to her menses.

In addition, recommend reduced dietary fat (overall good health). This is good advice for any patient. There were 2 small studies that showed improvement in breast pain with a 15% reduction in dietary fat.[7,8]

Finally, advise that patients stop smoking. Smoking aggravates and exacerbates fibrocystic changes, and these will lead to more breast pain.

Medical management. Over-the-counter medications that are found in the vitamin section of a local drug store are *vitamin E* and *evening primrose oil*. There are no significant adverse effects with these treatments. Their efficacy is theoretical, however; 3 randomized controlled trials demonstrated no significant clinical benefit with evening primrose oil versus placebo for treatment of mastalgia.[14]

Topical or oral nonsteroidal anti-inflammatory drugs (*NSAIDs*; Voltaren gel, topical compound pain creams) are useful as second-line management after using a supportive bra. Three randomized controlled trials have demonstrated up to 90% improvement of mastalgia with topical NSAIDs.[15-17]

Tamoxifen is a selective estrogen-receptor modulator (SERM), which is an antagonist to the estrogen receptor (ER) in the breast and an agonist to the ER in the endometrium. Tamoxifen has been found to reduce symptoms of mastalgia by 70% even at a lower dosage of 10-mg per day (for 6 months), or as a topical gel (afimoxifene). The oral form can have some adverse effects, including hot flashes, and has a low risk for thromboembolic events and endometrial neoplasia.[18-20]

Danazol is very effective in reducing breast pain symptoms (by 80%), with a higher relapse after stopping the medication. Danazol is less tolerated due to its androgenic effects, such as hirsutism, acne, menorrhagia, and voice changes. Both danazol and tamoxifen can be teratogenic and should be used with caution in women of child-bearing age.[21]

Finally, *bromocriptine* inhibits serum prolactin and has been reported to provide 65% improvement in breast pain. Its use for breast pain is not US Food and Drug Administration–approved and adverse effects include nausea, dizziness, and hypotension.[22]

Tamoxifen, danazol, and bromocriptine can be considered as third-line management options for severe treatment-resistant mastalgia.

In summary

Evaluation and counseling for breast pain should be managed by women's health care providers in a primary care setting. Most patients need reassurance and medical explanation of their symptoms. They should be educated that more than 95% of the time breast pain is not caused by an underlying malignancy but rather due to hormonal and fibrocystic changes, which can be managed conservatively. If the clinical breast examination and recent screening mammogram (in women over age 40) results are negative, patients should be educated that their pain is benign and undergo a trial of conservative measures: wear and sleep in a supporting bra; keep a calendar of symptoms to determine any relation to cyclical changes; and avoid nicotine, caffeine, and fatty food. Topical pain creams with diclofenac and evening primrose oil also can be effective in ameliorating the symptoms. Breast pain is not a surgical disease; referral to a surgical specialist and diagnostic imaging can be unnecessary and expensive.

FAST TRACK

First-line management strategies for breast pain include: reassurance and education, wearing a supportive bra, keeping a symptom diary to identify patterns, and diet and lifestyle modification

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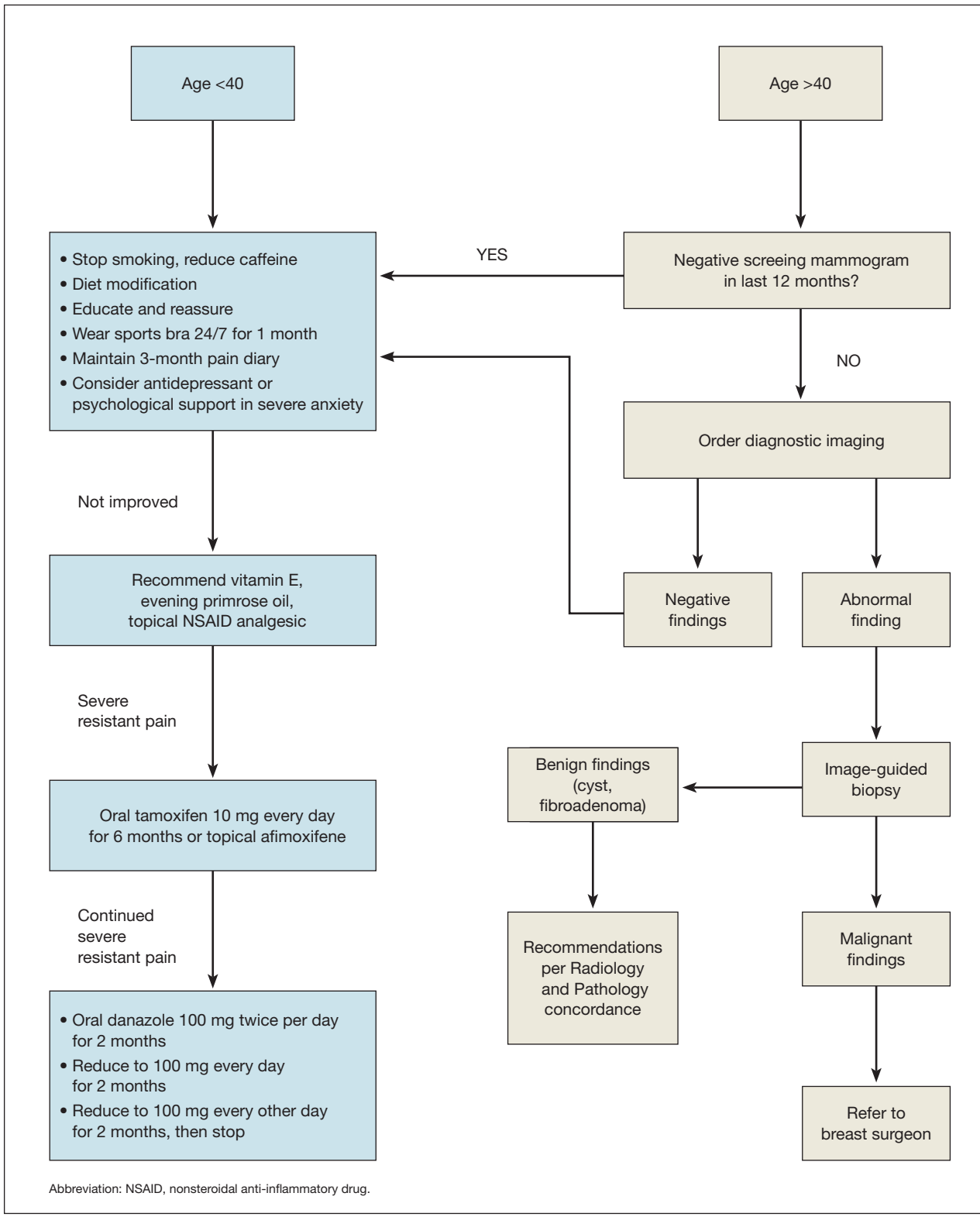
FIGURE 2 Treatment algorithm for breast pain with normal clinical breast examination



Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

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An app to help women and clinicians manage menopausal symptoms

This menopause app facilitates personalized treatment decisions

Katherine T. Chen, MD, MPH

In North America, women experience menopause (the permanent cessation of menstruation due to loss of ovarian activity) at a median age of 51 years. They may experience symptoms of perimenopause, or the menopause transition, for several years before menstruation ceases. Menopausal symptoms include vasomotor symptoms, such as hot flushes, and vaginal symptoms, such as vaginal dryness and pain during intercourse.[1]

Women may have questions about treating menopausal symptoms, maintaining their health, and preventing such age-related diseases as osteoporosis and cardiovascular disease. The decision to treat menopausal symptoms is challenging for women as well as their clinicians given that recommendations have changed over the past few years.

A free app with multiple features. The North American Menopause Society (NAMS) has developed a no-cost mobile health application called MenoPro for menopausal symptom management based on the organization's 2017 recommendations.[2] The app has 2 modes: one for clinicians and one for women/patients to support shared decision making.

For clinicians, the app helps identify which patients with menopausal symptoms are candidates for pharmacologic treatment and the options for optimal therapy. The app also can be used to calculate a 10-year cardiovascular disease (heart disease and stroke) risk assessment. In addition, it contains links to a breast cancer risk assessment as well as an osteoporosis/bone fracture risk assessment tool (FRAX model calculator). Finally, MenoPro includes NAMS's educational materials and information pages on lifestyle modifications to reduce hot flushes, contraindications and cautions to hormone therapy, pros and cons of hormonal versus nonhormonal options, a comparison of oral (pills) and transdermal (patches, gels, sprays) therapies, treatment options for vaginal dryness and pain with sexual activities, and direct links to tables with the various formulations and doses of medications.

The **TABLE** details the features of the MenoPro app based on a shortened version of the APPLICATIONS scoring system, APPLI (app comprehensiveness, price, platform, literature used, and important special features).[3] I hope that the app described here will assist you in caring for women in the menopausal transition. ●

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The author reports being an advisory board member and receiving royalties from UpToDate, Inc.

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TABLE Recommended menopause app

App	App comprehensiveness	Price	Platform	Literature used	Important special features
 **MenoPro by NAMS** iTunes: https://itunes.apple.com/us/app/menopro/id922540237?mt=8 Google Play: https://play.google.com/store/apps/details?id=org.menopause.menopro&hl=en_US	Clinical decision making (clinical decision support systems, clinical treatment guidelines, medical calculators)	Free	iTunes and Google Play store	2017 NAMS hormone therapy position statement	• Uses patient data to decide on candidates for pharmacologic treatment of menopausal symptoms and optimal therapy • Calculates a cardiovascular disease risk score • Includes links to a breast cancer risk score assessment and an osteoporosis/bone fracture risk assessment

Abbreviation: NAMS, The North American Menopause Society.

UPDATE menopause

CONTINUED FROM PAGE 31

treating depressive disorders in *postmenopausal* women. Estrogen therapy also may augment the clinical response to antidepressants in midlife and older women.[12,13] The data on combined HT (estrogen plus progestogen) or for different progestogens in treating depressive disorders in perimenopausal women are lacking and inconclusive.

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Excision of abdominal wall endometriosis

Surgical technique in an obese patient with a 5-cm abdominal nodule

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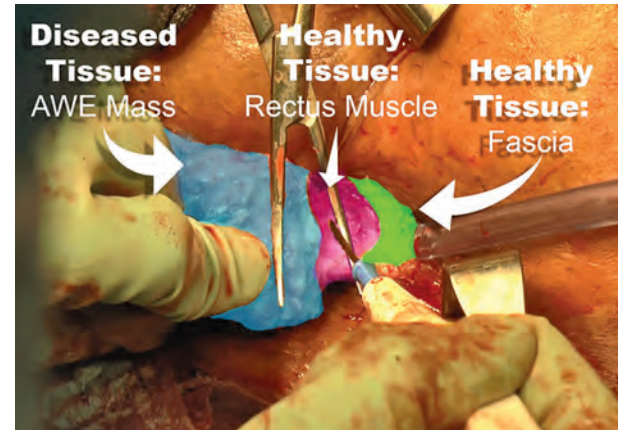
Endometriosis, defined by the ectopic growth of functioning endometrial glands and stroma,[1,2] usually affects the peritoneal cavity. However, endometriosis has been identified in the pneumothorax, brain, and within the extraperitoneum, such as the abdominal wall.[1-3] Incidence of abdominal wall endometriosis can be up to 12%.[3-5] If patients report symptoms, they can include abdominal pain, a palpable mass, pelvic pain consistent with endometriosis, and bleeding from involvement of the overlying skin. Abdominal wall endometriosis can be surgically resected, with complete resolution and a low rate of recurrence.

In the following video, we review the diagnosis of abdominal wall endometriosis, including our imaging of choice, and treatment options. In addition, we illustrate a surgical technique for the excision of abdominal wall endometriosis in a 38-year-old patient with symptomatic disease. We conclude with a review of key surgical steps.

We hope that you find this video useful to your clinical practice.

›› DR. ARNOLD P. ADVINCULA, AND COLLEAGUES



To view the video

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