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OBG MANAGEMENT

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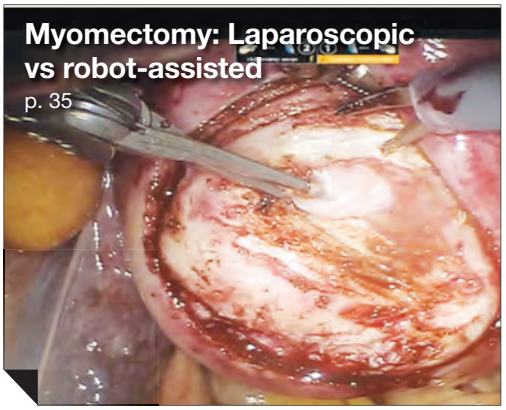
5 options for using newly approved elagolix for endometriosis pain
Robert L. Barbieri, MD



NOW APPROVED

A NEXT STEP IN ENDOMETRIOSIS PAIN RELIEF[1]

NEW

rilissa

elagolix tablets 150 mg 200 mg

- **The first FDA-approved oral treatment for MODERATE TO SEVERE endometriosis pain in over a decade**[1]
- Efficacy, safety, and tolerability evaluated in the **largest endometriosis phase 3 study program** to date (N=1686)[1]
- **Relief across the 3 most common types of endometriosis pain**[1,2]
- **Two oral dosage options** let you choose an appropriate dose for your patients[1]
- The **most common adverse reactions** associated with ORILISSA (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions, and mood changes[1]
- Discontinuations for both dosage forms were most commonly due to hot flushes or night sweats and nausea. Discontinuation rates for 150 mg QD and 200 mg BID dosages of ORILISSA were 1.1% and 2.5% for hot flushes or night sweats, and 0.8% and 1.5% for nausea, respectively[1]

*Statistical significance for dyspareunia was not achieved with the 150 mg 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.

abbvie

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.

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

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

These are not all the possible side effects of ORILISSA.

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

References: 1. Orilissa [package insert]. North Chicago, IL: AbbVie Inc; 2018. **2.** Fuldeore MJ, Soliman AM. Prevalence and symptomatic burden of diagnosed endometriosis in the United States: national estimates from a cross-sectional survey of 59,411 women. *Gynecol Obstet Invest.* 2016;82(5):453-461.

Discover a next step at ORILISSA.com/hcp

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

Orilissa™
elagolix tablets 150 mg 200 mg

ORILISSA™ (elagolix) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Important Dosing Information

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

Table 1. Recommended Dosage and Duration of Use

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

Hepatic Impairment

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

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

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

Missed Dose

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

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

CONTRAINDICATIONS

ORILISSA is contraindicated in women:

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

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

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

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

Clinical Trials Experience

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

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

Serious Adverse Events

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

Adverse Reactions Leading to Study Discontinuation

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

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

Common Adverse Reactions:

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

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

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

Less Common Adverse Reactions:

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

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

Bone Loss

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

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

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

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

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

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

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

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

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

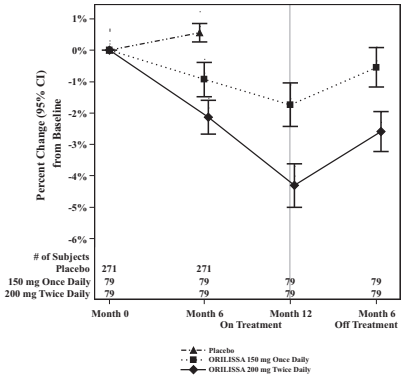
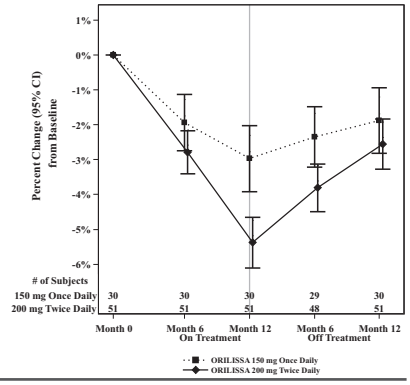


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

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

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

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

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

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

Hepatic Transaminase Elevations

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

Changes in Lipid Parameters

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

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

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

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

Hypersensitivity Reactions

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

Endometrial Effects

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

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

Effects on menstrual bleeding patterns

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

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

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

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

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

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

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

DRUG INTERACTIONS

Potential for ORILISSA to Affect Other Drugs

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

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

Potential for Other Drugs to Affect ORILISSA

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

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

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

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

Drug Interactions - Examples and Clinical Management

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

Table 7. Established Drug Interactions Based on Drug Interaction Trials

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

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

Data

Human Data

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

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

Animal Data

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

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

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

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

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

Lactation

Risk Summary

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

Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Renal Impairment

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

Hepatic Impairment

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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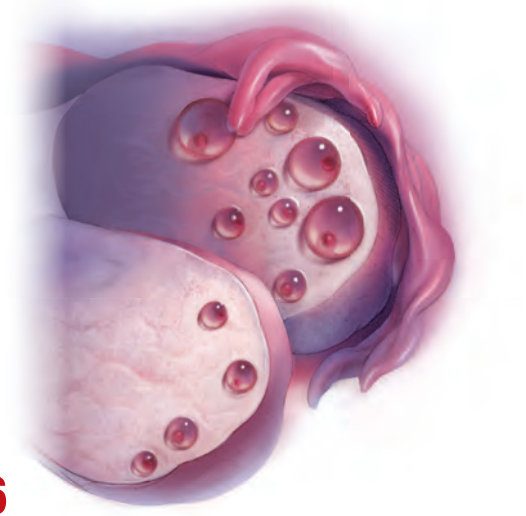

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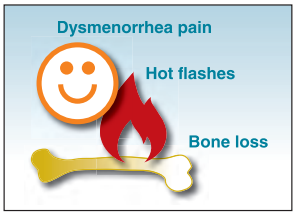

Endometriosis treatment
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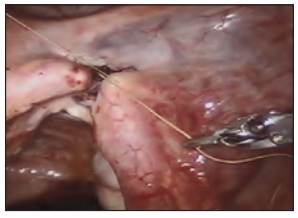
Tubal anastomosis
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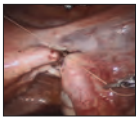

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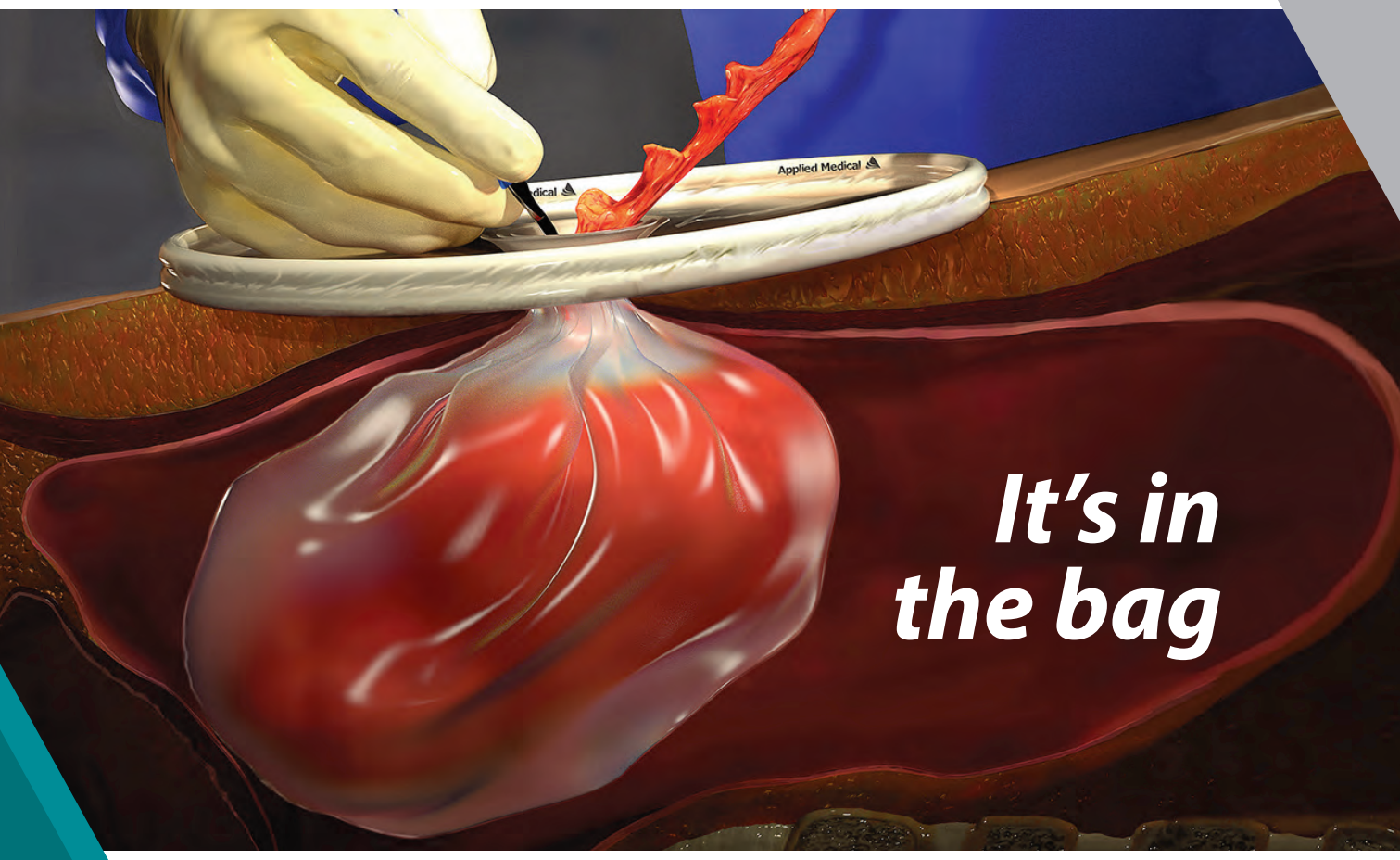

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EDITORIAL

Elagolix: A new treatment for pelvic pain caused by endometriosis

Two doses of elagolix are now FDA approved for treatment of pelvic pain caused by endometriosis. These two doses allow clinicians to opt for gentle (150 mg once daily) or strong (200 mg twice daily) suppression of estradiol to manage pelvic pain, as well as the associated effects of low estradiol levels.

Robert L. Barbieri, MD
Editor in Chief, OBG Management
Chair, Obstetrics and Gynecology
Brigham and Women's Hospital, Boston, Massachusetts
Kate Macy Ladd Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School, Boston

Endometriosis is the presence of tissue resembling endometrial glands and stroma outside of the uterine cavity. Women with endometriosis often present for medical care with at least one of 3 problems: pelvic pain, infertility, and/or an adnexal mass due to endometriosis.[1] Many clinical observations demonstrate that endometriosis lesions require estrogen to grow and maintain their viability, including that: (1) endometriosis is uncommon before puberty or after menopause, (2) surgical removal of both ovaries results in regression of endometriosis lesions, and (3) gonadotropin-releasing hormone (GnRH) analogues cause a hypoestrogenic hormonal environment, resulting in regression of endometriosis lesions and improvement in pelvic pain. Since endometriosis lesions require estrogen to maintain their viability, suppressing estradiol is a logical approach to hormonal treatment of the disease.

The estrogen threshold hypothesis

The estradiol concentration that causes endometriosis lesions to grow or regress varies among women, but a concentration less than 20 pg/mL usually causes lesions to regress, and a concentration greater than 60 pg/mL usually supports lesion growth and maintains lesion viability.[2] Although an estradiol concentration below 20 pg/mL may cause lesions to regress, it also is associated with moderate to severe hot flashes and accelerated bone loss. These adverse effects limit the use of strong suppression of estrogen as a long-term treatment strategy. The estrogen threshold hypothesis posits that gently suppressing estradiol to a concentration between 20 and 45 pg/mL may simultaneously cause endometriosis lesions to regress, resulting in reduced pelvic pain, minimal bone loss, and few hot flashes.[2]

Building on the estrogen threshold hypothesis, clinicians have two options for treatment of pelvic pain caused by endometriosis:

1. strong suppression of estradiol to a concentration below 20 pg/mL
2. gentle suppression of estradiol to a concentration in the range of 20 to 45 pg/mL.

Strong suppression of estradiol to levels below 20 pg/mL will reliably induce amenorrhea and cause regression of endometriosis lesions, thereby reducing pelvic pain. Strong suppression of estradiol also will cause moderate to severe hot flashes and accelerated bone loss in many women. By contrast, gentle suppression of circulating estradiol to a concentration in the range of 20 to 45 pg/mL may result in amenorrhea or oligomenorrhea, suppression of the growth of endometriosis lesions, a modest reduction in pelvic pain, mild hot flashes, and minimal bone loss.

Recently, the US Food and Drug Administration (FDA) approved elagolix, an oral GnRH antagonist, for treatment of endometriosis.[3] Elagolix

CONTINUED ON PAGE 12

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The American College of Obstetricians and Gynecologists (ACOG) recommends screening patients at least once during the perinatal period using a standardized, validated tool.[15]

Some examples of these tools include the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire-9 (PHQ-9).

It only takes **~5 minutes** to know your patient's score.[15]

References: 1. Ko JY, Rockhill KM, Tong VT, Morrow B, Farr SL. Trends in postpartum depressive symptoms - 27 states, 2004, 2008, and 2012. *MMWR Morb Mortal Wkly Rep.* 2017;66(6):153-158. **2.** DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007-2010. *Prev Chronic Dis.* 2014;11:E104. **3.** Data on Selected Pregnancy Complications in the United States. 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-complications-data.html. Accessed May 8, 2017. **4.** Pregnancy-Related Mortality Surveillance. Centers for Disease Control and Prevention website. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html. Accessed April 17, 2018. **5.** Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. *BMC Pregnancy Childbirth.* 2009;9:55. **6.** Reddy UM, Rice MM, Grobman WA, et al; the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Serious maternal complications after early preterm delivery (24-33 weeks' gestation). *Am J Obstet Gynecol.* 2015;213(4):538.e1-9. **7.** Cox EQ, Sowa NA, Meltzer-Brody SE, Gaynes BN. The perinatal depression treatment cascade: baby steps toward improving outcomes. *J Clin Psychiatry.* 2016;77(9):1189-1200. **8.** Georgiopoulos AM, Bryan TL, Wollan P, Yawn BP. Routine screening for postpartum depression. *J Fam Pract.* 2001;50(2):117-122. **9.** Evins GG, Theofrastous JP, Galvin SL. Postpartum depression: a comparison of screening and routine clinical evaluation. *Am J Obstet Gynecol.* 2000;182(5):1080-1082. **10.** Georgiopoulos AM, Bryan TL, Yawn BP, Houston MS, Rummans TA, Therneau TM. Population-based screening for postpartum depression. *Obstet Gynecol.* 1999;93(5 Pt 1):653-657. **11.** Coates AO, Schaefer CA, Alexander JL. Detection of postpartum depression and anxiety in a large health plan. *J Behav Health Serv Res.* 2004;31(2):117-133. **12.** Ko JY, Farr SL, Dietz PM, Robbins CL. Depression and treatment among US pregnant and nonpregnant women of reproductive age, 2005-2009. *J Womens Health (Larchmt).* 2012;21(8):830-836. **13.** Spitzer RL, Williams JB, Kroenke K, Hornyak R, McMurray J. Validity and utility of the PRIME-MD Patient Health Questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. *Am J Obstet Gynecol.* 2000;183(3):759-769. **14.** Goodman JH, Tyer-Viola L. Detection, treatment, and referral of perinatal depression and anxiety by obstetrical providers. *J Womens Health (Larchmt).* 2010;19(3):477-490. **15.** The American College of Obstetricians and Gynecologists. Committee Opinion: screening for perinatal depression. 2015:630.

SAGE THERAPEUTICS

CONTINUED FROM PAGE 10

blocks GnRH receptors in the pituitary gland, resulting in reduced production of luteinizing hormone and follicle stimulating hormone and a decrease in sex steroid secretion in the ovarian follicles, which leads to a reduction in the production and circulating concentration of estradiol. The FDA approved two doses of elagolix: 150 mg once daily for up to 24 months and 200 mg twice daily for up to 6 months. Importantly, elagolix at a dose of 150 mg once daily results in a mean circulating estradiol concentration of 41 pg/mL, indicating gentle suppression of ovarian estradiol production, and 200 mg twice daily results in a mean circulating ovarian estradiol concentration of 12 pg/mL, indicating strong suppression of ovarian estradiol production.[3] For clinicians treating women with pelvic pain caused by endometriosis, these two elagolix regimens permit the individualization of hormonal therapy to the unique needs of each woman.

Elagolix benefits and adverse effects

In one large clinical trial (Elaris Endometriosis I), 872 women were randomly assigned to treatment with one of two doses of elagolix (200 mg twice daily [high-dose group] or 150 mg once daily [low-dose group]) or placebo.[4] After 3 months of treatment, a clinically meaningful reduction in dysmenorrhea pain was reported by 76%, 46%, and 20% of women in the high-dose, low-dose, and placebo groups, respectively ($P<.001$ for comparisons of elagolix to placebo). In addition, at 3 months, a clinically meaningful reduction in nonmenstrual pain or decreased or stable use of rescue analgesics was reported by 55%, 50%, and 37% of women in the high-dose, low-dose, and placebo groups, respectively (low-dose vs placebo, $P<.01$; high-dose vs placebo, $P<.001$). Hot flashes that were severe enough to be classified as adverse events by study participants were reported by 42%, 24%, and 7% of the women in the high-dose, low-dose, and placebo groups, respectively. Bone density was measured at baseline and after 6 months of treatment. Lumbar bone density changes were -2.61%, -0.32%, and +0.47%, and hip/femoral/neck bone density changes were -1.89%, -0.39%, and +0.02% in the high-dose, low-dose, and placebo groups, respectively.

Another large clinical trial of elagolix for treatment of pelvic pain caused by endometriosis (Elaris II) involving 817 women produced results that were similar to those reported in Elaris I.[4] The elagolix continuation studies, Elaris III and IV, demonstrated efficacy and safety of elagolix through 12 months of treatment.[5]

Depot leuprolide acetate and nafarelin acetate

Depot leuprolide acetate and nafarelin acetate are GnRH analogues approved by the FDA more than 25 years ago for treatment of pelvic pain caused by endometriosis. Over the past two decades, depot leuprolide acetate has been one of the most commonly used hormonal treatments for endometriosis in the United States. A 3-month formulation of depot leuprolide acetate with an 11.25-mg injection has resulted in mean circulating estradiol concentrations of 8 pg/mL, indicating very strong suppression of estradiol production.[6] A twice-daily 200-µg dose of nafarelin acetate nasal spray has resulted in a circulating estradiol concentration of approximately 28 pg/mL, indicating gentle suppression of estradiol production.[7]

At current prices, elagolix treatment is substantially less expensive than treatment with leuprolide or nafarelin. In addition, many women in my practice prefer to use an oral medication over an intramuscular injection or a nasal spray medication. It is likely that clinicians and patients will evolve to prioritize and favor elagolix therapy over depot leuprolide or nafarelin treatment.

5 options for using elagolix

There are many potential options for using elagolix in the treatment of pelvic pain caused by endometriosis. **Option 1.** Prescribe elagolix 200 mg twice daily for 6 months to achieve

CONTINUED ON PAGE 14

Safety information for elagolix[3]

- Contraindications: Elagolix should not be prescribed to women who are currently pregnant or have known osteoporosis or severe hepatic impairment. Elagolix should not be used in women taking cyclosporine or gemfibrozil (organic anion transporting polypeptide inhibitors).
- Elagolix may cause dose-dependent bone loss.
- Elagolix reduces menstrual bleeding, which may make it difficult to recognize the occurrence of pregnancy. Nonhormonal contraceptives should be utilized during elagolix treatment.
- Elagolix may be associated with an increase in reported depressive symptoms and mood changes.
- Elagolix may be associated with an increase in alanine aminotransferase more than 3 times the upper limit of the reference range. If elevated liver function tests are detected, the benefits and risks of continuing elagolix treatment should be evaluated.

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5 options for using elagolix to treat endometriosis-associated pelvic pain

Option	Dysmenorrhea pain	Hot flashes	Bone loss
1 elagolix 200 mg twice daily for 6 months[a]	strong improvement	increase	greater
2 elagolix 150 mg once daily for up to 24 months[a]	modest improvement	fewer	minimal
3 elagolix 200 mg twice daily for 3 months, switch to elagolix 150 mg once daily for up to 24 months[b]	strong improvement	fewer	minimal
4 alternating regimen of elagolix 200 mg twice daily on even days of the month and one pill daily on odd days of the month[b]	moderate improvement	[not clear]	[not clear]
5 elagolix 200 mg twice daily and initiate add-back therapy with norethindrone acetate at a dose of 5 mg once daily[c]	strong improvement	fewer	minimal

[a]FDA-approved treatment option. [b]Treatment option is not FDA approved. [c]Based on FDA approved combination leuprolide-norethindrone acetate regimen.

strong suppression of estradiol and marked improvement in dysmenorrhea, although at the cost of more hot flashes and greater bone loss.

Option 2. Prescribe elagolix 150 mg once daily for up to 24 months to achieve gentle suppression of estradiol and modest improvement in dysmenorrhea with fewer hot flashes and minimal bone loss.

Options 1 and 2 have been studied in high quality clinical trials involving more than 1,500 women and are approved by the FDA.

Option 3. Initiate treatment with elagolix 200 mg twice daily for 3 months, immediately accruing the benefits of strong suppression of estradiol, and then switch to elagolix 150 mg once daily for up to 24 months to achieve continuing pain control with fewer adverse effects. This regimen combines strong initial suppression of estradiol, which will result in marked improvement in dysmenorrhea, along with long-term gentle suppression of estradiol, which is likely to maintain decreased pain symptoms with minimal long-term bone loss and fewer hot flashes.

Option 4. Prescribe an alternating regimen of elagolix 200 mg twice daily on even days of the month (two pills daily is an even number of pills) and one pill daily on odd days of the month (1 pill daily is an odd number of pills). This regimen should produce a mean estradiol concentration between 12 and 41 pg/mL, resulting in moderate rather than strong or gentle suppression of estradiol.

Options 3 and 4 are based on extrapolation using our knowledge about the hormonal treatment of endometriosis and are not regimens approved by the FDA.

Option 5. Prescribe elagolix 200 mg twice daily and initiate add-back therapy with norethindrone acetate 5 mg once daily. Substantial evidence supports the combination of a GnRH analogue that strongly suppresses estradiol production with norethindrone acetate add-back, which helps mitigate the bone loss that occurs with strong suppression of estradiol and reduces the frequency of moderate to severe hot flashes.

Option 5 is based on extrapolation from high-quality studies of leuprolide acetate depot plus norethindrone acetate add-back.[8] The combination regimen is approved by the FDA.[3]

Elagolix availability increases treatment choices for women

Pelvic pain caused by endometriosis is common, affecting approximately 8% of women of reproductive age.[9] Endometriosis is a vexing disease because diagnosis is often delayed many years after the onset of symptoms, causing great frustration among patients.[10] Some effective hormonal treatment options, including danazol and depot leuprolide, are poorly tolerated by patients because of adverse effects, including weight gain (danazol), hot flashes, and bone loss (depot leuprolide).

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Are patients more satisfied with combination or monotherapy for hirsutism in PCOS?

Combination therapy, using oral contraceptives and spironolactone, in a cohort of 138 patients with polycystic ovary syndrome (PCOS) was associated with increased rates of improvement of hirsutism, acne, and menstrual irregularity. Therapeutic benefit was seen starting at 6 months. Patients' satisfaction with their therapeutic response at any point could be predicted by their pretreatment hirsutism score and serum sex hormone–binding globulin levels.

EXPERT COMMENTARY
Elie Hobeika, MD, is a Fellow, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Illinois College of Medicine, Chicago.
Bert Scoccia, MD, is Professor and Director, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Illinois College of Medicine.

Ezeh U, Huang A, Landay M, et al. Long-term response of hirsutism and other hyperandrogenic symptoms to combination therapy in polycystic ovary syndrome. J Women Health (Larchmont). 2018;27:892-902.

Ezeh and colleagues conducted a retrospective analysis to evaluate the effectiveness of long-term combination suppressive therapy on hirsutism, acne, and menstrual disturbances in patients with PCOS and to identify the elements that could predict therapeutic response.

Details of the study

This chart review examined data from 200 nondiabetic patients with PCOS who presented between October 1987 and June 2002. PCOS diagnosis was based on the National Institutes of Health (NIH) 1990 criteria. During the initial visit, patients underwent a detailed medical history and physical exam, including a modified Ferriman-Gallwey hirsutism score and hormonal evaluation.

Treatment regimens. Patients were treated with suppressive therapy that consisted of an oral contraceptive (OC) (35 µg ethinyl estradiol plus 1 mg ethynodiol diacetate), an antiandrogen (spironolactone 200 mg/day), or a combination of these drugs. They were followed every 4 to 12 months (mean follow-up time, 34.2 months; range, 6–155 months), and subjective therapy response was assessed from medical records and by improvements in hirsutism scores.

Study findings. The 138 patients treated with combination suppressive therapy reported higher rates of subjective improvement in hirsutism compared with patients treated with other regimens (89.9% vs 72.0%, $P<.0001$). They also had a significant objective reduction in their modified Ferriman-Gallwey hirsutism score (6.0 vs 3.2; $P=.0001$). The combination therapy was superior to either regimen alone; the response to therapy for symptom resolution took at least 6 months and continued for up to 60 months of combination suppressive therapy.

Adding electrolysis treatment to the combination regimen resulted in improved patient satisfaction, but the differences were

CONTINUED ON PAGE 20

The authors report no financial relationships relevant to this article.

FAST TRACK

The 138 patients treated with combination suppressive therapy reported higher rates of subjective improvement in hirsutism compared with patients treated with other regimens (89.9% vs 72.0%, P<.0001)

FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

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DISCOVER A TREATMENT EXPERIENCE WITH

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IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

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

Estrogen Plus Progestin Therapy

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

Imvexxy™
(estradiol vaginal inserts)
4 mcg • 10 mcg

NOW AVAILABLE

IMVEXXY is the only ultra-low-dose vaginal estradiol available in both 4-mcg and 10-mcg doses, offering comfortable and convenient, any time of day, applicator-free, mess-free administration.[1-3]

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

INDICATION

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

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

References: 1. Imvexxy [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2018. **2.** Constantine GD, Simon JA, Pickar JH, et al. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. *Menopause*. 2017;24(4): 409-416. **3.** Vaginal Estrogen PIs as of 10/2018. **4.** Test ID: EEST—estradiol, serum. Mayo Clinic. https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/81816. Accessed on May 29, 2018.

IVXY-20192.2 10/2018

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For Her. For Life.

IMPORTANT IMVEXXY FEATURES

Applicator-free, any time of day administration[1]

Mess-free administration with no applicator, dose preparation, or cleanup needed[1,2]

Freedom to enjoy her everyday activities without interruption after insertion

Improvement in moderate to severe dyspareunia seen at week 12 and beginning as early as week 2 (a secondary endpoint)[1,2]

Both doses of IMVEXXY resulted in average systemic hormone levels that were within the normal postmenopausal range[1,4*]

*Systemic absorption may occur with IMVEXXY. The risks associated with systemic estrogen therapy should be considered.

IMVEXXY™ (estradiol vaginal inserts)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use **IMVEXXY™** safely and effectively. See package insert for Full Prescribing Information.

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

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.3) in full prescribing information].*

Cardiovascular Disorders and Probable Dementia

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

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

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

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

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

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

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

Breast Cancer

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

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

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.3, 5.15) in full prescribing information].*

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

CONTRAINDICATIONS

IMVEXXY is contraindicated in women with any of the following conditions:

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

WARNINGS AND PRECAUTIONS

Risks from Systemic Absorption

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

Cardiovascular Disorders

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

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

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.2) in full prescribing information]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.2) in full prescribing information]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.2) in full prescribing information].*

Subgroup analysis of women 50 to 59 years of age suggests a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.2) in full prescribing information].*

In postmenopausal women with documented heart disease (n=2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3] *[see Clinical Studies (14.2) in full prescribing information]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[4] *[see Clinical Studies (14.2) in full prescribing information]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

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

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

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

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80][5] *[see Clinical Studies (14.2) in full prescribing information].*

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely

(continued on next page)

to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[6] *[see Clinical Studies (14.2) **in full prescribing information**]*.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77 to 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7]

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) **in full prescribing information**]*.

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) **in full prescribing information**]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) **in full prescribing information**]*.

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogen-alone is prescribed.

Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

Exacerbation of Endometriosis

Cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

Drug Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with IMVEXXY.

Metabolic Interactions

In-vitro and *in-vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort *(Hypericum perforatum)* preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

USE IN SPECIFIC POPULATIONS

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

Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing IMVEXXY to determine whether those over 65 years of age differ from younger subjects in their response to IMVEXXY.

The Women's Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.2) **in full prescribing information**]*.

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.2) **in full prescribing information**]*.

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.4), and Clinical Studies (14.3) **in full prescribing information**]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Warnings and Precautions (5.4), and Clinical Studies (14.3) **in full prescribing information**]*.

OVERDOSAGE

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of IMVEXXY therapy with institution of appropriate symptomatic care.

PATIENT COUNSELING INFORMATION

See FDA-approved PATIENT COUNSELING INFORMATION

Based on IVXY-20009
Revised: 05/2018

TherapeuticsMD®

CONTINUED FROM PAGE 15

WHAT THIS EVIDENCE MEANS FOR PRACTICE

This retrospective study offers Level II evidence confirming the superiority of a combined OC plus spironolactone (compared with either agent alone) in the treatment of hirsutism in women with PCOS. In addition, this study emphasizes the importance of using combination suppressive therapy for at least 6 months to see a clinical response. Electrolysis may be helpful to patients especially during the initial 6 months of suppressive treatment. Finally, spironolactone alone could be reserved for cases in which OCs are contraindicated in women not interested in becoming pregnant.

In our practice, we treat patients with hirsutism using OC pills containing the progestogen levonorgestrel plus spironolactone at a lower dose of 100 mg/day, since patients treated with higher spironolactone doses report irregular bleeding and fatigue.

ELIE HOBEIKA, MD, AND BERT SCOCCIA, MD

not significant. Patients' satisfaction with the therapeutic response could be predicted from their pretreatment hirsutism scores or circulating sex hormone–binding globulin levels.

Study strengths and weaknesses

The study's major strengths are the large number of patients included, the uniformity of criteria for diagnosis, and the prolonged follow-up. This is one of the few studies to report the impact of therapy on health-related quality of life in patients with PCOS and to assess response to therapy with use of objective measures, such as changes in the modified Ferriman-Gallwey score.

However, the criteria used to diagnose PCOS—the NIH 1990 criteria—currently are used less commonly than the Rotterdam 2003 criteria, and they are less inclusive for the diagnosis of PCOS.

The OC pill formulation used in this study contained the progestogen ethynodiol diacetate, which is not used routinely in modern clinical practice. In addition, the majority of patients were non-Hispanic white, which limits extrapolating these findings to other races and ethnicities. ●

EDITORIAL

CONTINUED FROM PAGE 14

Combination oral contraceptives used in a continuous or cyclic fashion often result in inadequate improvement in pelvic pain.[11] The synthesis of an orally active, small-molecule GnRH antagonist is an innovative advance in endocrine pharmacology. The Elaris Endometriosis clinical trials have demonstrated that elagolix is effective in the treatment of pelvic pain caused by endometriosis.[4,5] A great advantage of elagolix is that dosing can be tailored for each patient to achieve reduction in pain while minimizing unwanted adverse effects such as hot flashes and bone loss. In Elaris Endometriosis I, fewer than 10% of women discontinued elagolix due to adverse effects.[4] Elagolix is also less expensive than depot leuprolide and nafarelin.

Millions of women in the United States have pelvic pain caused by endometriosis. Obstetrician-gynecologists are the clinicians best trained to care for these women, and patients trust that we will effectively treat their problem. ●

RBARBIERI@MDEDGE.COM

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

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Low sexual desire: Appropriate use of testosterone in menopausal women

Low-dose testosterone treatment may be considered for HSDD in carefully selected menopausal women after standard therapies have been tried but symptoms and distress continue. Thorough counseling and close follow-up are essential.

Jan L. Shifren, MD

CASE Midlife woman with low libido causing distress

At her annual gynecologic visit, a 55-year-old woman notes that she has almost no interest in sex. In the past, her libido was good and relations were pleasurable. Since her mid-40s, she has noticed a gradual decline in libido and orgasmic response. Sexual frequency has declined from once or twice weekly to just a few times per month. She has been married for 25 years and describes the relationship as caring and strong. Her husband is healthy with a good libido; his intermittent erectile dysfunction is treated with a phosphodiesterase-5 inhibitor. The patient's low libido is distressing, as the decline in sexual frequency is causing some conflict for the couple. She requests that her testosterone level be checked because she heard that treatment with testosterone cream will solve this problem.

Dr. Shifren is Director, Midlife Women's Health Center, Department of Obstetrics and Gynecology, Massachusetts General Hospital, and Vincent Trustees Professor of Obstetrics, Gynecology and Reproductive Biology; Harvard Medical School, Boston, Massachusetts.

The author reports that she is a consultant for the New England Research Institutes.

Evaluating and treating low libido in menopausal women

Low libido is a very common sexual problem for women. When sexual problems are accompanied by distress, they are classified as sexual dysfunctions. Although ObGyns should discuss sexual concerns at every comprehensive visit, if the patient has no associated distress, treatment is not necessarily indicated. A woman with low libido or anorgasmia who is satisfied with her sex life and is not bothered by these issues does not require any intervention.

Currently, the only indication for testosterone therapy that is supported by clinical trial evidence is low sexual desire with associated distress, known as hypoactive sexual desire disorder (HSDD). Although other sexual problems also commonly occur in menopausal women, such as disorders of orgasm and pain, testosterone is not recommended for these problems. In addition, testosterone is not approved by the US Food and Drug Administration (FDA) for the treatment of female sexual dysfunction.

Routinely inquire about sexual functioning

Ask your patients about sexual concerns at every comprehensive visit. You can easily incorporate into the review of systems a general

CONTINUED ON PAGE 26

IN THIS ARTICLE

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

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.

WARNINGS and PRECAUTIONS

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 the nonradiopaque etonogestrel implant have included pulmonary emboli (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.

WOMN-1267530-0000 09/18

NEXPLANON is the only non-uterine LARC option

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

- Provides Up to **3 years** of pregnancy prevention*
- **>99%** effective†
- **Reversible** if her plans change

Placed subdermally in the inner upper arm just under the skin

(Actual implant shown; actual implant is 4 cm)

*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.

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

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 in the upper arm. To reduce the risk of neural or vascular injury, the implant should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. The implant should be inserted subdermally just under the skin, avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissues. 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.

1. **Complications of Insertion and Removal**

   NEXPLANON should be inserted subdermally so that it is 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 reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. NEXPLANON should be inserted subdermally just under the skin avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissues. 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.

2. **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.

3. **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.

4. **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.

5. **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.

6. **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.

7. **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]*.

8. **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.

9. **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.

10. **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.

11. **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.

12. **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.

13. **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.

14. **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.
15. **Contact Lenses**
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.
16. ***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].*
17. **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.
18. **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 ncrease 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

1. **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.
2. **Nursing Mothers**
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.
3. **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.
4. **Geriatric Use**
This product has not been studied in women over 65 years of age and is not indicated in this population.
5. **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].*
6. **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 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-1705r019
Revised: 05/17

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Key points

- Evidence supports low-dose transdermal testosterone in carefully selected menopausal women with HSDD and no other identifiable reason for the sexual dysfunction
- Inform women considering testosterone for HSDD of the limited effectiveness and high placebo responses seen in clinical trials
- Women also must be informed that treatment is off-label (no testosterone formulations are FDA approved for women)
- Review with patients the limitations of compounded medications, and discuss possible adverse effects of androgens. Long-term safety is unknown and, as androgens are converted to estrogens, there may be an effect on breast cancer or cardiovascular risk.

question, such as, "Do you have any sexual concerns?" If the patient does mention a sexual problem, schedule a separate visit (given appointment time constraints) to address it. History and physical examination information you gather during the comprehensive visit will be helpful in the subsequent problem-focused visit.

Taking a thorough history is key when addressing a patient's sexual problems, since identifying possible etiologies guides treatment. Often, the cause of female sexual dysfunction is multifactorial and includes physiologic, psychologic, and relationship issues.

FAST TRACK

Consider the many therapies for low sexual desire prior to initiating a testosterone trial; this should be considered for HSDD only if the disorder persists after addressing all other possible contributing factors

Explore potential causes, recommend standard therapies

Common causes of low libido in menopausal women include vasomotor symptoms, insomnia, urinary incontinence, cancer or another major medical problem, weight gain, poor body image, genitourinary syndrome of menopause (GSM) with dyspareunia, fatigue, stress, aging, relationship duration, lack of novelty, relationship conflict, and a partner's sexual problems. Other common etiologies include depression, anxiety, and substance use disorders, as well as medications used to treat these disorders, including selective serotonin reuptake inhibitors (SSRIs).

There are many effective therapies for low sexual desire to consider prior to initiating a trial of testosterone, which should be considered for HSDD only if the disorder persists after addressing all other possible contributing factors (**TABLE 1**, page 28).

Sex therapy, for example, provides information on sexual functioning and helps improve communication and mutual pleasure and satisfaction. Strongly encourage—if not require—a consultation with a sex therapist before prescribing testosterone for low libido. Any testosterone-derived improvement in sexual functioning will be enhanced by improved communication and additional strategies to achieve mutual pleasure.

Hormone therapy. Vasomotor symptoms, with their associated sleep disruption, fatigue, and reduced quality of life (QOL), often adversely impact sexual desire. Estrogen therapy does not appear to improve libido in otherwise asymptomatic women; however, in women with bothersome vasomotor symptoms treated with estrogen, sexual interest may increase as a result of improved sleep, fatigue, and overall QOL. The benefits of systemic hormone therapy generally outweigh its risks for most healthy women younger than age 60 who have bothersome hot flashes and night sweats.[1]

Nonhormonal and other therapies. GSM with dyspareunia is a principal cause of sexual dysfunction in older women.[2] Many safe and effective treatments are available, including low-dose vaginal estrogen therapy, nonhormonal moisturizers and lubricants, ospemifene, vaginal dehydroepiandrosterone, and pelvic floor physical therapy.[3] Urinary incontinence commonly occurs in midlife women and contributes to low libido.[4]

Lifestyle approaches. Address fatigue and stress by having the patient adjust her work and sleep schedules, obtain help with housework and meals, and engage in mind-body interventions, counseling, or yoga. Sexual function may benefit from yoga practice, likely as a result of the patient experiencing reduced stress and enhanced body image. Improving overall health and body image with regular exercise, optimal diet, and weight management may contribute to a more satisfying sex life after the onset of menopause.

Relationship refresh. Women's sexual interest often declines with relationship duration, and both men and women who are in

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*S. Maheux-Lacroix et al. Hum Reprod 2014;29(5):953-63.

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TABLE 1 Common causes of low sexual desire in menopausal women and interventions to consider prior to a trial of testosterone therapy

Common causes of low sexual desire	Interventions
Physical factors	
Vasomotor symptoms	Lifestyle changes, hormone therapy
Dyspareunia, GSM	Lubricants, moisturizers, low-dose vaginal estrogen therapy, vaginal DHEA, ospemifene, pelvic floor PT
Incontinence	Pelvic floor PT, devices, medications, surgery
Weight gain, poor body image	Dietary changes, exercise
Major medical problem, cancer	Treatment, support
Pelvic pain	Treatment
Psychosocial factors	
Fatigue	Lifestyle interventions
Stress	Mind-body interventions, counseling, yoga, exercise
Depression	Psychotherapy, medications
Anxiety	Psychotherapy, medications
Substance use disorders	Treatment
Abuse (current, past)	Psychotherapy, counseling, support
Medications (eg, SSRIs)	Adjust medications (eg, bupropion trial), psychopharmacology consult
Relationship factors	
Relationship conflict	Counseling, sex therapy
Limited quality, novelty	Sex therapy, devices, films, novel experiences, vacations, date nights, counseling
Partner's sexual dysfunction	Treatment, sex therapy

Abbreviations: DHEA, dehydroepiandrosterone; GSM, genitourinary syndrome of menopause; PT, physical therapy; SSRIs, selective serotonin reuptake inhibitors.

new relationships generally have increased libido, affirming the importance of novelty over the long term. Couples will benefit from "date nights," weekends away from home, and trying novel positions, locations, and times for sex. Couple's counseling may address relationship conflict.

Expert referral. Depression, anxiety, and substance use disorders are prevalent in menopausal women and contribute to sexual dysfunction. Effective therapy is available, although some pharmacologic treatments (including SSRIs) may be an additional cause of sexual dysfunction. In addition to recommending appropriate counseling and support, referring the patient to a psychopharmacologist with expertise in managing sexual adverse effects of medications may optimize care.

CASE Sexual function improves, but patient still wants to try testosterone

The patient returns for follow-up visits scheduled specifically to address her sexual concerns. Sex is more comfortable and pleasurable since initiating low-dose vaginal estrogen therapy. Having been on an SSRI since her mid-40s for mild depression, the patient switched to bupropion and notes improved libido and orgasmic response. She is exercising more regularly and working with a nutritionist to address a 15-lb weight gain after menopause. The couple saw a sex therapist and is communicating better about sex with more novelty in their repertoire.

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They are enjoying a regular date night. Although the patient's sex life has improved with these interventions, she is still very interested in trying testosterone.

Testosterone's effects on HSDD in menopausal women

After addressing the many factors that contribute to sexual disinterest, a trial of testosterone may be appropriate for a menopausal woman who continues to experience low libido with associated distress.

Testosterone levels decrease with aging in both men and women. Although testosterone levels decline by approximately 50% with bilateral oophorectomy, there is no decline in androgen levels with natural menopause.[5] Testosterone circulates tightly bound to sex hormone–binding globulin (SHBG), so free or active testosterone will be reduced by oral estrogens, which increase SHBG levels.[6] As most menopausal women will have a low testosterone level due to aging, measuring the testosterone level does not provide information about the etiology of the sexual problem.

Although some studies have identified an association between endogenous androgen levels and sexual function, the associations are modest and are of uncertain clinical significance.[7-9] Not surprisingly, other factors, such as physical and psychologic health and the quality of the relationship, often are reported as more important predictors of sexual satisfaction than androgen levels.[10]

While endogenous testosterone levels may not correlate with sexual function, clinical trials of carefully selected menopausal women with HSDD have shown that androgen treatment generally results in improved sexual function.[11] Studies demonstrate substantial improvements in sexual desire, orgasmic response, and frequency in menopausal women treated with high doses of intramuscular testosterone, which result in supraphysiologic androgen levels.[12,13] While it is interesting that women with testosterone levels in the male low range have sizeable increases in sexual desire and response, long-term use of high-dose testosterone would result in unacceptable androgenic adverse effects and risks.

FAST TRACK

It is more relevant to consider the impact on female sexual function of low doses of testosterone, which raise the reduced testosterone levels seen in older women to the higher levels seen in reproductive-aged women

Testosterone in low doses. It is more relevant to consider the impact on female sexual function of low doses of testosterone, which raise the reduced testosterone levels seen in older women to the higher levels seen in reproductive-aged women.

A series of double-blind, multicenter, randomized, placebo-controlled trials in menopausal women with HSDD examined the impact on sexual function of a transdermal testosterone patch (300 µg) that increased blood testosterone levels to the upper limit of normal for young women.[14-17] In these studies, compared with placebo, women using testosterone reported significant improvements in sexual desire, arousal, orgasmic response, frequency, and sexually related distress. Findings were consistent in surgically and naturally menopausal women, with and without the use of concurrent estrogen therapy. Improvements were clinically limited, however. On average, testosterone-treated women experienced 1 to 1.5 additional satisfying sexual events in a 4-week period compared with those treated with placebo. The percentage of women reporting a clinically meaningful benefit from treatment was significantly greater in women treated with testosterone (52%) compared with the placebo-treated women (31%).[18] An appreciable placebo response was seen, typical of most studies of therapies for sexual dysfunction.

Safety concerns

Potential risks of testosterone treatment include acne, hirsutism, irreversible deepening of the voice, and adverse changes in lipids and liver function (**TABLE 2**).[19] Adverse effects are dose dependent and are unlikely with physiologically dosed testosterone.

A 1-year study of testosterone patches in approximately 800 menopausal women with HSDD (with a subgroup of women followed for an additional year) provides the most comprehensive safety data available.[17] Unwanted hair growth occurred more often in women receiving testosterone, without significant differences in blood biochemistry,

hematologic parameters, carbohydrate metabolism, or lipids. Breast cancer was diagnosed in more women receiving testosterone than placebo. Although this finding may have been due to chance, the investigators concluded that long-term effects of testosterone treatment remain uncertain.

The FDA reviewed the data from the testosterone patch studies and determined that testosterone patches were effective for the treatment of HSDD in menopausal women, but more information was needed on long-term safety before approval could be granted. Another company then developed a testosterone gel product that produced similar blood levels as the testosterone patch. It was presumed that there would be similar efficacy; the principal goal of these studies was to examine long-term safety, particularly with respect to breast cancer and cardiovascular disease. Unexpectedly, although it raised testosterone blood levels to the upper limit of normal for young women, the testosterone gel product was no more effective than placebo.[20] The clinical trial was ended, with safety data never published.

Availability of testosterone formulations

Currently, no androgen therapies are FDA approved for the treatment of female sexual dysfunction. Although the best evidence regarding testosterone efficacy and safety involves the use of testosterone patches (300 µg), appropriately dosed for women, these patches are not currently available. FDA-approved testosterone patches are approved for the treatment of male hypogonadism, but use of these patches in women is not recommended since they would result in very high circulating testosterone levels.

Testosterone subcutaneous implants, pellets, and intramuscular injections also are not recommended for women because of the risk of excessive dosing. Small trials of menopausal women taking oral estrogen with low sexual desire found that oral formulations of testosterone improved libido in this study population.[21] The combination of esterified estrogens (0.625 mg) and methyltestosterone (1.25 mg) is available as a compounded, non-FDA approved product. Oral androgen formulations generally are not advised, due to potential adverse effects on lipids and liver function.[22]

TABLE 2 Adverse effects and risks of testosterone treatment in menopausal women

Adverse effects
• Hirsutism
• Acne
• Application site reaction (skin irritation, local hair growth)
Risks with compounded products
• Batch-to-batch variability
• Limited or no testing of product purity and quality
• Variable absorption and bioavailability
• Inadvertent supraphysiologic dosing
Risks with supraphysiologic dosing
• Virilization
• Liver dysfunction
• Lowering of HDL cholesterol
• Psychologic changes
Potential risks with long-term use
• Breast cancer
• Cardiovascular disease

Abbreviation: HDL, high-density lipoprotein.

Compounded testosterone products. Ointments and creams may be compounded by prescription (**TABLE 3**, page 32). Product purity, dose, bioavailability, and quality typically are untested, and substantial variability exists between formulations and batches.[23] Applying 1% testosterone cream or gel (0.5 g/day) topically to the thigh or lower abdomen should increase the low testosterone levels typically seen in menopausal women to the higher levels seen in younger women.[24,25] Application to the vulva or vagina is not advised, as it may cause local irritation and is unpredictably absorbed.

Adapting male testosterone products. High-quality FDA-approved testosterone gel formulations are available for male hypogonadism. However, since women have

FAST TRACK

Currently, no androgen therapies are FDA approved for the treatment of female sexual dysfunction

TABLE 3 Testosterone treatment options for menopausal women

Topical compounded testosterone
1% Testosterone compounded cream or gel
Apply 0.5 g topically to thigh or low abdomen daily
Monitor testosterone level approximately 2 weeks after receiving a new tube or jar of compounded cream or gel to confirm that the testosterone level remains within the normal range for reproductive-aged women
Dose-adjusted topical testosterone product approved for men
1% Testosterone gel (Testim)
Apply 3–4 drops topically to thigh or low abdomen daily (warm gel slightly before use)
Re-cap tube tightly after use
Reduce dose as needed to ensure 1 tube lasts for 10 days
Monitor testosterone level approximately every 3–6 months to confirm testosterone level remains within the normal range for reproductive-aged women
Testosterone formulations not recommended
Due to risk of supraphysiologic dosing
• Testosterone injections
• Testosterone implants or subcutaneous pellets
Due to adverse effects associated with oral administration
• Oral methyltestosterone

FAST TRACK

Women who elect to use transdermal testosterone therapy should be seen at 8 to 12 weeks to assess treatment response. Regular follow-up visits are required to assess response, satisfaction, and adverse effects.

approximately one-tenth the circulating testosterone levels of men, supraphysiologic dosing is a risk when these products are prescribed for women. Most testosterone products approved for men are provided in pumps or packets, and they are difficult to dose-adjust for women. Applying one-tenth the male dose of 1% testosterone gel (Testim), which comes in a resealable unit-dose tube, is an alternative to compounding. For men, the dose is 1 tube per day, so women should make 1 tube last for 10 days by using 3 to 4 drops of testosterone gel per day. Close physical contact must be avoided immediately after application, as topical hormone creams and gels are easily transferred to others. The safety and efficacy of compounded or dose-adjusted male testosterone products used in women are unknown.

Follow treated women closely. Women who elect to use transdermal testosterone therapy should be seen at 8 to 12 weeks to assess treatment response. Regular follow-up visits are required to assess response, satisfaction, and adverse effects, including acne and hirsutism. Since there may be little correlation between serum testosterone levels and the prescribed dose of a compounded testosterone product, testosterone levels should be measured regularly as a safety measure. The goal is to keep serum testosterone concentrations within the normal range for reproductive-aged women to reduce the likelihood of adverse effects. Testosterone levels should not be tested as an efficacy measure, however, as there is no testosterone level that will assure a satisfactory sex life.

CASE Conclusion

After a thorough discussion of high placebo response rates, potential adverse effects, unknown long-term risks, and off-label nature of testosterone use, the patient elects a trial of compounded 1% testosterone cream. Her clinician informs her of the limitations of compounded formulations and the need for regular

CONTINUED ON PAGE 45

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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, Inc
95 Corporate Drive
Trumbull, CT 06611

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

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Chetna Arora, MD
Dr. Arora is Minimally Invasive Gynecologic Surgery Fellow, Division of Gynecologic Specialty Surgery, Department of Obstetrics and Gynecology, Columbia University Medical Center/New York–Presbyterian Hospital, New York, New York.

Arnold P. Advincula, MD
Dr. Advincula is Levine Family Professor of Women's Health, Vice-Chair, Department of Obstetrics & Gynecology, Chief of Gynecologic Specialty Surgery, Sloane Hospital for Women; Medical Director, Mary and Michael Jaharis Simulation Center, Columbia University Medical Center/New York–Presbyterian Hospital.

Dr. Advincula reports serving as a consultant to AbbVie, Applied Medical, ConMed, CooperSurgical, Intuitive Surgical, and Titan Medical and receiving royalties from CooperSurgical. Dr. Arora reports receiving research support from Applied Medical, CooperSurgical, and Medtronic.

Which patients with uterine fibroids are good candidates for conventional laparoscopic versus robot-assisted laparoscopic myomectomy? A literature comparison of these 2 approaches plus step-by-step details on the authors' preferred surgical technique (with emphasis on advanced surgical skill and experience to ensure successful outcomes).

IN THIS ARTICLE

Uterine fibroids are the most common solid pelvic tumor in women and a leading indication for hysterectomy in the United States.[1] As a result, they represent significant morbidity for many women and are a major public health problem. By age 50, 70% of white women and 80% of black women have fibroids.[2]

Although fibroids are sometimes asymptomatic, the symptoms most commonly reported are abnormal uterine bleeding (AUB) with resultant anemia and bulk/pressure symptoms. Uterine fibroids also are associated with reproductive dysfunction, such as recurrent pregnancy loss, and even infertility.[3]

The clinical diagnosis of uterine fibroids is made based on a combination of physical examination and imaging studies, including pelvic ultrasonography, saline infusion sonography, and magnetic resonance imaging (MRI). When medical management, such as combination oral contraceptive pills, fails in patients with AUB and/or bulk predominant symptoms or patients present with compromised fertility, the only option for conservative surgical management is a myomectomy.[4]

The route of myomectomy—hysteroscopy, laparotomy, conventional laparoscopic myomectomy (LM), or robot-assisted laparoscopic myomectomy (RALM)—depends on the size, number, location, and consistency of the uterine fibroids and, to a certain extent, the indication for the myomectomy. In some cases, multiple routes must be used to achieve optimal results, and sometimes these procedures have to be staged. In this literature review and technical summary, we focus on conventional LM and RALM approaches.

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Literature review: In the right hands, LM and RALM have clear benefits

In the past, laparotomy was the surgical route of choice for fibroid removal. This surgery was associated with a long hospital stay, a high rate of blood transfusions, postoperative pain, and a lengthy recovery period. As minimally invasive surgery gained popularity, conventional LM became more commonly performed and was accepted by many as the gold standard approach for myomectomy.[5]

LM has considerable advantages over laparotomy

Compared with the traditional, more invasive route, the conventional LM approach has many benefits. These include less blood loss, decreased postoperative pain, shorter recovery time, shorter hospitalization stay, and decreased perioperative complications.[6] LM should be considered the first-line approach unless the size of an intramural myoma exceeds 10 to 12 cm or multiple myomas (consensus, approximately 4 or more) are present and necessitate several incisions according to their varying locations within the uterus.[7,8] While this is a recommendation, reports have been published on the successful laparoscopic approach to myomas larger than 20 cm, demonstrating that a skilled, experienced surgeon can perform this procedure safely.[9-11]

Many studies comparing LM with the abdominal approach showed that LM is associated with decreased blood loss, less postoperative pain, shorter hospital stay, and quicker recovery.[12-14] Unfortunately, myomectomy via conventional laparoscopy can be technically challenging, thereby limiting patient accessibility to this approach. Major challenges with conventional LM include enucleation of the fibroid along the correct plane and a multilayered hysterotomy closure.[15] The obvious concern with the latter is the potential risk for uterine rupture when improperly performed as a result of deficient suturing skills. Accordingly, several cases of uterine rupture in the second and third trimester of pregnancy after LM led to recommendations for stricter selection criteria, which excluded patients with fibroids larger than 5 cm, multiple fibroids, and deep intramural fibroids.[16]

FAST TRACK

RALM was developed as a surgical alternative, to help overcome conventional laparoscopy challenges such as suturing, and to offer minimally invasive options to a broader patient pool

The RALM approach

RALM was developed as a surgical alternative and to help overcome conventional laparoscopy challenges, such as suturing, as well as to offer minimally invasive options to a broader patient pool. In 2004, Advincula and colleagues reported the first case series of 35 women who underwent RALM.[17] Since that report was published, multiple retrospective studies have confirmed RALM's safety, feasibility, and efficacy.

How RALM stacks up against laparotomy. Compared with traditional abdominal myomectomy (AM), RALM has been associated with less blood loss, shorter hospital stay, quicker recovery time, fewer complications, and higher costs.[18] In a comparative analysis of surgical outcomes and costs of RALM versus AM, Nash and colleagues found that RALM patients required less intravenous narcotics, had shorter hospital stays, and had equivalent clinical outcomes compared with AM-treated patients.[19] In addition, the authors observed a correlation between increased specimen size and decreased operative efficiency with RALM. Retrospective cohort studies by Mansour and colleagues and Sangha and colleagues echoed similar conclusions.[20,21]

RALM versus conventional LM. The comparisons between conventional LM and RALM are not as clear-cut, and although evidence strongly suggests a role for RALM, more comparative studies are needed.

In 2013, Pundir and colleagues com-

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pleted a meta-analysis and systematic review comparing RALM with AM and LM.[22] They reviewed 10 observational studies; 7 compared RALM with AM, 4 compared RALM with LM, and 1 study compared RALM with AM and LM (this was included in both groups). In the comparison between RALM and AM, estimated blood loss, blood transfusion, and length of hospital stay were significantly lower with RALM, risk of complication was similar, and operating time and costs were significantly higher. The cost findings were not too dissimilar to conclusions drawn by Advincula and colleagues in an earlier study.[18]

Further, when Pundir and colleagues compared RALM with LM, blood transfusion risk and costs were higher with RALM, but no significant differences were noted in estimated blood loss, operating time, length of hospital stay, and complications.[22] In this analysis, RALM showed significant short-term benefits when compared with AM but no benefit when compared with LM.

Benefits after RALM over time

Long-term benefits from RALM, such as symptom recurrence rates and fertility outcomes, have been demonstrated. In 2015, Pitter and colleagues published the first paper on symptom recurrence after RALM.[23] In this retrospective survey, 426 women underwent RALM for symptom relief or infertility across 3 practice sites; 62.9% reported being symptom free after 3 years. In addition, 80% of symptom-free women who had undergone RALM to improve fertility outcomes conceived after 3 years. The mean (SD) time to pregnancy was 7.9 (9.4) months. Overall, pregnancy rates improved and symptom recurrence increased with the interval of time since surgery.[23]

In another study, Pitter and colleagues reported on pregnancy outcomes in greater detail.[24] They evaluated 872 women who underwent RALM between October 2005 and November 2010 at 3 centers. Of these women, 107 conceived, resulting in 127 pregnancies and 92 deliveries through 2011. The means (SD) for age at myomectomy, number of myomas removed, and myoma size were 34.8 (4.5) years, 3.9 (3.2), and 7.5 (3.0) cm (weight, 191.7 [144.8] g), respectively. Overall, the pregnancy outcomes in this study were comparable to those reported in the literature for conventional LM.

Cela and colleagues reported similar outcomes based on their review of 48 patients who underwent RALM between 2007 and 2011.[25] Seven women became pregnant (8 pregnancies). There were no spontaneous abortions or uterine ruptures. Following suit, Kang and colleagues reported outcomes in 100 women who underwent RALM for deep intramural fibroids (FIGO type 2 to 5).[26] The average (SD) number of fibroids was 3.8 (3.5) with a mean (SD) size of 7.5 (2.1) cm. All patients recovered without major complications, and 75% of those pursuing pregnancy conceived.

The importance of LM and RALM

After this brief review of the data on conventional LM and RALM, it is fair to conclude that both surgical options are a game changer for the minimally invasive management of uterine fibroids. Despite strong evidence that suggests laparoscopy is superior to laparotomy for myomectomy, the technical demands required for performing conventional LM may explain why it is underutilized and why the advantages of robotic surgery—with its 3-dimensional imaging and articulated instruments—make this approach an attractive alternative.

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INDICATIONS AND USAGE

Balcoltra is a progestin/estrogen combination oral contraceptive (COC) indicated for use by females of reproductive potential to prevent pregnancy.

IMPORTANT SAFETY INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke.

CONTRAINDICATIONS

Balcoltra is contraindicated in women with a high risk of arterial or venous thrombotic diseases, liver tumors (benign or malignant) or liver disease, undiagnosed abnormal uterine bleeding, during pregnancy, with breast cancer or other estrogen- or progestin-sensitive cancer (now or in the past), hypersensitivity to any of the components, or in women who are currently taking Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir (with or without dasabuvir).

WARNINGS AND PRECAUTIONS

- Discontinue Balcoltra if an arterial thrombotic event or venous thromboembolic event (VTE) occurs, and at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during prolonged immobilization. Balcoltra should not be started any earlier than 4 weeks after delivery, in women who are not breastfeeding. The use of COCs increases the risk of VTE. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions. Use COCs with caution in women with cardiovascular disease risk factors.
- If jaundice occurs, treatment should be discontinued.
- Balcoltra should not be prescribed for women with uncontrolled hypertension or hypertension with vascular disease. An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. If Balcoltra is used in women with well-controlled hypertension, monitor blood pressure and stop treatment if blood pressure rises significantly.
- Women who are prediabetic or diabetic should be monitored while using Balcoltra. Alternate contraceptive methods should be considered for women with uncontrolled dyslipidemia.
- Patients using Balcoltra who have a significant change in headaches or who develop new headaches that are recurrent, persistent, or severe should be evaluated, and Balcoltra should be discontinued if indicated.
- Irregular bleeding and spotting sometimes occurs in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles on Balcoltra, check for causes such as pregnancy or malignancy.
- This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Sensitivity to tartrazine is frequently seen in patients who have aspirin hypersensitivity.

ADVERSE REACTIONS

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg, the most common adverse reactions (incidence ≥ 2%) were headache (14%), metrorrhagia (8%), dysmenorrhea (7%), nausea (7%), abdominal pain (4%), breast pain (4%), emotional lability (3%), acne (3%), depression (2%), amenorrhea (2%), and vaginal moniliasis (2%).

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding.

Patients should be counseled that COCs do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Please see full Prescribing Information, including BOXED WARNING, for Balcoltra.

References: 1. Balcoltra [package insert]. Alpharetta, GA: Avion Pharmaceuticals LLC; 2018.

Avion PHARMACEUTICALS
1-888-612-8466
Alpharetta, GA 30005

Balcoltra™ (levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets and ferrous bisglycinate 36.5 mg tablets) for oral administration

Brief Summary of Prescribing Information

For additional information, refer to the full Prescribing Information.

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Patients should take one tablet by mouth at the same time every day in the order directed on the blister pack.

CONTRAINDICATIONS

Balcoltra is contraindicated in individuals with:

- A high risk of arterial or venous thrombotic diseases, including in women who:
  - -Smoke, if over age 35
  - -Have deep vein thrombosis or pulmonary embolism, now or in the past
  - -Have inherited or acquired hypercoagulopathies
  - -Have cerebrovascular disease
  - -Have coronary artery disease
  - -Have thrombogenic valvular or rhythm diseases of the heart
  - -Have uncontrolled hypertension
  - -Have diabetes mellitus with vascular disease
  - -Have headaches with focal neurological symptoms or have migraine headaches with aura
- Women over age 35 with any migraine headaches
- Liver tumors or liver disease
- Undiagnosed abnormal uterine bleeding
- Pregnancy
- Breast cancer or other estrogen- or progestin-sensitive cancer or history of these cancers
- Hypersensitivity of any of the components
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir

WARNINGS AND PRECAUTIONS

Thrombotic Disorders and Other Vascular Problems

Stop Balcoltra if an arterial thrombotic event or venous thromboembolic (VTE) event occurs, or if unexplained visual loss, proptosis, diplopia, papilledema or retinal vascular lesions occur. If possible, stop at least 4 weeks before through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during the following prolonged immobilization. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding.

The use of COCs increases the risk of VTE; however, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke. Use COCs with caution in women with cardiovascular disease risk factors.

Liver Disease

Do not use Balcoltra in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Balcoltra if jaundice develops. Balcoltra is contraindicated in women with benign and malignant liver tumors. Hepatic adenomas are associated with COC use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

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

High Blood Pressure

Balcoltra is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease.

If used in women with well-controlled hypertension, monitor blood pressure and stop Balcoltra if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. COCs may worsen existing gallbladder disease. A history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

Carbohydrate and Lipid Metabolic Effects

Monitor prediabetic and diabetic women taking Balcoltra, as COCs may decrease glucose tolerance. Consider an alternative contraceptive method for women with uncontrolled dyslipidemia. Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

Headache

If a woman taking Balcoltra develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Balcoltra if indicated. Consider discontinuation of Balcoltra in the case of increased frequency or severity of migraine during COC use.

Bleeding Irregularities and Amenorrhea

Evaluate irregular bleeding or amenorrhea.

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different contraceptive product.

Women who use Balcoltra may experience amenorrhea. In the clinical trial, 2.6% of the evaluable cycles were amenorrheic. Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was preexistent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

FD&C Yellow No. 5 Allergic-type Reaction

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Depression

Carefully observe women with a history of depression and discontinue Balcoltra if depression recurs to a serious degree.

Carcinoma of the Breast and Cervix

Balcoltra is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive.

Effect on Binding Globulins

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

Monitoring

A woman who is taking COCs should have her blood pressure checked periodically with her healthcare provider.

Hereditary Angioedema

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

Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Balcoltra.

ADVERSE REACTIONS

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets, a total of 1477 healthy women of child-bearing potential were enrolled and had 7870 cycles of exposure. Of these, 792 subjects had completed 6 cycles of treatment. The women ranged in age from 17 to 49 years and 87% were Caucasian.

Common Adverse Reactions (≥ 2% of women):

Headache (14%), metrorrhagia (8%), dysmenorrhea (7%), nausea (7%), abdominal pain (4%), breast pain (4%), emotional lability (3%), acne (3%), depression (2%), amenorrhea (2%), and vaginal moniliasis (2%).

At the time of the report, 133 (9%) subjects had withdrawn from the study due to adverse events. The most frequent were due to headache and metrorrhagia (1% each). Other adverse events occurring in < 1% of those who discontinued included amenorrhea, depression, emotional lability, hypertension, acne, menorrhagia, nausea, hypercholesterolemia, weight gain, dysmenorrhea, and flatulence. All other reasons for discontinuation were reported by 3 or fewer subjects. These are not all of the possible adverse reactions of Balcoltra.

DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain more information about interactions with hormonal contraceptives. Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of ethinyl estradiol (EE). The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors, such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, tipranavir/ritonavir, boceprevir, telaprevir, nevirapine and efavirenz] or increase [e.g., indinavir, atazanavir/ritonavir and etravirine]).

Combined oral contraceptives containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. Combined oral contraceptives have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs.

Do not co-administer Balcoltra with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations.

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

USE IN SPECIFIC POPULATIONS

Pregnant Women

Balcoltra is contraindicated in pregnancy because there is no reason to use combined hormonal contraceptives (CHCs) in pregnancy. Discontinue Balcoltra if pregnancy occurs. Based on epidemiologic studies and meta-analyses, there is little or no increased risk of birth defects in the children of females who inadvertently use COCs during early pregnancy.

Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to COCs before conception or during early pregnancy.

Nursing Mothers

Combined hormonal contraceptives (CHCs) and/or metabolites are present in human milk and in breast-fed infants. CHCs, including Balcoltra, can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Balcoltra and any potential adverse effects on the breast-fed child from Balcoltra or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of Balcoltra have been established in women of reproductive age. Efficacy is expected to be the same in post-pubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

Geriatric Use

Balcoltra has not been studied in postmenopausal women and is not indicated in this population.

Hepatic Impairment

The pharmacokinetics of Balcoltra has not been studied in women with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

OVERDOSAGE

There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

The FDA-approved product labeling can be found at www.balcoltra.com, or call 1-888-612-8466.

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Avion PHARMACEUTICALS

CONTINUED FROM PAGE 38

The myomectomy technique we prefer at our institution

At our medical center, we approach the majority of abdominal myomectomies via conventional LM or RALM. We carefully select candidates with the goal of ensuring a successful procedure and minimizing the risk of conversion. When selecting candidates, we consider these factors:

- size, number, location, and consistency of the fibroids
- patient's body habitus, and
- relative size of the uterus to the length of the patient's torso.

Additionally, any concerns raised during the preoperative workup regarding a suspected risk of occult leiomyosarcoma preclude a minimally invasive approach. Otherwise, deciding between conventional LM and RALM is based on surgeon preference.

Preoperative MRI guides surgical approach

An MRI scan is a critical component of the patient's preoperative evaluation. It helps to define the uterine architecture as it relates to fibroids and to rule out the presence of adenomyosis. In general, we do not offer RALM to patients who have more than 15 myomas, a single myoma that is larger than 12 to 15 cm, or when the uterus is more than 2 fingerbreadths above the umbilicus (unless the patient's torso allows for an adequate insufflated workspace). We also try to avoid preoperative treatment

Watch how it's done

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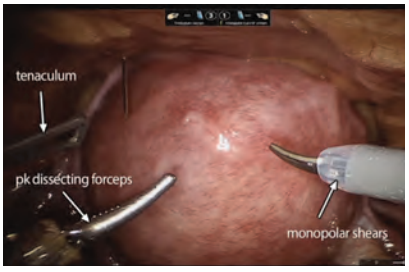
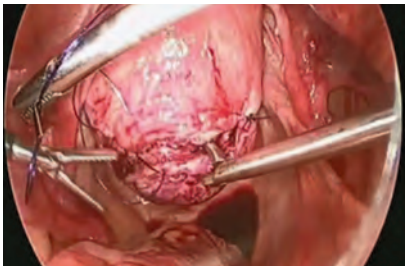
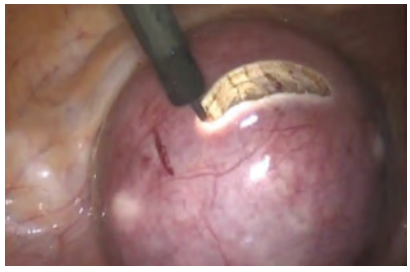


Robot-assisted laparoscopic myomectomy
Arnold P. Advincula, MD, Victoria M. Fratto, MD, and Caroline Key
A systematic approach to surgery in a 39-year-old woman with heavy menstrual bleeding who desires future fertility. Features include robot-specific techniques that facilitate fibroid enucleation and hysterotomy repair and demonstration of the ExCITE technique for tissue extraction.



Laparoscopic myomectomy technique
William H. Parker, MD
A step-by-step demonstration of the laparoscopic myomectomy technique used to resect a 7-cm posterior fibroid in a 44-year-old woman.



Laparoscopic myomectomy with enclosed transvaginal tissue extraction
Ceana Nezhat, MD, and Erica Dun, MD, MPH
A surgical case of a 41-year-old woman with radiating lower abdominal pain and menorrhagia who desired removal of symptomatic myomas. Preoperative transvaginal ultrasonography revealed a 4-cm posterior pedunculated myoma and a 5-cm fundal intramural myoma.

FIGURE 1 Surgical system

da Vinci Xi Surgical System (Intuitive Surgical, Sunnyvale, California); patient side cart.

FIGURE 2 Uterine positioning system

ALLY Uterine Positioning System (CooperSurgical, Trumbull, Connecticut) mounted to the operating room table.

with a gonadotropin–releasing hormone agonist to minimize softening of the myoma and blurring of the dissection planes.

Steps in the procedure

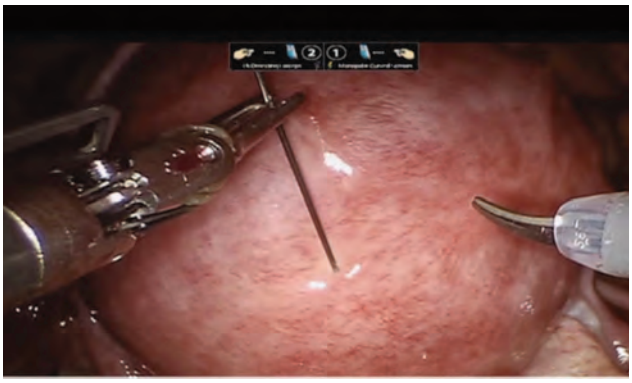
Once the patient is intubated, properly positioned, prepped, and draped, we turn our attention toward **peritoneal entry**. Factors that influence entry include the patient's surgical history, radiologic imaging, physical examination (particularly the exam under anesthesia), and surgeon preference for optimizing access. Quite often we use a left upper quadrant entry via Palmer's point, with subsequent port placement individualized to the patient's pathology and abdominal topography. Three or more incisions are required to accommodate the camera and at least 2 to 3 operative instruments. Port sizes vary from 5 to 12 mm depending on the desired equipment and surgeon preference (conventional LM versus RALM [**FIGURE 1**]).

A uterine manipulator is a crucial tool used when performing LM.[27] This instrument enables elevation of the uterus to allow for adequate visualization of the targeted myomas, traction-countertraction during enucleation, and strategic positioning during hysterotomy repair. We also use a bedside-mounted **electric uterine positioning system** that provides static orientation of the uterus by interfacing with the uterine manipulator, thereby obviating the need for a bedside assistant to provide that service (**FIGURE 2**)

To minimize blood loss during the course of the myomectomy, we inject a dilute concentration of vasopressin (20 U in 50 mL of saline) via a 7-inch, 22-gauge spinal needle into the myometrium surrounding the targeted myomas (**FIGURE 3**). Additional methods for mitigating blood loss include the use of vascular clamps, clips, or ties (both permanent and temporary) on the bilateral uterine arteries; intravaginal prostaglandins; intravenous tranexamic acid; gelatin-thrombin matrices; and cell salvage systems.[28]

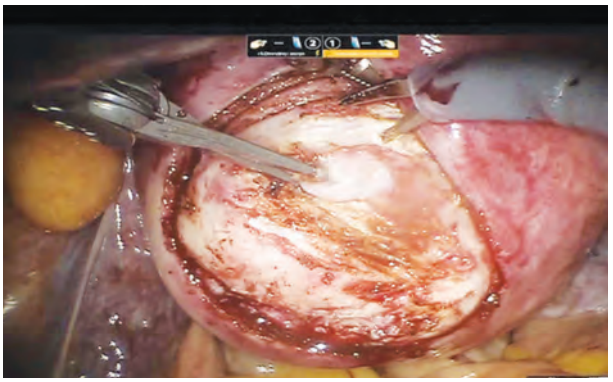
Once we observe adequate myometrial blanching from the vasopressin administration, we make a strategic **hysterotomy**

FIGURE 3 Minimize blood loss



Administration of dilute vasopressin via a 7-inch, 22-gauge spinal needle.

FIGURE 4 Enucleation



Enucleation of a myoma with a tenaculum during robot-assisted laparoscopic myomectomy.

incision (preferably transverse) to allow the surgeon to more ergonomically close the defect. We then identify the pseudocapsule so that the surgeon can circumferentially **enucleate the myoma** and dissect it from its fibrous attachments to the surrounding myometrium.

The energy devices used to perform the hysterotomy and enucleation are selected largely based on surgeon preference, but various instruments can be used to accomplish these steps, including an ultrasonically activated scalpel or such electrosurgical instruments as monopolar scissors or hooks.

A reliable tenaculum is critical to the success of any enucleation, whether the approach is conventional LM or RALM, in order to provide adequate traction on the myoma (**FIGURE 4**). We try to minimize the number of hysterotomy incisions not only to reduce further blood loss, as the majority of bleeding ensues from the surrounding myometrium, but also to minimize compromise of myometrial integrity. Additionally, we take care to avoid entry into the endometrial cavity.

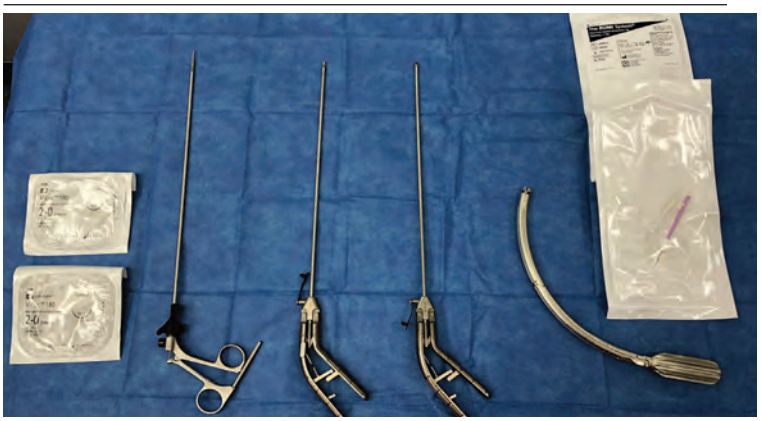
As we enucleate a myoma, we place it in either the anterior or posterior cul de sac. Most important, if we enucleate multiple myomas, we keep careful track of their number. We string the myomas together with suture until we extract them to ensure this.

While **hysterotomy closure** can be performed with either barbed or nonbarbed sutures in a single- or a multi-layered fashion, we prefer to use a barbed suture.[29,30] Just as enucleation requires appropriate instruments, suturing requires proper needle drivers (**FIGURE 5**). We advise judicious use of energy to minimize thermal effects and maintain the viability of the surrounding myometrium. Once we have sutured the myometrium closed, we place an adhesion barrier.

Although discussion of tissue extraction is beyond the scope of this Update, any surgeon embarking on either conventional LM or RALM must have a strategy for safe contained tissue extraction given the recent concerns over uncontained power morcellation.[31,32]

CONTINUED ON PAGE 44

FIGURE 5 Conventional laparoscopic myomectomy instrumentation



Left to right: Conventional laparoscopic needle drivers and tenaculum (Karl Storz, Tubingen, Germany) along with 2-0 V-Loc 180 barbed suture (Medtronic, Minneapolis, Minnesota) and Advincula Arch Uterine Manipulator with RUMI tip (CooperSurgical, Trumbull, Connecticut).

CONTINUED FROM PAGE 43

Surgical skill and careful patient selection are key to optimal outcomes

Patients seeking conservative surgical management of their uterine fibroids should be considered candidates for either a conventional LM or RALM. Both the scientific literature and technologic advances make these approaches viable options, especially when the surgeon's skill is appropriate and the patient's candidacy is adequately vetted. A well thought out surgical strategy from start to finish will ensure the chances for successful completion and optimized outcomes. ●

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testing of testosterone levels to prevent supraphysiologic dosing. At a follow-up visit 8 weeks later, she reports improved sexual desire and elects to continue treatment and monitoring. After using testosterone for 2 years, the patient is uncertain that she still is experiencing a significant benefit, stops testosterone treatment, and remains satisfied with her sex life. ●

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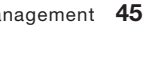

How ovarian reserve testing can (and cannot) address your patients' fertility concerns

Your patient questions her ovarian reserve. These expert answers to 6 common questions help guide your clinical approach.

Paula C. Brady, MD, and Zev Williams, MD, PhD

IN THIS ARTICLE

CASE Your patient wants ovarian reserve testing. Is her request reasonable?

A 34-year-old woman, recently married, plans to delay attempting pregnancy for a few years. She requests ovarian reserve testing to inform this timeline.

This is not an unreasonable inquiry, given her age (<35 years), after which there is natural acceleration in the rate of decline in the quality of oocytes. Regardless of the results of testing, attempting pregnancy or pursuing fertility preservation as soon as possible (particularly in patients >35 years) is associated with better outcomes.

Dr. Brady is Reproductive Endocrinologist and Assistant Professor, Columbia University Fertility Center, New York, New York.

Dr. Williams is Chief, Division of Reproductive Endocrinology and Infertility and Wendy D. Havens Associate Professor, Columbia University Fertility Center.

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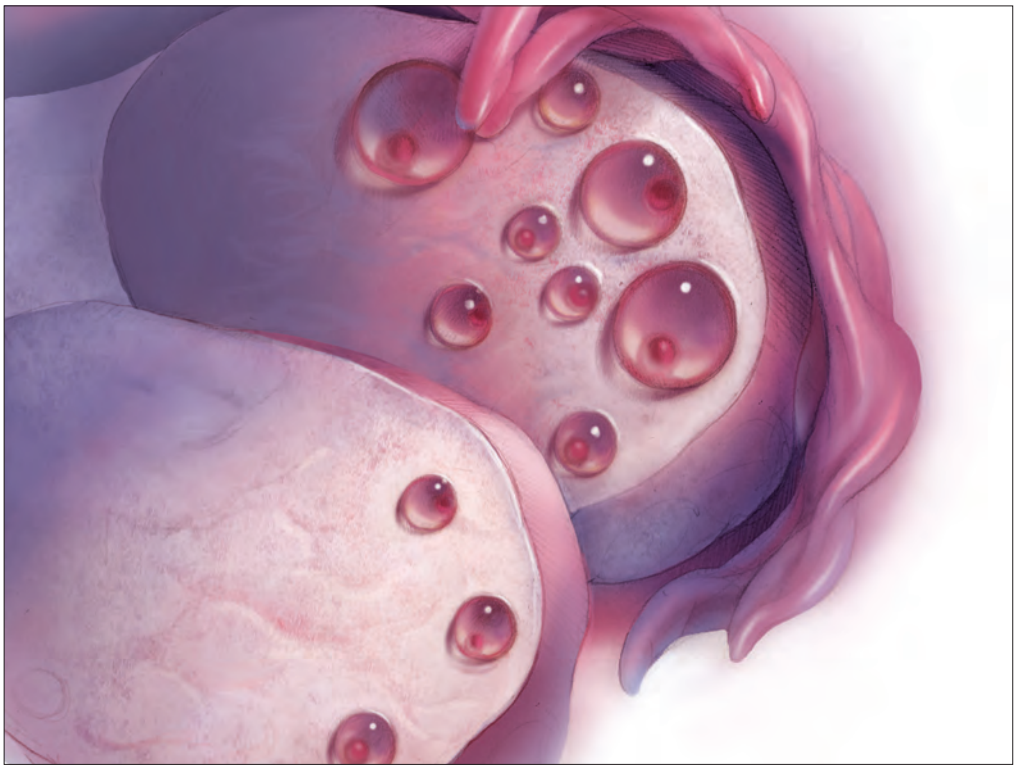
A woman is born with all the eggs she will ever have. Oocyte atresia occurs throughout a woman's lifetime, from 1,000,000 eggs at birth to only 1,000 by the time of menopause.[1] A woman's ovarian reserve reflects the number of oocytes present in the ovaries and is the result of complex interactions of age, genetics, and environmental variables.

Ovarian reserve testing, however, only has been consistently shown to predict ovarian response to stimulation with gonadotropins; these tests might reflect in vitro fertilization (IVF) birth outcomes to a lesser degree, but have not been shown to predict natural fecundability.[2,3] Essentially, ovarian reserve testing provides a partial view of reproductive potential.

Ovarian reserve testing also does not reflect an age-related decline in oocyte quality, particularly after age 35.[4,5] As such, female age is the principal driver of fertility potential, regardless of oocyte number. A woman with abnormal ovarian reserve tests may benefit from referral to a fertility specialist for counseling that integrates her results, age, and medical history, with the caveat that abnormal results do not necessarily mean she needs assisted reproductive technology (ART) to conceive.

In this article, we review 6 common questions about the ovarian reserve, providing current data to support the answers.



#1 What tests are part of an ovarian reserve assessment? What is their utility?

FSH and estradiol

Follicle-stimulating hormone (FSH) and estradiol should be checked together in the early follicular phase (days 2 to 4 of the cycle). Elevated levels of one or both hormones suggest diminished ovarian reserve; an FSH level greater than 10 mIU/mL and/or an estradiol level greater than 80 pg/mL represent abnormal results[6] (**TABLE 1**). Because FSH demonstrates significant intercycle variability, a single abnormal result should be confirmed in a subsequent cycle.[7]

Although the basal FSH level does not reflect egg quality or predict natural fecundity, an elevated FSH level predicts poor ovarian response (<3 or 4 eggs retrieved) to ovarian hyperstimulation, with good specificity.[3,6,8,9] In patients younger than age 35 years undergoing IVF, basal FSH levels do not predict live birth or pregnancy loss.[10] In older patients undergoing IVF, however, an elevated FSH level is associated with a reduced live birth rate (a 5% reduction in women <40 years to a 26% reduction in women >42 years) and a higher miscarriage rate, reflecting the positive correlation of oocyte aneuploidy and age.

FAST TRACK

An elevated FSH level predicts poor ovarian response to ovarian hyperstimulation, with good specificity

TABLE 1 Ovarian reserve tests: When to measure, what findings to look for

Test	When to measure	Abnormal value
Anti-Müllerian hormone[2,3,14,18-31]	Any time (except not while pregnant or using hormone-based medications)	< 0.8–1.1 ng/mL[a]
Antral follicle count[6,12-17]	Ideally, cycle days 2 to 4	< 6 to 10
Estradiol[7]	Cycle days 2 to 4, with test of FSH	> 80 pg/mL
FSH[6-11]	Cycle days 2 to 4, with test of estradiol	> 10 mIU/mL

[a]Age-specific lower limits may be more accurate[11]: 25 years, 3.0 ng/mL; 30 years, 2.5 ng/mL; 35 years, 2.0 ng/mL; 40 years, 1.5 ng/mL; 45 years, 0.5 ng/mL.

Abbreviation: FSH, follicle-stimulating hormone.

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ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

CONTINUED FROM PAGE 47

In addition to high intercycle variability, an FSH level is reliable only in the setting of normal hypothalamic and pituitary function.[7] Conditions such a prolactinoma (or other causes of hyperprolactinemia), other intracranial masses, prior central radiation, hormone-based medication use, and inadequate energy reserve (as the result of anorexia nervosa, resulting in hypothalamic suppression), might result in a low or inappropriately normal FSH level that does not reflect ovarian function.[11]

Antral follicle count

Antral follicle count (AFC) is defined as the total number of follicles measuring 2 to 10 mm, in both ovaries, in the early follicular phase (days 2 to 4 of the cycle). A count of fewer than 6 to 10 antral follicles in total is considered consistent with diminished ovarian reserve[6,12,13] (**TABLE 1,** page 47). Antral follicle count is not predictive of natural fecundity but, rather, projects ovarian response during IVF. Antral follicle count has been shown to decrease by 5% a year with increasing age among women with or without infertility.[14]

Studies have highlighted concerns regarding interobserver and intraobserver variability in determining the AFC but, in experienced hands, the AFC is a reliable test of ovarian reserve.[15,16] Visualization of antral follicles can be compromised in obese patients.[11] Conversely, AFC sometimes also overestimates ovarian reserve, because atretic follicles might be included in the count.[11,15] Last, AFC is reduced in patients who take a hormone-based medication but recovers with cessation of the medication.[17] Ideally, a woman should stop all hormone-based medications for 2 or 3 months (≥2 or 3 spontaneous cycles) before AFC is measured.

Anti-Müllerian hormone

A transforming growth factor β superfamily peptide produced by preantral and early antral follicles of the ovary, anti-Müllerian hormone (AMH) is a direct and quantitative marker of ovarian reserve.[18] AMH is detectable at birth; the level rises slowly until puberty, reaching a peak at approximately 16 years of age,[19] then remains relatively stable until 25 years, after which AMH and age are inversely correlated, reflecting ongoing oocyte atresia. AMH declines roughly 5% a year with increasing age.[14]

A low level of AMH (<1 ng/mL) suggests diminished ovarian reserve[20,21] (**TABLE 1**). AMH has been consistently validated only for predicting ovarian response during IVF.[2,20] To a lesser extent, AMH might reflect the likelihood of pregnancy following ART, although studies are inconsistent on this point.[22] AMH is not predictive of natural fecundity or time to spontaneous conception.[3,23] Among 700 women younger than age 40, AMH levels were not significantly different among those with or without infertility, and a similar percentage of women in both groups had what was characterized as a "very low" AMH level (<0.7 ng/mL).[14]

At the other extreme, a high AMH value (>3.5 ng/mL) predicts a hyper-response to ovarian stimulation with gonadotropins and elevated risk of ovarian hyperstimulation syndrome. In conjunction with clinical and other laboratory findings, an elevated level of AMH also can suggest polycystic ovary syndrome. No AMH cutoff for a diagnosis of polycystic ovary syndrome exists, although a level of greater than 5 to 7.8 ng/mL has been proposed as a point of delineation.[24,25]

Unlike FSH and AFC, AMH is generally considered to be a valid marker of ovarian reserve throughout the menstrual cycle. AMH levels are higher in the follicular phase of the cycle and lower in the midluteal phase, but the differences are minor and seldom alter the patient's overall prognosis.[26-29] As with FSH and AFC, levels of AMH are significantly lower in patients who are pregnant or taking hormone-based medications: Hormonal contraception lowers AMH level by 30% to 50%.[17,30,31] Ideally, patients should stop all hormone-based medications for 2 or 3 months (≥2 or 3 spontaneous cycles) before testing ovarian reserve.

FAST TRACK

Anti-Müllerian hormone has been validated consistently only for predicting ovarian response during IVF

#2 Who should have ovarian reserve testing?

The clinical criteria and specific indications for proceeding with ovarian reserve testing are summarized in **TABLE 2.**[13,32-34] Such testing is

TABLE 2 **Who is a candidate for ovarian reserve testing?**[13,32-34]

Clinical criterion	Details
Family history of early menopause (<40 to 45 years)	
High risk of iatrogenic diminished ovarian reserve	Prior chemotherapy or pelvic radiation Prior oophorectomy, ovarian cystectomy, or extensive pelvic surgery Smoker
In preparation for treatment with assisted reproductive technology	Guides protocol selection and medication dosing
Infertility	Women <35 years: >12 months without a successful pregnancy Women ≥35 years: >6 months without a successful pregnancy Women ≥40 years: Immediately
Medical conditions associated with diminished ovarian reserve	Autoimmune disease (Addison disease, Hashimoto thyroiditis, lymphocytic oophoritis, polyglandular syndrome) *BRCA1* or *BRCA2* mutation Fanconi anemia Fragile X premutation[a] Galactosemia Severe endometriosis Turner syndrome
Oligo-ovulation and anovulation	Irregular menses might suggest: • PCOS (reflected in an elevated AMH level) • Premature ovarian insufficiency (reflected in low or undetectable AMH level and elevated FSH level)
Patients interested in preserving fertility	In preparation for chemotherapy or radiation In preparation for ovarian surgery or other potentially destructive pelvic surgery Planning to delay childbearing (social)
In preparation for treatment with ART	Guides protocol selection and medication dosing

[a]55 to 200 trinucleotide repeats of the *FMR1* gene on the X chromosome.

Abbreviations: AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; *FMR1*, fragile X mental retardation 1; PCOS, polycystic ovary syndrome.

not indicated in women who are planning to attempt pregnancy but who do not have risk factors for diminished ovarian reserve. These tests cannot predict their success at becoming pregnant; age is a far more appropriate predictor of pregnancy and risk of miscarriage.[3] At most, an abnormal result in a patient who meets one of the clinical criteria for testing could prompt earlier referral to a reproductive specialist for consultation—after it is explained to her that abnormal ovarian reserve tests do not, alone, mean that ART is required.

#3 Can I reassure my patient about her reproductive potential using these tests?

Normal findings on ovarian reserve testing suggests that a woman might have a normal (that is, commensurate with age-matched peers) number of eggs in her ovaries. But normal test results do not mean she will have an easy time conceiving. Similarly, abnormal results do not mean that she will have difficulty conceiving.

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Ovarian reserve testing reflects only the number of oocytes, not their quality, which is primarily determined by maternal age.[35] Genetic testing of embryos during IVF shows that the percentage of embryos that are aneuploid (usually resulting from abnormal eggs) rises with advancing maternal age, beginning at 35 years.[5] The increasing rate of oocyte aneuploidy is also reflected in the rising rate of loss of clinically recognized pregnancies with advancing maternal age: from 11% in women younger than age 34 to greater than 36% in women older than age 42.[4]

Furthermore, ovarian reserve testing does not reflect other potential genetic barriers to reproduction, such as a chromosomal translocation that can result in recurrent pregnancy loss. Fallopian tube obstruction and uterine issues, such as fibroids or septa, and male factors are also not reflected in ovarian reserve testing.

FAST TRACK

Abnormal results on a currently available ovarian reserve test should not be the sole reason for the use of ART

#4 My patient is trying to get pregnant and has abnormal ovarian reserve testing results. Will she need IVF?

Not necessarily. Consultation with a fertility specialist to discuss the nuances of abnormal test results and management options is ideal but, essentially, as the American Society for Reproductive Medicine states, "evidence of [diminished ovarian reserve] does not necessarily equate with inability to conceive." Furthermore, the Society states, "there is insufficient evidence to recommend that any ovarian reserve test now available should be used as a sole criterion for the use of ART."

Once counseled, patients might elect to pursue more aggressive treatment, but they might not necessarily need it. Age must figure significantly into treatment decisions, because oocyte quality—regardless of number—begins to decline at 35 years of age, with an associated increasing risk of infertility and miscarriage.

In a recently published study of 750 women attempting pregnancy, women with a low AMH level (<0.7 ng/mL) or high FSH level (>10 mIU/mL), or both, did not have a significantly lower likelihood of achieving spontaneous pregnancy within 1 year, compared with women with normal results of ovarian reserve testing.[3]

#5 My patient is not ready to be pregnant. If her results are abnormal, should she freeze eggs?

For patients who might be interested in seeking fertility preservation and ART, earlier referral to a reproductive specialist to discuss risks and benefits of oocyte or embryo cryopreservation is always preferable. The younger a woman is when she undergoes fertility preservation, the better. Among patients planning to delay conception, each one's decision is driven by her personal calculations of the cost, risk, and benefit of egg or embryo freezing—a picture of which ovarian reserve testing is only one piece.

#6 Can these tests predict menopause?

Menopause is a clinical diagnosis, defined as 12 months without menses (without hormone use or other causes of amenorrhea). In such women, FSH levels are elevated, but biochemical tests are not part of the menopause diagnosis.[36] In the years leading to menopause, FSH levels are highly variable and unreliable in predicting time to menopause.

AMH has been shown to correlate with time to menopause. (Once the AMH level becomes undetectable, menopause occurs in a mean of 6 years.[37,38]) Patients do not typically have serial AMH measurements, however, so it is not usually known when the hormone became undetectable. Therefore, AMH is not a useful test for predicting time to menopause.

Premature ovarian insufficiency (loss of ovarian function in women younger than age 40), should be considered in women with secondary amenorrhea of 4 months or longer. The diagnosis requires confirmatory laboratory assessment,[36] and findings include an FSH level greater than 25 mIU/mL on 2 tests performed at least 1 month apart.[39,40]

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2018

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COURSE CHAIRS

Tommaso Falcone, MD
Cleveland Clinic London

Mickey M. Karram, MD
The Christ Hospital

SPECIAL KEYNOTE SPEAKER

Sawsan As-Sanie, MD, MPH
University of Michigan

Faculty

Michael S. Baggish, MD
St. Helena Hospital

Linda D. Bradley, MD
Cleveland Clinic

Andrew I. Brill, MD
California Pacific Medical Center

Amanda Nickles Fader, MD
Johns Hopkins Hospital

John B. Gebhart, MD, MS
Mayo Clinic

Rosanne M. Kho, MD
Cleveland Clinic

Javier F. Magrina, MD
Mayo Clinic Phoenix

Beri M. Ridgeway, MD
Cleveland Clinic

ENCORE AT WYNN Las Vegas

OPTIONAL OPIOID REMS COURSE
December 4, 2018 *Free to PAGS Attendees*

OPTIONAL HANDS-ON WORKSHOPS
LIMITED SPACE AVAILABLE. FIRST COME. FIRST SERVED!
December 5, 2018

SCIENTIFIC GENERAL SESSIONS
December 6-8, 2018

OPTIONAL HANDS-ON WORKSHOPS
- Tissue Extraction Techniques
- Laparoscopic Suturing
- Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
- Office-Based Gynecologic Procedures

SPECIAL KEYNOTES
- Management of Chronic Pelvic Pain
- Non-Opioid Pain Management after Minimally Invasive Hysterectomy

PLUS
- Hysterectomy Techniques
  Vaginal • Single Port • Robotic • Total Laparoscopic • Morcellation • Preserving Level 1 Support • When is it Appropriate to Remove the Ovaries?
- Incontinence and Prolapse Surgery
- Avoiding and Managing Complications
- Gynecologic Oncology for the Generalist
- Medical Legal Cases
- Fibroid Management
- Surgical Tips for Successful Pelvic Surgery Video Session
- Non-Surgical Management of Incontinence and Pelvic Floor Disorders

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

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

PAGS AGENDA

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

TUESDAY, DECEMBER 4, 2018

Optional Opioid REMS Course NEW!
Optional, free course. Pre-registration required
Pain Management and Opioids: Balancing Risks and Benefits
3:00 PM - 6:15 PM

WEDNESDAY, DECEMBER 5, 2018

Optional Hands-On Workshops

Tissue Extraction Techniques
8:30 AM–12:30 PM

Laparoscopic Suturing - The "Vertical Zone"
8:30 AM–12:30 PM

Office-Based Gynecologic Procedures
8:30 AM–5:30 PM

Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
1:30 PM–5:30 PM

THURSDAY, DECEMBER 6, 2018

6:30 AM **Registration/Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

7:55 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**

11:10 AM **Surgery for Stress Incontinence and the Future of Synthetic Slings**
Beri M. Ridgeway, MD

11:40 AM **Surgery for Pelvic Organ Prolapse: Do We Need to Perform and Teach More Transvaginal Native Tissue Suture Repairs?**
John B. Gebhart, MD, MS

12:10 PM **Mesh-Augmented Prolapse Repair: Is There Any Role for Vaginal Mesh: Indication and Technique of Sacral Colpopexy**
Beri M. Ridgeway, MD

12:40 PM **Question and Answer Session**

1:10 PM **Luncheon Symposium**

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

THURSDAY'S KEYNOTE LECTURE

2:40 PM **Management of Chronic Pelvic Pain in Women**
Sawsan As-Sanie, MD, MPH

FIBROID MANAGEMENT & PRINCIPLES OF ELECTROSURGERY

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

3:55PM **Myomectomy: Open to Robotic Approaches**
Tommaso Falcone, MD

4:25 PM **Break/Exhibits**

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

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

FRIDAY, DECEMBER 7, 2018

7:00 AM **Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

HYSTERECTOMY - TECHNIQUE

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

8:50 AM **When is it Appropriate to Remove Ovaries at Hysterectomy?**
Amanda Nickles Fader, MD

9:25 AM **Total Laparoscopic Hysterectomy**
Andrew I. Brill, MD

10:00 AM **Break /Exhibits**

10:45 AM **Robotic Hysterectomy**
Javier F. Magrina, MD

11:15 AM **Tissue Extraction Techniques (Morcellation)**
Tommaso Falcone, MD

11:45 AM **Techniques to Preserve Level 1 Support at the Time of Vaginal Laparoscopic and Robotic Hysterectomy**
Beri M. Ridgeway, MD

12:15 PM **Which Hysterectomy Approach is Best?**
Case Presentation and
Audience Participation – all speakers

12:45 PM **Question and Answer Session**

1:00 PM **Luncheon Symposium**

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

FRIDAY'S KEYNOTE LECTURE

2:30 PM **Non-Opioid Pain Management after Minimally Invasive Hysterectomy**
Sawsan As-Sanie, MD, MPH

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 8, 2018

6:30 AM **Breakfast**

7:30 AM **Management of Endometriosis**
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 **Medical Legal Cases**
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 **PAGS Scientific Program Adjournment**

Open to Non-Attendees So bring your staff!

3.25 CME Credits Available

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

Make Your Practice More Profitable, Efficient, and Productive!

Director
Neil H. Baum, MD
Former Associate Clinical Professor of Urology
Tulane Medical School
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 8, 2018

2:00 PM **Course Overview**

2:10 PM **Looking at the 4 Pillars of a Successful Practice in the Current Healthcare Environment**
- 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

Tommaso Falcone, MD
Chief of Staff
Chief Academic Officer
Cleveland Clinic London
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
Cleveland, Ohio

Mickey M. Karram, MD
Director of Urogynecology
The Christ Hospital
Volunteer Professor of OB/GYN
University of Cincinnati
Cincinnati, Ohio

Special Keynote Speaker

Sawsan As-Sanie, MD, MPH
Director
Minimally Invasive Gyn Surgery and Chronic Pelvic Pain
University of Michigan
Ann Arbor, Michigan

Faculty

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

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

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

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

John B. Gebhart, MD, MS
Professor, Obstetrics and Gynecology
Mayo Clinic
Rochester, Minnesota

Rosanne M. Kho, MD
Head, Section Benign Gynecology
Director
Benign Gyn Surgery
Women's Health Institute
Cleveland Clinic
Cleveland, Ohio

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

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

Optional Workshops

For complete information please see PAGS-CME.org.

Tuesday, December 4, 2018, Encore at Wynn Las Vegas

Optional Opioid REMS Course *Free to PAGS attendees*

OPIOID RISK EVALUATION AND MITIGATION STRATEGIES (REMS) COURSE "PAIN MANAGEMENT AND OPIOIDS: BALANCING RISKS AND BENEFITS"
3.0 CME/CNE Credits Available
3:00 PM - 6:15 PM Pre-registration required. See PAGS website for complete details.

Wednesday, December 5, 2018, 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 details.)**

WORKSHOP A
TISSUE EXTRACTION TECHNIQUES
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 NEW!
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; 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 *SOLD OUT!*
4 CME Credits Available
1:30 PM - 5:30 PM
Led by: Mickey 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.

2018

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Optional **OPIOID REMS COURSE 3 CME Credits Available**
December 4, 2018

Optional **HANDS-ON WORKSHOPS 8 CME Credits Available**
December 5, 2018

SCIENTIFIC SESSIONS 20 CME Credits Available
December 6-8, 2018

Optional **"P.E.P." PRACTICE MANAGEMENT PROGRAM**
3.25 CME Credits Available
December 8, 2018

About Our Venue Encore at Wynn Las Vegas

The 2018 Pelvic Anatomy and Gynecologic Surgery Symposium (PAGS) will take place at the Encore Wynn Las Vegas where we have arranged for a discount room rate of **just $189* a night for PAGS participants** (subject to availibility). To make your reservation, please call (866) 770-7555. You must identify yourself as a Pelvic Anatomy and Gynecologic Surgery Symposium 2018 attendee or reference the block code: 6PAG1218 to receive the discounted rate.

*Plus $25 amenity fee

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

Highlights Include

- *Optional* **Opioid REMS Course** *Free to PAGS Attendees*
  Pain Management and Opioids: Balancing Risks and Benefits
  3 CME Credits Available
- *Optional* **Hands-on Workshops**
  Limited space available. First come. First served!
  - Tissue Extraction Techniques Workshop
  - Laparoscopic Suturing
  - Office-Based Gynecologic Procedures
  - Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist *Sold Out!*
- **Incontinence and Prolapse Surgery**
- **Gynecologic Oncology for the Generalist**
- **Hysterectomy Techniques**
- **Avoiding and Managing Complications**
- **Fibroid Management & Principles of Electrosurgery**
- **Surgical Tips for Successful Pelvic Surgery**

SPECIAL KEYNOTES:

- **Management of Chronic Pelvic Pain**
- **Non-Opioid Pain Management after Minimally Invasive Hysterectomy**

- *Optional* **P.E.P. Practice Management Program**
  Make your practice more Profitable, Efficient, and Productive
  3.25 CME Credits Available

How to Register for PAGS

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

Cancellation Policy: Full refund less a $50 administrative fee as follows: Cancellations can be made using our online registration system until November 6, 2018. After November 6, 2018 no refunds will be granted. After the refund date, you have two options: you can send someone in your place, or we can mark a credit in the amount you paid minus $50 administration fee (plus additional $35 administration fee per workshop) to be applied to your registration for next year's conference. Refunds will not be issued to no-shows.

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Ovarian reserve tests: A partial view of reproductive potential

The answers we have provided highlight several key concepts and conclusions that should guide clinical practice and decisions made by patients:

1. Ovarian reserve tests best serve to predict ovarian response during IVF; to a far lesser extent, they might predict birth outcomes from IVF. These tests have not, however, been shown to predict spontaneous pregnancy.
2. Ovarian reserve tests should be administered purposefully, with counseling beforehand regarding their limitations.
3. Abnormal ovarian reserve test results do not necessitate ART; however, they may prompt a patient to accelerate her reproductive timeline and consult with a reproductive endocrinologist to consider her age and health-related risks of infertility or pregnancy loss.
4. Patients should be counseled that, regardless of the results of ovarian reserve testing, attempting conception or pursuing fertility preservation at a younger age (in particular, at <35 years of age) is associated with better outcomes. ●

FAST TRACK

Ovarian reserve tests should be administered purposefully, with counseling beforehand about their limitations

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Calculate your patient's appropriate drug dosage on the spot

Katherine T. Chen, MD, MPH

The most useful applications (apps) for health care professionals and students? Medical calculator apps (along with drug reference and disease diagnosis apps), according to surveys of clinicians and students.[1,2] The utility of calculator apps to these groups is not surprising; calculator apps fall in the category of clinical decision-making apps, which also includes decision support systems, clinical treatment guidelines, disease diagnosis aids, differential diagnosis aids, laboratory test ordering, laboratory test interpretation, and medical exams.[3] Calculator apps obviously save time as most health care providers have not memorized the many medical formulas and do not have computational speed. I have previously discussed other, more ObGyn-specific calculators, such as due date calculators.[4,5] In this App Review column, however, I would like to highlight 3 general calculator apps: Calculate by QxMD, CliniCalc Medical Calculator, and Medscape. Researchers found all 3 apps 100% accurate and contained the most functions desired by internists.[6] The apps are available at no cost and include many unique calculators. My colleagues and I actually used Calculate by QxMD to verify calculations in a previous study.[7]

Dr. Chen is Professor of Obstetrics, Gynecology, and Reproductive Science and Medical Education, Vice-Chair of Ob-Gyn Education for the Mount Sinai Health System, Icahn School of Medicine, Mount Sinai, New York, New York. She is an OBG MANAGEMENT Contributing Editor.

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A clinical example for how to apply calculators in practice is as follows: A multiparous patient at term has undergone an unscheduled cesarean delivery for arrest of dilation and intra-amniotic infection. You need to decide if the patient requires anticoagulants for deep venous thrombosis (DVT) prophylaxis and her necessary daily dose for gentamicin for postpartum infection prophylaxis. You can use Medscape's body mass index (BMI) calculator to find out that this patient's BMI is 45 kg/m^2 and that DVT prophylaxis is in fact indicated. You also can use QxMD's ideal body weight calculator to get the patient's weight and determine the appropriate daily dose for gentamicin.

The **TABLE** (page 58) provides more information on the apps, with its inclusions based on a shortened version of the APPLICATIONS scoring system, APPLI (app comprehensiveness, price, platform, literature used, and important special features).[7]

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Details on recommended apps

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TABLE Recommended general medical calculator apps

App	App comprehensiveness	Price	Platform	Literature used	Important special features
Calculate by QxMD iTunes: https://itunes.apple.com/us/app/calculate-by-qxmd/id361811483?mt=8 Google Play: https://play.google.com/store/apps/details?id=com.qxmd.calculate&hl=en_US	Multiple disciplines	Free	iTunes and Google Play store	Yes	• Accurate • Easy to navigate
CliniCalc Medical Calculator iTunes: https://itunes.apple.com/us/app/clinicalc-medical-calculator/id353404314?mt=8	Multiple disciplines	Free	iTunes only	No	• Accurate • Easy to navigate
Medscape iTunes Preview: https://itunes.apple.com/us/app/medscape/id321367289?mt=8 Google Play: https://play.google.com/store/apps/details?id=com.medscape.android&hl=en	Multiple disciplines	Free	iTunes and Google Play stores	References provided in diseases, conditions, medical procedures, and medical news sections	• Accurate • Info on diseases, conditions, and medical procedures, with tables, images, and videos covering pathophysiology, epidemiology, differential diagnosis, and treatment options • Drug interaction checker • Pill identifier • Medical news

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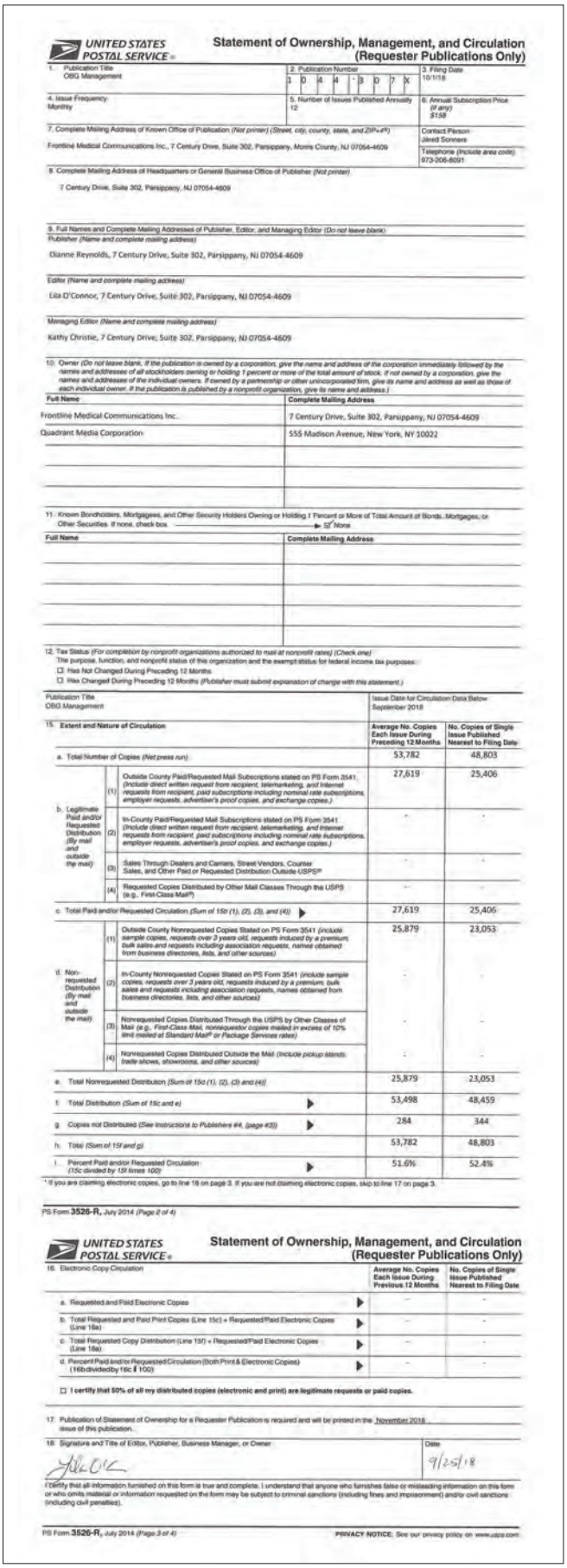

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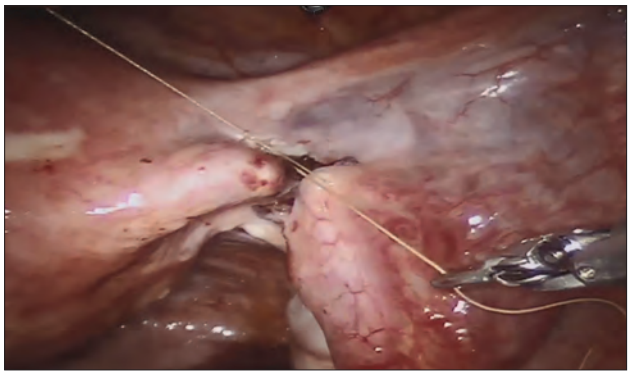
Robot-assisted laparoscopic tubal anastomosis following sterilization

Streamlined robotic interpretation of a 2-stitch anastomosis technique in a 26-year-old woman

Patricia J. Mattingly, MD; Arielle R. Gumer, MD; and Arnold P. Advincula, MD

Female sterilization is the most common method of contraception worldwide, and the second most common contraceptive method used in the United States. Approximately 643,000 sterilization procedures are performed annually.[1] Approximately 1% to 3% of women who undergo sterilization will subsequently undergo a sterilization reversal.[2] Although multiple variables have been identified, change in marital status is the most commonly cited reason for desiring a tubal reversal.[3,4] Tubal anastomosis can be a technically challenging surgical procedure when done by laparoscopy, especially given the microsurgical elements that are required. Several modifications, including limiting the number of sutures, have evolved as a result of its tedious nature.[5] By leveraging 3D magnification, articulating instruments, and tremor filtration, it is only natural that robotic surgery has been applied to tubal anastomosis.

In this video, we review some background information surrounding a tubal reversal, followed by demonstration of a robotic interpretation of a 2-stitch anastomosis technique in a patient who successfully conceived and delivered.[6] Overall robot-assisted laparoscopic tubal anastomosis is a feasible and safe option for women who desire reversal of surgical sterilization, with pregnancy and live-birth rates comparable to those observed when an open technique is utilized.[7] I hope that you will find this video beneficial to your clinical practice.



To view the video

Visit Arnold Advincula's Surgical Techniques Video Channel in the Multimedia Library at **mdedge.com/obgyn** or use the QR code

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Dr. Mattingly is Program Director, Minimally Invasive Gynecologic Surgery, Novant Health Pelvic Health & Surgery, Charlotte, North Carolina.

Dr. Gumer is from Columbia University Medical Center, New York-Presbyterian Hospital.

Dr. Advincula is Levine Family Professor of Women's Health; Vice-Chair, Department of Obstetrics & Gynecology; Chief of Gynecology, Sloane Hospital for Women; and Medical Director, Mary & Michael Jaharis Simulation Center, Columbia University Medical Center, New York-Presbyterian Hospital. He serves on the OBG MANAGEMENT Board of Editors.

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