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OBG MANAGEMENT

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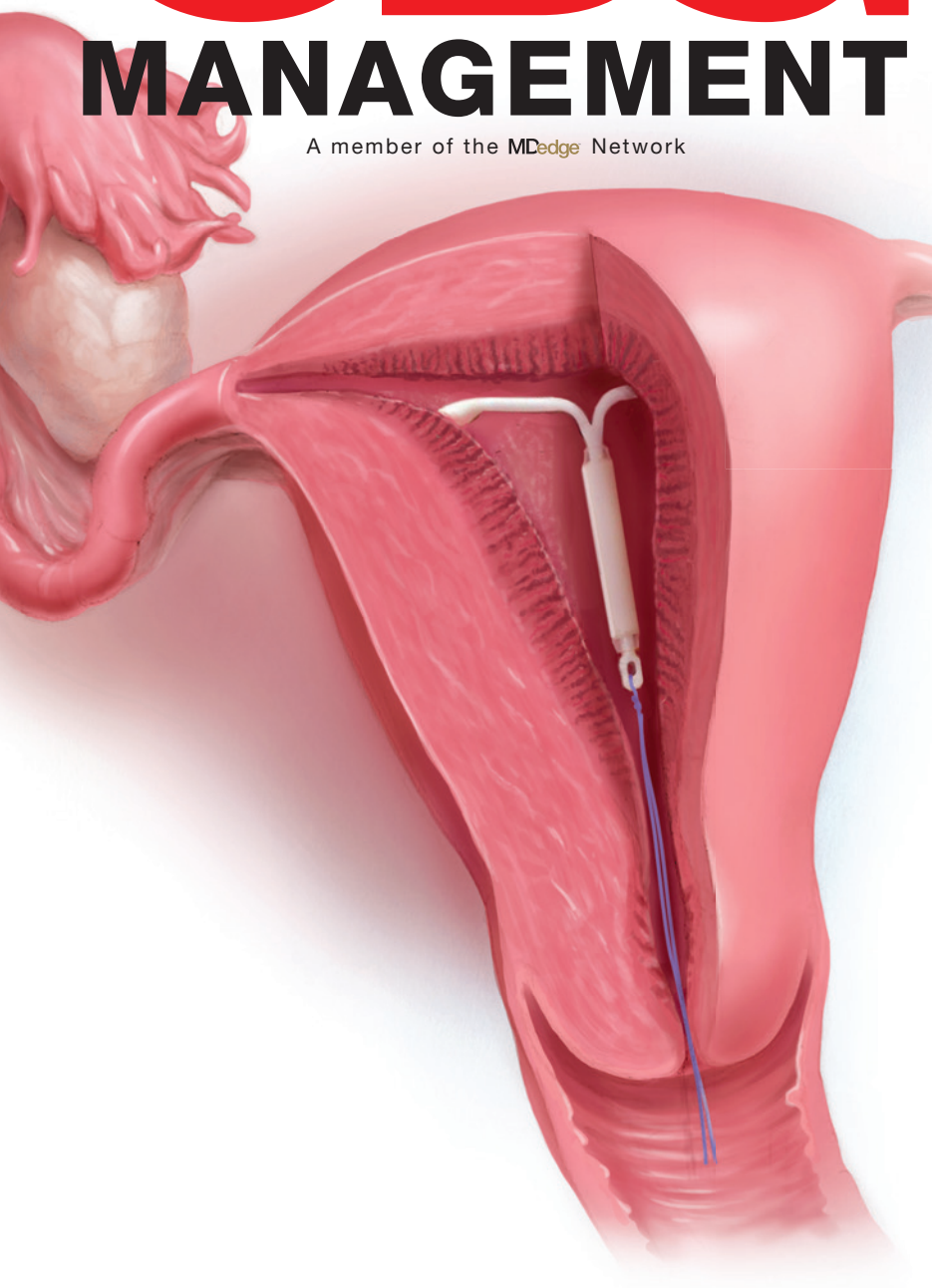


The IUD string check

Benefit, or a burden for patients?

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

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

OVER 10,000 HCPs HAVE ALREADY PRESCRIBED ORILISSA FOR MORE THAN 30,000 patients[2,3†]

ORILISSA may be appropriate for patients with unresolved endometriosis pain who have failed first-line medical management options such as one course of birth control or NSAIDs[4-6]

> "On ORILISSA, I have less pain. I hope my experience empowers other women and gives them hope that there are other options out there."
>
> — Darby, a real patient taking ORILISSA

Consider ORILISSA for your patients like Darby with unresolved endometriosis pain[4,6]

†These data reflect the number of HCPs who have prescribed and the number of women prescribed since ORILISSA was FDA-approved. Data were sourced as of September and October 2019, respectively.

Hepatic Transaminase Elevations

- In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range occurred with 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.

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

References: 1. AbbVie receives U.S. FDA approval of Orilissa™ (elagolix) for the management of moderate to severe pain associated with endometriosis [press release]. North Chicago, IL: AbbVie Inc; July 24, 2018. https://news.abbvie.com/news/abbvie-receives-us-fda-approval-orilissa-elagolix-for-management-moderate-to-severe-pain-associated-with-endometriosis.htm. Accessed August 28, 2019. **2.** Data on file. AbbVie Inc. ORILISSA cumulative writers. IQVIA data from DSL; August 2018 - September 2019.**3.** Data on file. AbbVie Inc. ORILISSA NBRx. IQVIA and UBC/Medvantx; August 2018 - October 2019. **4.** Orilissa [package insert]. North Chicago, IL: AbbVie Inc. **5.** Data on file. ABVRRTI65829. **6.** Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377(1):28-40.

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 *[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

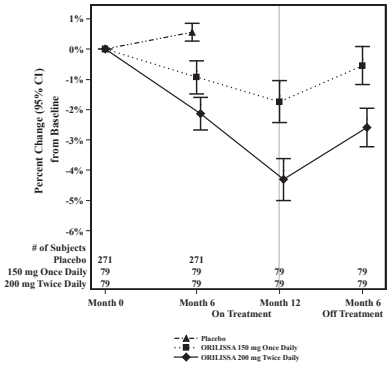
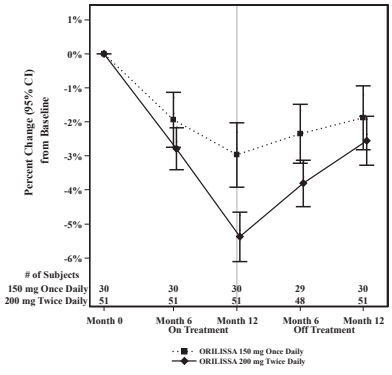


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



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

	ORILISSA		
Adverse Reactions	**150 mg Once Daily (N=475) n (%)**	**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**	
	Base-line	**Month 3**	**Base-line**	**Month 3**	**Base-line**	**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 a weak inhibitor of CYP 2C19. Co-administration with ORILISSA may increase plasma concentrations of drugs that are substrates of CYP2C19 (e.g., omeprazole).

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.
Antimycobacterial 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.
Proton pump inhibitors omeprazole	↑ omeprazole	No dose adjustments are needed for omeprazole at doses of 40 mg once daily or lower. When ORILISSA is used concomitantly with higher doses of omeprazole, e.g. in patients with Zollinger-Ellison syndrome, consider dosage reduction of omeprazole.

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors outcomes in women who become pregnant while treated with ORILISSA. Patients should be encouraged to enroll by calling 1-833-782-7241.

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]*.
  - There is a pregnancy registry that monitors outcomes in women who become pregnant while treated with ORILISSA. Inform patients they can enroll by calling 1-833-782-7241 *[see Use in Specific Populations]*.
- Inform patients that estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA.
- Inform patients about the risk of bone loss. Advise adequate intake of calcium and vitamin D *[see Warnings and Precautions]*.
- Advise patients to seek immediate medical attention for suicidal ideation and behavior. Instruct patients with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention *[see Warnings and Precautions]*.
- Counsel patients on signs and symptoms of liver injury *[see Warnings and Precautions]*.
- Instruct patients who miss a dose of ORILISSA to take the missed dose on the same day as soon as she remembers and then resume the regular dosing schedule:
  - 150 mg once daily: no more than 1 tablet each day should be taken.
  - 200 mg twice daily: no more than 2 tablets each day should be taken.
- Instruct patients to dispose of unused medication via a take-back option if available or to otherwise follow FDA instructions for disposing of medication in the household trash, www.fda.gov/drugdisposal, and not to flush down the toilet.

Manufactured by AbbVie Inc.
North Chicago, IL 60064

Ref: 03-C007 Revised: August, 2019

LAB-2821 **MASTER**

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Enhancing the quality of women's health care and the professional development of ObGyns and all women's health care clinicians†

*Source: Kantar Media, Medical Surgical Study December 2019, Obstetrics/Gynecology Combined Office & Hospital Readers.
†OBG MANAGEMENT recognizes the importance of addressing the reproductive health of gender-diverse individuals.

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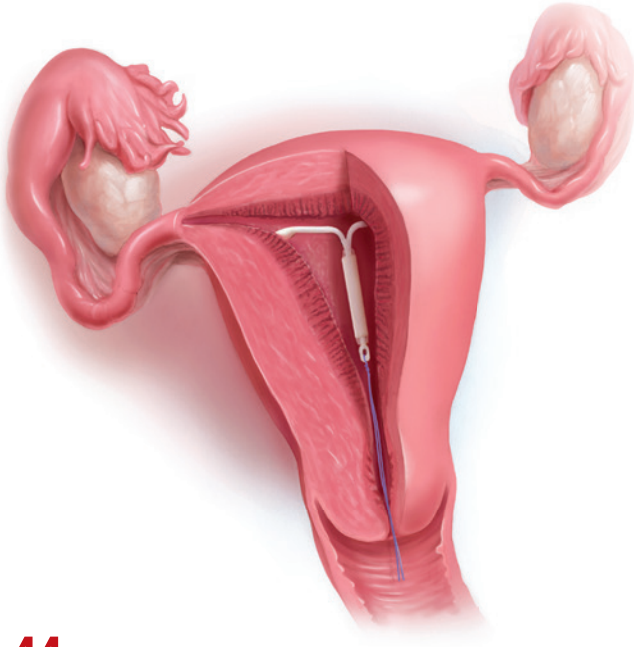

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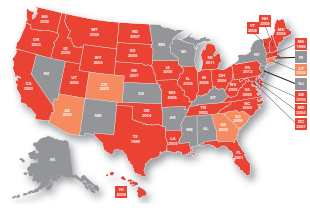

US apology laws

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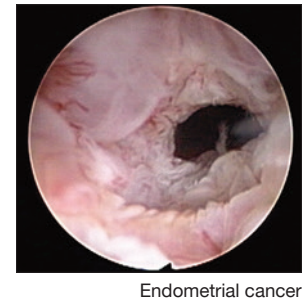

Endometrial cancer

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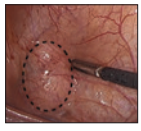

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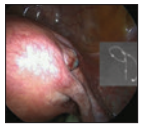

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Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

BE HER TRUSTED SOURCE FOR BIRTH CONTROL INFORMATION, SO SHE DOESN'T HAVE TO SEARCH

NEXPLANON is indicated for use by women to prevent pregnancy.

A woman searching for birth control online

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

Complications of insertion and removal

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

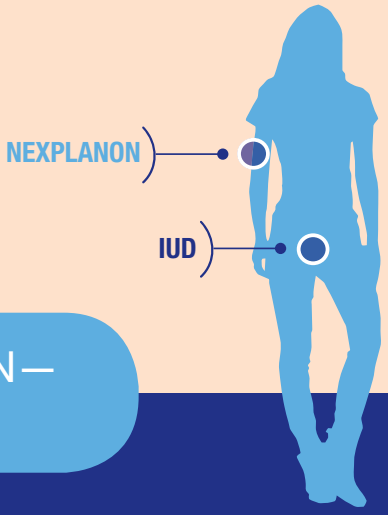
NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

Help your patients understand both LARC location options



Talk to your patients about NEXPLANON—
the only non-uterine LARC option

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

>99% effective†

Reversible if plans change

LARC = long-acting reversible contraceptive.
*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)*

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.

MERCK

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

Complications of Insertion and Removal

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

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

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

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

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

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

Changes in Menstrual Bleeding Patterns

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

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

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

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

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

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

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

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

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

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

Ectopic Pregnancies

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

Thrombotic and Other Vascular Events

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

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

Ovarian Cysts

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

Carcinoma of the Breast and Reproductive Organs

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

Liver Disease

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

Weight Gain

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

Elevated Blood Pressure

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

Gallbladder Disease

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

Carbohydrate and Lipid Metabolic Effects

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

Depressed Mood

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

Return to Ovulation

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

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

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

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

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

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

ADVERSE REACTIONS
In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant]) (11.1% of women).

Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

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

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

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

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

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

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

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

Effects of Other Drugs on Hormonal Contraceptives
Substances decreasing the plasma concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding.

Some drugs or herbal products that may decrease the effectiveness of HCs include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

For more detailed information, please read the Prescribing Information.
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EDITORIAL

What is the role of the ObGyn in preventing and treating obesity?

As frontline clinicians, obstetrician-gynecologists play an important role in identifying and treating obesity. For overweight and obese patients, interventions that facilitate weight loss include a calorie-restricted diet, exercise, metformin, and sleeve gastrectomy.

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Obesity is a disease causing a public health crisis. In the United States, tobacco use and obesity are the two most important causes of preventable premature death. They result in an estimated 480,000[1] and 300,000[2] premature deaths per year, respectively. Obesity is a major contributor to diabetes mellitus, hypertension, dyslipidemia, and coronary heart disease. Obesity is also associated with increased rates of colon, breast, and endometrial cancer. Experts predict that in 2030, 50% of adults in the United States will have a body mass index (BMI) ≥ 30 kg/m^2, and 25% will have a BMI ≥ 35 kg/m^2.[3] More women than men are predicted to be severely obese (**FIGURE**, page 15).[3]

As clinicians we need to increase our efforts to reduce the epidemic of obesity. ObGyns can play an important role in preventing and managing obesity, by recommending primary-care weight management practices, prescribing medications that influence central metabolism, and referring appropriate patients to bariatric surgery centers of excellence.

Primary-care weight management

Measuring BMI and recommending interventions to prevent and treat obesity are important components of a health maintenance encounter. For women who are overweight or obese, dietary changes and exercise are important recommendations. The American Heart Association recommends the following lifestyle interventions[4]:

- Eat a high-quality diet that includes vegetables, fruit, whole grains, beans, legumes, nuts, plant-based protein, lean animal protein, and fish.
- Limit intake of sugary drinks and foods, fatty or processed meats, full-fat dairy products, eggs, highly processed foods, and tropical oils.
- Exercise at least 150 minutes weekly at a moderate activity level, including muscle-strengthening activity.
- Reduce prolonged intervals of sitting.
- Consider using an activity tracker to monitor activity level.

Clinicians should consider referring overweight and obese patients to a nutritionist for a consultation to plan how to consume a high-quality, low-calorie diet. A nutritionist can spend time with patients explaining options for implementing a calorie-restricted diet. In addition, some health insurers will require patients to participate in a supervised calorie-restricted diet plan for at least 6 months before authorizing coverage of expensive weight loss medications or bariatric surgery. In addition to recommending diet and exercise, ObGyns may consider prescribing metformin for their obese patients.

Metformin

Metformin is approved for the treatment of type 2 diabetes mellitus. Unlike insulin therapy, which is associated with weight gain, metformin is associated with modest weight loss. The Diabetes Prevention Program (DPP) randomly assigned 3,234 nondiabetic participants with a fasting glucose level between 95 and 125 mg/dL and impaired glucose

CONTINUED ON PAGE 15

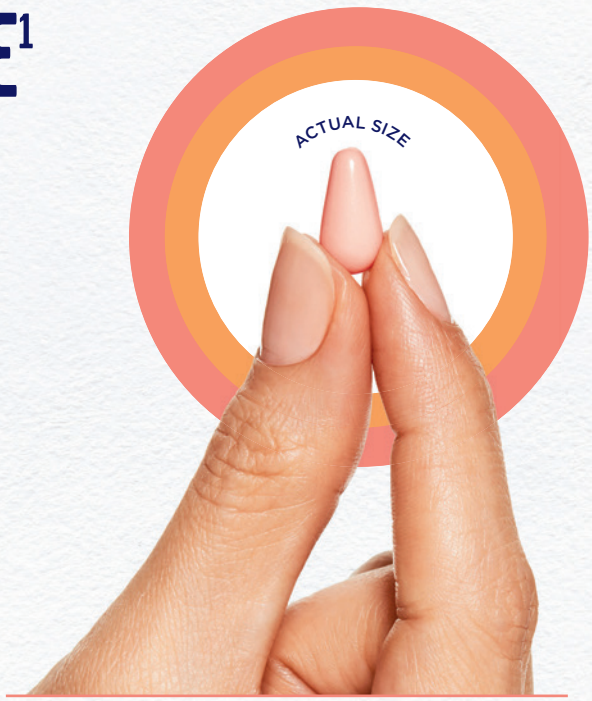
FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

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

DISCOVER A TREATMENT EXPERIENCE WITH

SIMPLICITY AT ITS CORE[1]

- THE ONLY ULTRA-LOW-DOSE VAGINAL ESTRADIOL AVAILABLE IN BOTH 4-MCG AND 10-MCG DOSES[1,2]
- PROVEN EFFICACY AT WEEK 12 AND BEGINNING AS EARLY AS WEEK 2 (A SECONDARY ENDPOINT)[1,3]
- MESS-FREE ADMINISTRATION WITH NO APPLICATOR, DOSE PREPARATION, OR CLEANUP NEEDED[1,3]



TO LEARN MORE AND REQUEST SAMPLES, VISIT IMVEXXYINFO.COM

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.

IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

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

Estrogen Plus Progestin Therapy

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

References: 1. Imvexxy [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2019. **2.** Data on file. Vaginal Estrogen PIs. **3.** 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.

TherapeuticsMD®
For Her. For Life.

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. Please visit www.IMVEXXYHCP.com 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

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

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.

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

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 WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations.

Ovarian Cancer

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

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

Probable Dementia

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

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

Other Warnings and Precautions include:

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

Geriatric Use

An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative.

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IVXY-20054.3 09/2019

CONTINUED FROM PAGE 12

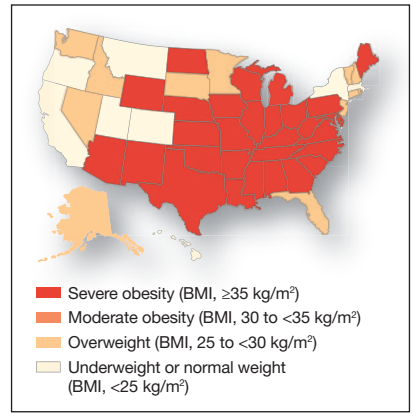
tolerance (140 to 199 mg/dL) after a 75-g oral glucose load to intensive lifestyle changes (calorie-restricted diet to achieve 7% weight loss plus 150 minutes of exercise weekly), metformin (850 mg twice daily), or placebo.[5,6] The mean age of the participants was 51 years, with a mean BMI of 34 kg/m^2. Most (68%) of the participants were women.

After 12 months of follow-up, mean weight loss in the intensive lifestyle change, metformin, and placebo groups was 6.5%, 2.7%, and 0.4%, respectively. After 2 years of treatment, weight loss among those who reliably took their metformin pills was approximately 4%, while participants in the placebo group had a 1% weight gain. Among those who continued to reliably take their metformin pills, the weight loss persisted through 9 years of follow up.

The mechanisms by which metformin causes weight loss are not clear. Metformin stimulates phosphorylation of adenosine monophosphate (AMP)-activated protein kinase, which regulates mitochondrial function, hepatic and muscle fatty acid oxidation, glucose transport, insulin secretion, and lipogenesis.[7]

Many ObGyns have experience in using metformin for the treatment of polycystic ovary syndrome or gestational diabetes. Hence, the dosing and adverse effects of metformin are familiar to many obstetricians-gynecologists. Metformin is contraindicated in individuals with creatinine clearance less than 30 mL/min. Rarely, metformin can cause lactic acidosis. According to Lexicomp,[8] the most common adverse effects of metformin extended release (metformin ER) are diarrhea (17%), nausea and vomiting (7%), and decreased vitamin B12 concentration (7%) due to malabsorption in the terminal ileum. Of note, in the DPP study, hemoglobin concentration was slightly lower over time in the metformin compared with the placebo group (13.6 mg/dL vs 13.8 mg/dL, respectively; $P<.001$).[6] Some experts recommend annual vitamin B12 measurement in individuals taking metformin.

FIGURE Projected most common body mass index (BMI) category among US women in 2030[3]



In my practice, I only prescribe metformin ER. I usually start metformin treatment with one 750 mg ER tablet with dinner. If the patient tolerates that dose, I increase the dose to two 750 mg ER tablets with dinner. Metformin-induced adverse effects include diarrhea (17%) and nausea and vomiting (7%). Metformin ER is inexpensive. A one-month supply of metformin (sixty 750 mg tablets) costs between $4 and $21 at major pharmacies.[9] Health insurance companies generally do not require preauthorization to cover metformin prescriptions.

Weight loss medications

US Food and Drug Administration (FDA)-approved weight loss medications include: liraglutide (Victoza), orlistat (Xenical, Alli), combination phentermine-extended release topiramate (Qsymia), and combination extended release naltrexone-bupropion (Contrave). All FDA-approved weight loss medications result in mean weight loss in the range of 6% to 10%. Many of these medications are very expensive (more than $200 per month).[10] Insurance preauthorization is commonly required for these medications. For ObGyns, it may be best to refer patients who would like to use a weight loss medication to a specialist or specialty center with expertise in using these medications.

Sleeve gastrectomy

Two children are playing in a school yard. One child proudly states, "My mother is an endocrinologist. She treats diabetes." Not to be outdone, the other child replies, "My mother is a bariatric surgeon. She cures diabetes."

The dialogue reflects the reality that bariatric surgery results in more reliable and significant weight loss than diet, exercise, or weight loss medications. Diet, exercise, and weight loss medications often result in a 5% to 10% decrease in weight, but bariatric surgery typically results in a 25% decrease in weight. Until recently, 3 bariatric surgical procedures were commonly performed: Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and adjustable gastric banding (AGB). AGB is now seldom performed because it is less effective than RYGB and SG. Two recently published randomized trials compared the long-term outcomes associated with RYGB and SG. The studies found that SG and RYGB result in a similar degree of weight loss. RYGB resulted in slightly more weight loss than SG, but SG was associated with a lower rate of major complications, such as internal hernias. SG takes much less time to perform than RYGB. SG has become the most commonly performed bariatric surgery in premenopausal women considering pregnancy because of the low risk of internal hernias.

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Intermittent fasting: Miracle diet! Or diet fad?

Sustainable weight loss is very difficult to achieve through dieting alone. A multitude of dietary interventions have been presented as "revolutionary approaches" to the challenging problem of sustainable weight loss, including the Paleo diet, the Vegan diet, the low-carb diet, the Dukan diet, the ultra-low-fat diet, the Atkins diet, the HCG diet, the Zone diet, the South Beach diet, the plant-based diet, the Mediterranean diet, the Asian diet, and intermittent fasting. Recently, intermittent fasting has been presented as the latest and greatest approach to dieting, with the dual goals of achieving weight loss and improved health.[1] In some animal models, intermittent dieting has been shown to increase life-span, a finding that has attracted great interest. A major goal of intermittent fasting is to promote "metabolic switching" with increased reliance on ketones to fuel cellular energy needs.

Two approaches to "prescribing" an intermittent fasting diet are to limit food intake to a period of 6 to 10 hours each day or to markedly reduce caloric intake one or two days per week, for example to 750 calories in a 24-hour period. **There are no long-term studies of the health outcomes associated with intermittent fasting. In head-to-head clinical trials of intermittent fasting and daily calorie restriction (classic dieting), both diets result in similar weight loss.** For example, in one clinical trial 100 obese participants, with a mean body mass index (BMI) of 34 kg/m^2, including 86 women, were randomly assigned to[2]:

1. intermittent fasting (25% of energy needs every other day)
2. daily calorie restriction (75% of energy needs every day), or
3. no intervention.

After 12 months of follow up, the participants in the no intervention group had gained 0.5% of their starting weight. The intermittent fasting and the daily calorie restriction groups had similar amounts of weight loss, approximately 5% of their starting weight. More individuals dropped out of the study from the intermittent fasting group than the daily calorie restriction group (38% vs 29%, respectively).

In another clinical trial, 107 overweight or obese premenopausal women, average age 40 years and mean BMI 31 kg/m^2, were randomly assigned to intermittent fasting (25% of energy needs 2 days per week) or daily calorie restriction (75% of energy needs daily) for 6 months. The mean weight of the participants at baseline was 83 kg. Weight loss was similar in the intermittent fasting and daily calorie restriction groups, 6.4 kg (-7.7%) and 5.6 kg (-6.7%), respectively (*P*=.4).[3]

The investigators concluded that intermittent fasting and daily calorie restriction could both be offered as effective approaches to weight loss. My conclusion is that intermittent fasting is not a miracle dietary intervention, but it is another important option in the armamentarium of weight loss interventions.

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In the Swiss Multicenter Bypass or Sleeve Study (SM-BOSS), 217 participants with a mean BMI of 44 kg/m^2 and mean age of 45.5 years were randomly assigned to RYGB or SG and followed for 5 years.[11] The majority (72%) of the participants were women. At 5 years of follow-up, in the RYGB and SG groups, mean weight loss was 37 kg and 33 kg, respectively (*P*=.19). In both groups, weight loss nadir was reached 12 to 24 months after surgery. Expressed as a percentage of original weight, weight loss in the RYGB and SG groups was -29% and -25%, respectively (*P*=.02). Gastric reflux worsened in both the RYGB and SG groups (6% vs 32%, respectively). The number of reoperations in the RYGB and SG groups was 22% and 16%. Of note, among individuals with prevalent diabetes, RYGB and SG resulted in remission of the diabetes in 68% and 62% of participants, respectively.

In the Sleeve vs Bypass study (SLEEVEPASS), 240 participants, with mean BMI of 46 kg/m^2 and mean age of 48 years, were randomly assigned to RYGB or SG and followed for 5 years.[12] Most (70%) of the participants were women. Following bariatric surgery, BMI decreased significantly in both groups. In the RYGB group, BMI decreased from 48 kg/m^2 preoperatively to 35.4 kg/m^2 at 5 years of follow up. In the SG group, BMI decreased from 47 kg/m^2 preoperatively to 36.5 kg/m^2 at 5 years of follow up. Late major complications (defined as complications occurring from 30 days to 5 years postoperatively) occurred more frequently in the RYGB group (15%) versus the SG group (8%). All the late major complications required reoperation. In the SG group, 7 of 10 reoperations were for severe gastric reflux disease. In the RYGB group 17 of 18 reoperations were for suspected internal hernia, requiring closure of a mesenteric defect at reoperation. There was no treatment-related mortality during the 5-year follow up.

Guidelines for bariatric surgery are BMI ≥ 40 kg/m^2 without a comorbid illness or BMI ≥ 35 kg/m^2 with at least one serious comorbid disease, such as diabetes.[13] ObGyns can build a synergistic relationship with bariatric surgeons by referring eligible patients for surgical

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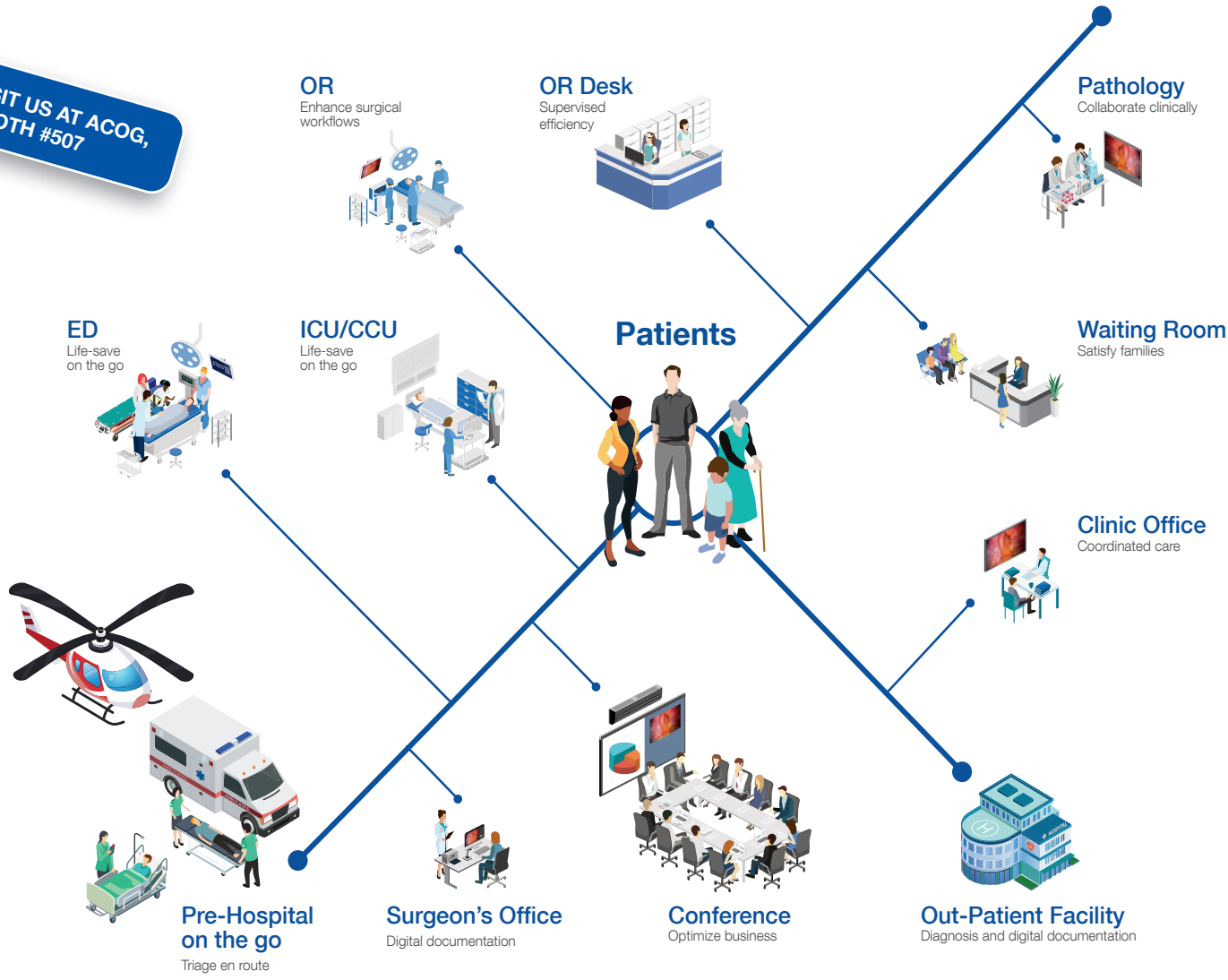

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In the management of cesarean scar defects, is there a superior surgical method for treatment?

According to this meta-analysis, which compared the data on laparoscopic, hysteroscopic, vaginal, and combined laparoscopic and hysteroscopic repair of cesarean scar defects, combined laparoscopic and hysteroscopic repair was associated with a shorter duration of abnormal bleeding. Combined laparoscopy and hysteroscopy also was found to decrease the depth of the defect when compared with vaginal repair. Although the findings are statistically significant, it is unclear if they are clinically significant; long-term outcomes are similarly unclear. More randomized controlled trials are required in order to make a clear distinction as to which method of repair is superior.

FAST TRACK

More study is needed to clearly distinguish which of the surgical methods analyzed is superior in terms of managing CSD

He Y, Zhong J, Zhou W, et al. Four surgical strategies for the treatment of cesarean scar defect: a systematic review and network meta-analysis. J Minim Invasive Gynecol. 2020;27:593-602.

EXPERT COMMENTARY

Stephanie Delgado, MD, is Fellow, Minimally Invasive Gynecologic Surgery, Baylor College of Medicine, Houston, Texas.

Xiaoming Guan, MD, PhD, is Professor and Director of Minimally Invasive Gynecologic Surgery, Baylor College of Medicine.

With the increase in cesarean deliveries performed over the decades, the sequelae of the surgery are now arising. Cesarean scar defects (CSDs) are a complication seen when the endometrium and muscular layers from a prior uterine scar are damaged. This damage in the uterine scar can lead to abnormal uterine bleeding and the implantation of an ectopic pregnancy, which can be life-threatening. Ultrasonography can be used to diagnose this defect, which can appear as a hypoechoic space filled with postmenstrual blood, representing a myometrial tear at the wound site.[1] There are several risk factors for CSD, including multiple cesarean deliveries, cesarean delivery during advanced stages of labor, and uterine incisions near the cervix. Elevated body mass index as well as gestational diabetes also have been found to be associated with inadequate healing of the prior cesarean incision.[2] Studies have shown that both single- and double-layer closure of the hysterotomy during a cesarean delivery have similar incidences of CSDs.[3,4] There are multiple ways to correct a CSD; however, there is no gold standard that has been identified in the literature.

The authors report no financial relationships relevant to this article.

Details about the study

The study by He and colleagues is a meta-analysis aimed at comparing the treatment

WHAT THIS EVIDENCE MEANS FOR PRACTICE

CSDs are a rising concern due to the increasing cesarean delivery rate. It is critical to be able to identify as well as correct these defects. This is the first systematic review to compare 4 techniques of managing CSDs. Based on this article, there may be some additional benefit from combined hysteroscopic and laparoscopic repair of these defects in terms of decreasing bleeding and decreasing the scar defect depth. However, how these results translate into long-term outcomes for patients and their future pregnancies is still unknown, and further research must be done.

STEPHANIE DELGADO, MD, AND XIAOMING GUAN, MD, PHD

of CSDs via laparoscopy, hysteroscopy, combined hysteroscopy and laparoscopy, and vaginal repair. The primary outcome measures were reduction in abnormal uterine bleeding and scar defect depth. A total of 10 studies (n = 858) were reviewed: 4 randomized controlled trials (RCTs) and 6 observational studies. The studies analyzed varied in terms of which techniques were compared.

Patients who underwent uterine scar resection by combined laparoscopy and hysteroscopy had a shorter duration of abnormal uterine bleeding when compared with hysteroscopy alone (standardized mean difference [SMD] = 1.36; 95% confidence interval [CI], 0.37–2.36; P = .007) and vaginal repair (SMD = 1.58; 95% CI, 0.97–2.19; P<.0001). Combined laparoscopic and hysteroscopic technique also was found to reduce the diverticulum depth more than in vaginal repair (SMD = 1.57; 95% CI, 0.54–2.61; P = .003).

Study strengths and weaknesses

This is the first meta-analysis to compare the different surgical techniques to correct a CSD. The authors were able to compare many of the characteristics regarding the routes of repair, including hysteroscopy, laparoscopy, and vaginal. The authors were able to analyze the combined laparoscopic and hysteroscopic approach, which facilitates evaluation of the location and satisfaction of defect repair during the procedure.

Some weaknesses of this study include the limited amount of RCTs available for review. All studies were also from China, where the rate of CSDs is higher. Therefore, the results may not be generalizable to all populations. Given that the included studies were done at different sites, it is difficult to determine surgical expertise and surgical technique. Additionally, the studies analyzed varied by which techniques were compared; therefore, indirect analyses were conducted to compare certain techniques. There was limited follow-up for these patients (anywhere from 3 to 6 months), so long-term data and future pregnancy data are needed to determine the efficacy of these procedures. ●

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WATCH FOR...

›› **Update on genetic testing**
from Stephanie H. Guseh, MD

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Dr. Wright reports that he is a consultant to Clovis Oncology and Tesaro, Inc, and has received research funding from Merck. Dr. Zhou reports no financial relationships relevant to this article.

Gynecologic malignancies continue to be a major cause of cancer-related mortality. In this article: adjuvant chemotherapy during and after radiation for high-risk endometrial cancers; PARP inhibitors with first-line chemotherapy and as maintenance therapy for ovarian cancer; and secondary cytoreductive surgeries for recurrent ovarian cancer.

Over the past year, major strides have been made in the treatment of gynecologic malignancies. In this Update, we highlight 3 notable studies. The first is a phase 3, multicenter, international, randomized clinical trial that demonstrated a significant improvement in both overall and failure-free survival with the use of adjuvant chemoradiation versus radiotherapy alone in patients with stage III or high-risk uterine cancer. Additionally, we describe the results of 2 phase 3, multicenter, international, randomized clinical trials in ovarian cancer treatment: use of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in combination with platinum and taxane-based chemotherapy followed by the PARP inhibitor as maintenance therapy, and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian cancer.

We provide a brief overview of current treatment strategies, summarize the key findings of these trials, and establish how these findings have changed our management of these gynecologic malignancies.

IN THIS ARTICLE

Adjuvant chemotherapy and radiotherapy improves survival in women with high-risk endometrial cancer

de Boer SM, Powell ME, Mileshkin L, et al; on behalf of the PORTEC Study Group. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 2019;1273-1285.

In the United States, it is estimated that more than 61,000 women were diagnosed with endometrial cancer in 2019.[1] Women with endometrial cancer usually have a favorable prognosis; more than 65% are diagnosed with early-stage disease, which is

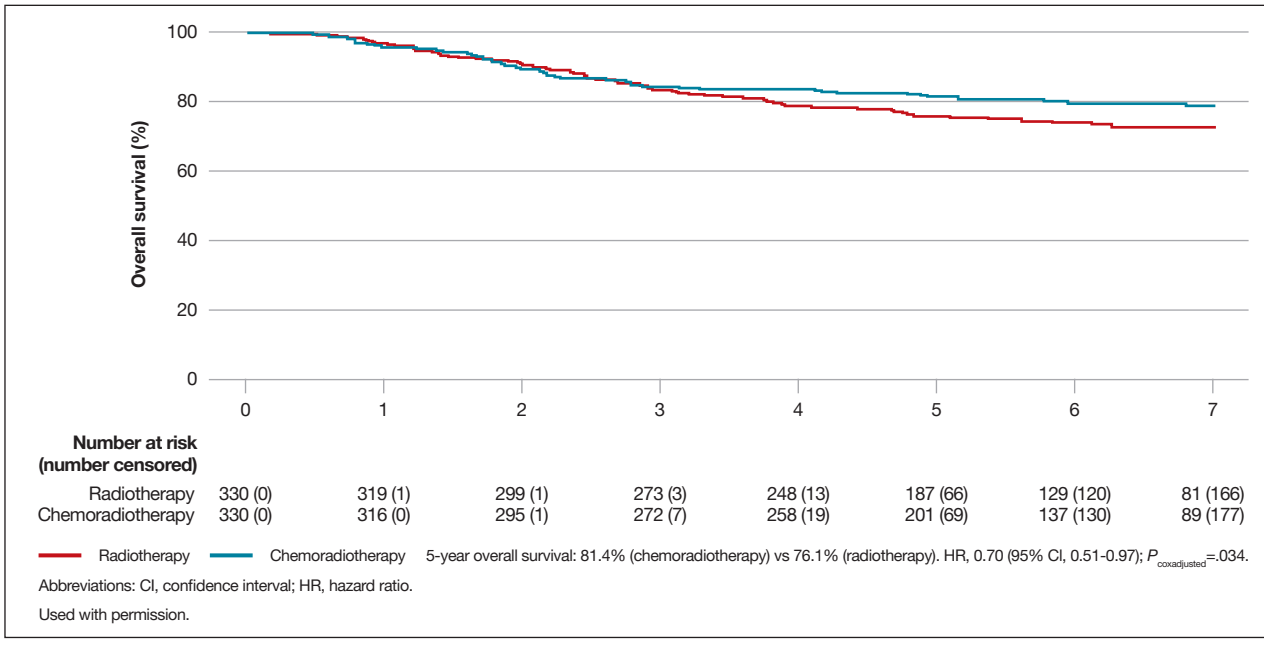

FIGURE Kaplan-Meier curve for overall survival among patients who previously were randomly assigned to chemoradiation (blue line) or radiation alone (red line)[7]

associated with a 95% 5-year survival rate.[1] However, 15% to 20% of patients have disease with high-risk features, including advanced stage (stage II–IV), high tumor grade, lymphovascular space invasion, deep myometrial invasion, or nonendometrioid histologic subtypes (serous or clear cell).[2] The presence of these high-risk disease features is associated with an increased incidence of distant metastases and cancer-related death.

Adjuvant therapy in high-risk endometrial cancer

To date, the optimal adjuvant therapy for patients with high-risk endometrial cancer remains controversial. Prior data from Gynecologic Oncology Group (GOG) protocol 122 demonstrated that chemotherapy significantly improved progression-free survival and overall survival when compared with radiotherapy in patients with advanced-stage endometrial cancer.[3] As such, chemotherapy now is frequently used in this population, often in combination with radiation, although data describing the benefit of chemoradiation are limited.[4] For women with earlier-stage disease with high-risk features, the value of chemotherapy plus radiation is uncertain.[5,6]

Benefit observed with adjuvant chemoradiotherapy

In a multicenter, international, randomized phase 3 trial, known as the PORTEC-3 trial, de Boer and colleagues sought to determine if combined adjuvant chemoradiation improved overall survival (OS) and failure-free survival when compared with external-beam radiation therapy (EBRT) alone in the treatment of women with high-risk endometrial cancer.[7] Women were eligible for the study if they had histologically confirmed stage I, grade 3 endometrioid endometrial cancer with deep invasion and/or lymphovascular space invasion, stage II or III disease, or stage I–III disease with serous or clear cell histology.

Participants were randomly assigned in a 1:1 ratio; 330 women received adjuvant EBRT alone (total dose of 48.6 Gy administered in 27 fractions), and 330 received adjuvant chemotherapy during and after radiation

therapy (CTRT) (2 cycles of cisplatin 50 mg/m^2 IV given on days 1 and 22 of EBRT followed by 4 cycles of carboplatin AUC 5 and paclitaxel 175 mg/m^2 IV every 3 weeks).

At a median follow-up of 73 months, treatment with adjuvant CTRT, compared with adjuvant EBRT alone, was associated with a significant improvement in both overall survival (5-year OS: 81.4% vs 76.1%, P = .034 [**FIGURE**]) and failure-free survival (5-year failure-free survival: 76.5% vs 69.1%, P = .016).

The greatest absolute benefit of adjuvant CTRT, compared with EBRT alone, in survival was among women with stage III endometrial cancer (5-year OS: 78.5% vs 68.5%, P = .043) or serous cancers (19% absolute improvement in 5-year OS), or both. Significant differences in 5-year OS and failure-free survival in women with stage I–II cancer were not observed with adjuvant CTRT when compared with adjuvant EBRT alone. At 5 years, significantly more adverse events of grade 2 or worse were reported in the adjuvant CTRT arm.

Results from similar trials

Since the publication of results from the updated analysis of PORTEC-3, results from 2 pertinent trials have been published.[8,9] In the GOG 249 trial, women with stage I–II endometrial cancer with high-risk features were randomly assigned to receive 3 cycles of carboplatin-paclitaxel chemotherapy with vaginal brachytherapy or EBRT.[8] There was no difference in survival, but a significant increase in both pelvic and para-aortic recurrences were seen after the combination of chemotherapy and vaginal brachytherapy.[8]

In GOG 258, women with stage III–IVA endometrial cancer were randomly assigned to receive chemotherapy alone (carboplatin-paclitaxel) or adjuvant chemotherapy after EBRT.[9] No differences in recurrence-free or overall survival were noted, but there was a significant increase in the number of vaginal and pelvic or para-aortic recurrences in patients in the chemotherapy-only arm.[9]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The conflicting data regarding the ideal adjuvant therapy for endometrial cancer suggests that treatment decisions should be individualized. Pelvic EBRT with concurrent adjuvant chemotherapy should be considered in women with stage III endometrial cancer or serous cancers as combination therapy improves survival, although dual modality treatment is associated with increased toxicity. Chemoradiation appears to have less benefit for women with stage I–II cancers with other pathologic risk factors.

Role for PARP inhibitor plus first-line chemotherapy, and as maintenance therapy, in ovarian cancer treatment

Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381:2403-2415.

Ovarian cancer is the leading cause of gynecologic cancer–related deaths among women in the United States.[10] Treatment consists of cytoreductive surgery combined with platinum and taxane-based chemotherapy.[11] Despite favorable initial responses, more than 80% of patients experience a recurrence, with an 18-month median time to progression.[12] As a result, recent efforts have focused on finding novel therapeutic approaches to improve treatment outcomes and mitigate the risk of disease recurrence.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

For women with newly diagnosed, previously untreated stage III or IV high-grade serous ovarian carcinoma, carboplatin, paclitaxel, and veliparib induction therapy followed by single-agent veliparib maintenance therapy resulted in a significant improvement in median progression-free survival compared with induction chemotherapy alone. However, veliparib use was also associated with a higher incidence of adverse effects that required dose reduction and/or interruption during both the combination and maintenance phases of treatment.

FAST TRACK

A significant improvement was observed in progression-free survival in the veliparib-throughout arm compared with the control arm in 3 cohorts: the BRCA-mutation cohort, the HRD cohort, and the intention-to-treat population

PARP inhibitors are changing the face of treatment

Poly(adenosine diphosphate-ribose) polymerases (PARPs) are a family of enzymes that play a critical role in DNA damage repair. These enzymes promote DNA repair by recruiting proteins involved in repairing single-strand and double-strand DNA breaks and in protecting and restarting stalled DNA replication forks.[13] The predominant mechanisms of action of PARP inhibitors in cells with homologous-recombination deficiency (HRD) include inhibiting repair of single-strand DNA breaks and trapping PARP-DNA complexes at stalled DNA replication forks.[14]

Germline or somatic *BRCA1/2* mutations and genetic alterations resulting in HRD are present in about 20% and 30% of ovarian carcinomas, respectively, and increase the susceptibility of tumors to platinum-based agents and PARP inhibitors.[15,16] Based on multiple clinical trials that demonstrated the efficacy of single-agent PARP in the treatment of recurrent ovarian carcinoma and as maintenance therapy after an initial response to platinum-based therapy, the US Food and Drug Administration approved olaparib, niraparib, and rucaparib for the treatment of high-grade epithelial ovarian cancer.[17-19] Only olaparib is approved for maintenance therapy after initial adjuvant therapy in patients with *BRCA* mutations.[20]

Given the robust response to PARP inhibitors, there has been great interest in using these agents earlier in the disease course in combination with chemotherapy.

Efficacy of veliparib with chemotherapy and as maintenance monotherapy

In a randomized, double-blind, placebo-controlled phase 3 trial, Coleman and colleagues sought to determine the efficacy of the PARP inhibitor veliparib when administered with first-line carboplatin and paclitaxel induction chemotherapy and subsequently continued as maintenance monotherapy.[21]

Women with stage III or IV high-grade epithelial ovarian, fallopian tube, or primary peritoneal carcinoma were eligible for the study. Cytoreductive surgery could be performed prior to the initiation of trial treatment or after 3 cycles of chemotherapy.

Participants were randomized in a 1:1:1 ratio: 371 women received carboplatin and paclitaxel plus placebo followed by placebo maintenance (control arm); 376 received chemotherapy plus veliparib followed by placebo maintenance (veliparib combination-only arm); and 377 received chemotherapy plus veliparib followed by veliparib maintenance therapy (veliparib-throughout arm). Combination chemotherapy consisted of 6 cycles, and maintenance therapy was an additional 30 cycles.

Progression-free survival extended

At a median follow-up of 28 months, investigators observed a significant improvement in progression-free survival in the veliparib-throughout (initial and maintenance therapy) arm compared with the control arm in 3 cohorts: the *BRCA*-mutation cohort, the HRD cohort, and the intention-to-treat population (all participants undergoing randomization).

In the *BRCA*-mutation cohort, the median progression-free survival was 12.7 months longer in the veliparib-throughout arm than in the control arm. Similarly, in the HRD cohort, the median progression-free survival was 11.4 months longer in the veliparib-throughout arm than in the control group. In the intention-to-treat population, the median progression-free

survival increased from 17.3 to 23.5 months in the veliparib-throughout arm compared with the control arm.

Women who received veliparib experienced increased rates of nausea, anemia, and fatigue and were more likely to require dose reductions and treatment interruptions. Myelodysplastic syndrome was reported in 1 patient (*BRCA1* positive) in the veliparib combination-only arm.

Secondary cytoreductive surgery or chemotherapy alone for platinum-sensitive recurrent ovarian carcinoma?

Coleman RL, Spirtos NM, Enserro D, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. N Engl J Med. 2019;381:1929-1939.

Primary surgical cytoreduction combined with platinum and taxane-based chemotherapy remains the mainstay of ovarian cancer treatment.[11] The role of surgery for women with recurrent ovarian cancer, so-called secondary cytoreduction, remains controversial.[22]

Data have shown that among women who undergo secondary surgery, those with little or no postoperative residual disease benefit the most from a secondary debulking.[23-26] Prior work largely is based on small retrospective reports and is limited by substantial bias in the selection of patients undergoing surgery. Additionally, with the availability of targeted therapies such as bevacizumab and PARP inhibitors as maintenance—medical interventions with a demonstrated benefit in progression-free survival[17-19,27]—the role of secondary cytoreduction in the treatment of ovarian carcinoma needs to be clarified.

Overall survival after secondary cytoreduction followed by chemotherapy

Coleman and colleagues conducted a prospective, multicenter, international, randomized phase 3 trial to assess whether secondary cytoreductive surgery followed by chemotherapy would improve overall survival versus chemotherapy alone among women with resectable platinum-sensitive, recurrent ovarian cancer.[22] Platinum sensitivity was defined as a disease-free interval of at least 6 months after the last cycle of platinum-based chemotherapy.

All women had recurrent epithelial ovarian carcinoma considered to be amenable to complete gross surgical resection by the investigator and a history of complete response to at least 3 cycles of platinum-based chemotherapy as determined by a normal CA-125 value or negative imaging studies (if obtained).

Participants were randomly assigned 1:1, with 240 women assigned to secondary surgical cytoreduction followed by platinum-based chemotherapy, and 245 assigned to chemotherapy alone. The type of adjuvant chemotherapy used (carboplatin-paclitaxel

FAST TRACK

Secondary cytoreduction followed by chemotherapy was not associated with improved overall survival compared with chemotherapy alone in women with platinum-sensitive, recurrent ovarian cancer

WHAT THIS EVIDENCE MEANS FOR PRACTICE

For women with platinum-sensitive, recurrent ovarian cancer, a secondary cytoreductive surgery followed by chemotherapy was not associated with an improvement in overall survival when compared with chemotherapy alone. Secondary cytoreductive surgery should not be used routinely in women with recurrent ovarian cancer.

or carboplatin-gemcitabine) and whether or not bevacizumab was administered were at the investigators' discretion.

Shorter survival, decline in quality of life

Among the participants assigned to and who underwent surgery, complete gross resection was achieved in 67%. Eighty-four percent of the entire study population received platinum-based chemotherapy with bevacizumab followed by bevacizumab maintenance therapy, which was equally distributed between the 2 study arms.

At a median follow-up of 48.1 months, median overall survival was 50.6 months in the surgery arm compared with 64.7 months in the chemotherapy arm, corresponding to a hazard ratio (HR) for death of 1.29 (95% confidence interval [CI], 0.97–1.72; P = .08). This effect was unchanged after adjusting for platinum-free interval, chemotherapy choice, and restricting the analysis to women who had a complete gross resection.

Similarly, the adjusted HR for disease progression or death was 0.82 (95% CI, 0.66–1.01) and corresponded to a median progression-free survival of 18.9 months for the surgery group and 16.2 months for the chemotherapy group. Surgical morbidity was reported in 9% of patients who underwent surgery, and 1 patient (0.4%) died from postoperative complications.

While a significant decline in both quality of life and patient-reported outcomes was reported immediately after surgery, significant differences were not noted between the 2 groups after the initial postoperative recovery period. ●

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EDITORIAL

CONTINUED FROM PAGE 16

consultation and, in return, accepting referrals. A paradox and challenge is that many health insurers require patients to complete a supervised medical weight loss management program prior to being approved for bariatric surgery. However, the medical weight loss program might result in the patient no longer being eligible for insurance coverage of their surgery. For example, a patient who had a BMI of 42 kg/m^2 prior to a medical weight loss management program who then lost enough weight to achieve a BMI of 38 kg/m^2 might no longer be eligible for insurance coverage of a bariatric operation.[14]

ObGyns need to prioritize treatment for obesity

Between 1959 and 2014, US life expectancy increased from 69.9 years to 79.1 years. However, in 2015 and 2016 life expectancy in the United States decreased slightly to 78.9 years, while continuing to improve in other countries.[15] What could cause such an unexpected trend? Some experts believe that excess overweight and obesity in the US population, resulting in increased rates of diabetes, hypertension, and heart disease, accounts for a significant proportion of the life expectancy gap between US citizens and those who reside in Australia, Finland, Japan, and Sweden.[16,17] All frontline clinicians play an important role in reversing the decades-long trend of increasing rates of overweight and obesity. Interventions that ObGyns could prioritize in their practices for treating overweight and obese patients include: a calorie-restricted diet, exercise, metformin, and SG. ●

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RISKY MEDICINE, PART 3

The apology in medicine—yes, no, or maybe?

The ethics of, the laws behind, and the effective apology

Steven R. Smith, MS, JD, and Joseph S. Sanfilippo, MD, MBA

IN THIS ARTICLE

This is the third and final article in a series focusing on malpractice, liability, and reform. In the first article, we looked at the background on malpractice and reasons malpractice rates have been so high—including large verdicts and lawsuit-prone physicians. In the second article we considered recent experience and developments in malpractice exposure, who is sued and why. Finally, in this third article, we focus on apologies, apology laws, and liability.

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"I'm sorry"

In childhood we are all taught the basic courtesies: "please" and "thank you," and "I'm sorry," when harm has occurred. Should we as adult health care providers fear the consequences of apologizing? Apologies are a way for clinicians to express empathy; they also serve as a tool to reduce medical malpractice claims.[1]

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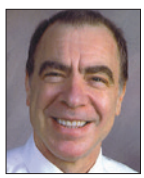

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Apologies, ethics, and care

The American Medical Association takes the position that a physician has an ethical duty to disclose a harmful error to a patient.[2,3] Indeed this approach has been an impetus for states to enact apology laws, which we discuss below. As pointed out in this 2013 article title, "Dealing with a medical mistake: Should physicians apologize to patients?",[4] the legal benefits of any apology are an issue. It is a controversial area in medicine still today, including in obstetrics and gynecology.

"Ethical codes for both M.D.s and D.O.s suggest providers should display honesty and empathy following adverse events and errors."[1,3,5] In addition, the American Medical Association states, "a physician should at all times deal honestly and openly with

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TABLE When an error occurs[4]

- Acknowledge the error and explain it
- Take responsibility and apologize
- Find the underlying cause and prevent its recurrence

patients."[2] Concerns about liability that may result from truthful disclosure should not affect the physician's honesty (**TABLE**). Increasingly, the law has sided with that principle through apology laws.

Some patients sue to get answers to the "What happened?" and "Why did it happen?" questions.[6] They also sometimes are motivated by a desire to help ensure that the same injury does not happen to others. Silence on the part of the clinician may be seen as a lack of sympathy or remorse and patients may fear that other patients will be harmed.[1]

The relationship between physician and patient involves vulnerability and requires trust. When an injury occurs, the relationship can be injured as well. Barriers to apology in part reflect "the culture of medicine" as well as the "inherent psychological difficulties in facing one's mistakes and apologizing for them." However, apology by the provider may result in "effective resolution of disputes related to medical error."[7]

The patient's perspective is critical to this type of outcome, of course. A study from the United Kingdom noted that one-third of patients who experience a medical error have a desire to receive an apology or explanation. Furthermore, patients need assurance that a plan of action to prevent such a future occurrence is in place.[8] Surveys reflect that patients desire, or even expect, the physician to acknowledge an error.[9] We will see that there is evidence that some kinds of apologies tend to diminish blame and make the injured patient less likely to pursue litigation.[10] For instance, Dahan and colleagues completed a study that highlights the "act of apology," which can be seen as a "language art."[11] Medical schools have recognized the importance of the apology and now incorporate training focused on error disclosure and provision of apologies into the curriculum.[12]

FAST TRACK

Apologies in medicine traditionally could be used against physicians in malpractice cases

Legal issues and medical apologies

From a legal standpoint, traditionally, an apology from a physician to a patient could be used against a physician in a medical liability (malpractice) case as proof of negligence.

Statements of interest. Such out-of-court statements ordinarily would be "hearsay" and excluded from evidence; there is, however, an exception to this hearsay rule that allows "confessions" or "statements against interest" to be admissible against the party making the statement. The theory is that when a statement is harmful to the person making it, the person likely thought that it was true, and the statement should be admissible at trial. We do not generally go around confessing to things that are not true. Following an auto crash, if one driver jumps out of the car saying, "I am so sorry I hit you. I was using my cell phone and did not see you stop," the statement is against the interest of the driver and could be used in court.

As a matter of general legal principle, the same issue can arise in medical practice. Suppose a physician says, "I am so sorry for your injury. We made a mistake in interpreting the data from the monitors." That sounds a lot like not just an apology but a statement against interest. Malpractice cases generally are based on the claim that a "doctor failed to do what a reasonable provider in the same specialty would have done in a similar situation."[13] An apology may be little more than general sympathy ("I'm sorry to tell you that we have not cured the infection. Unfortunately, that will mean more time in the hospital."), but it can include a confession of error ("I'm sorry we got the x-ray backward and removed the wrong kidney."). In the latter kind of apology, courts traditionally have found a "statement against interest."

The legal consequence of a statement against interest is that the statement may be admitted in court. Such statements do not automatically establish negligence, but they can be powerful evidence when presented to a jury.

Courts have struggled with medical apologies. General sympathy or feelings of regret or compassion do not generally rise to the level

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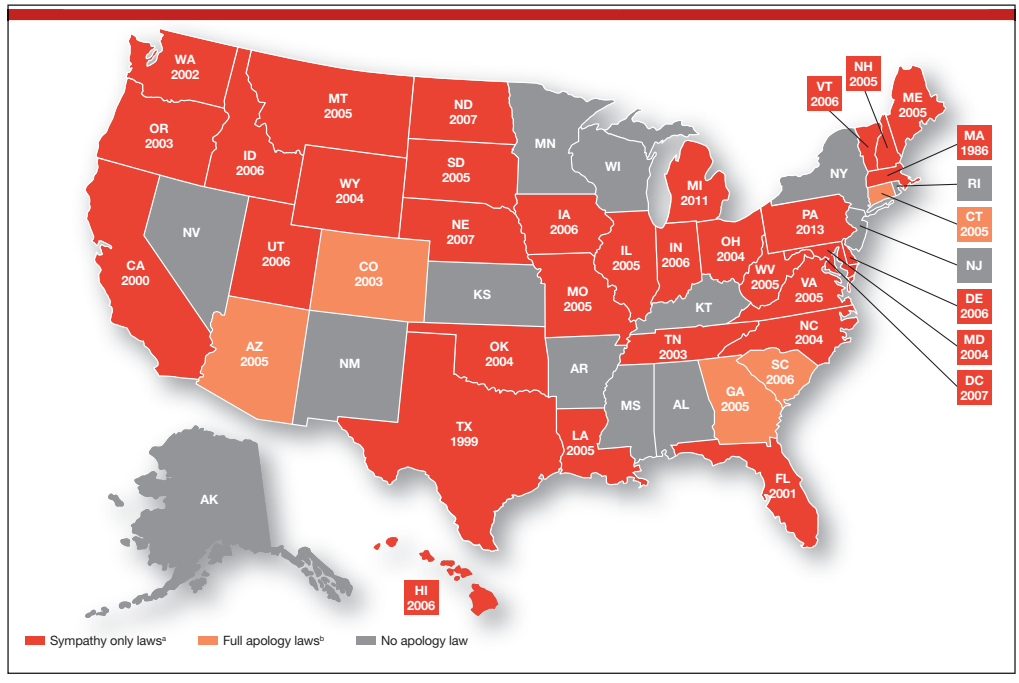
FIGURE 1 States with apology laws and years enacted[1]



[a]Pertains to sympathy statements.
[b]Offer protections for sympathy, fault, error, mistake, and negligence statements.

FAST TRACK

A clear majority of states now have apology laws—statutes that either provide broad protection for statements of fault, error, negligence, and sympathy or simply protection against statements of sympathy

of an admission that the physician did not use reasonable care under the circumstances and ordinarily are not admissible. (For further details, we refer you to the case of *Cobbs v. Grant*.[14] Even if a physician said to the patient that he "blamed himself for [the patient] being back in the hospital for a second time,…the statement signifies compassion, or at most, a feeling of remorse, for plaintiff's ordeal.") On the other hand, in cases in which a physician in an apology referred to a "careless" mistake or even a "negligent" mistake, courts have allowed it admitted at trial as a statement against interest. (A 1946 case, *Woronka v. Sewall*, is an example.[15] In that case, the physician said to the patient, "My God, what a mess…she had a very hard delivery, and it was a burning shame to get [an injury] on top of it, and it was because of negligence when they were upstairs.") Some of these cases come down to the provider's use of a single word: fault, careless, or negligence.

The ambiguity over the legal place of medical apologies in medicine led attorneys to urge medical providers to avoid statements that might even remotely be taken as statements against interest, including real apologies. The confusion over the admissibility of medical apologies led state legislatures to adopt apology laws. These laws essentially limit what statements against interest may be introduced in professional liability cases when a provider has issued a responsibility or apologized.

Apology statutes

Massachusetts was the first state to enact an apology law—in 1986.[1] As of 2019, a clear majority of states have some form of apology statute. "Apology laws are gaining traction," was the first sentence in a 2012 review on the subject by Saitta and colleagues.[3] Only a few (5 states) have "strong" statutes that have broad protection for statements of fault, error, and negligence, as well as sympathy. The other 33 states have statutes that only protect against statements of sympathy.[4,16]

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FIGURE 1 is a US map showing the apology laws by state.[1]

Do apology statutes and apologies reduce liability?

The positive aspects of apology include personal, psychological, and emotional benefits to both the one apologizing and the one receiving the apology. It also may have financial benefits to health care providers.[4] The assumption has been, and there has been some evidence for the proposition, that apologies reduce the possibility of malpractice claims. That is one of the reasons that institutions may have formal apology policies. Indeed, there is evidence that apologies reduce financial awards to patients, as manifest in the states of Pennsylvania and Kentucky.[4] Apologies appear to reduce patient anger and can open the door to better communication with the provider. There is evidence that some kinds of apologies tend to diminish blame and make the injured patient less likely to pursue litigation.[10] The conclusion from these studies might be that honest and open communication serves to decrease the incidence of medical malpractice lawsuit initiation and that honesty is the best policy.

It is important to note the difference, however, between apologies (or institutional apology policies) and apology laws. There is some evidence that apology and institutional apology policies may reduce malpractice claims or losses.[17,18] On the other hand, the studies of apology laws have not found that these laws have much impact on malpractice rates. An especially good and thorough study of the effect of apology laws nationwide, using insurance claims data, essentially found little net effect of the apology laws.[19,20] One other study could find no evidence that apology statutes reduce defensive medicine (so no reduction in provider concerns over liability).[21]

It should be noted that most studies on medical apology and its effects on malpractice claims generally have looked at the narrow or limited apology statutes (that do not cover expressions of fault or negligence). Few states have the broader statutes, and it is possible that those broader statutes would be more effective in reducing liability. Removing the disincentives to medical apologies is a good thing, but in and of itself it is probably not a liability game changer.

Institutional policy and apology

Some institutions have established an "inclusion of apology" strategy for medical errors. These policies appear to have a meaningful effect on reducing medical malpractice costs. These programs commonly include a proactive investigation, disclosure of error, and apologies. Such policies have been studied at the University of Michigan and the Veterans Affairs (VA) Hospital in Lexington, Kentucky. The University of Michigan program resulted in a 60% reduction in compensation costs for medical errors.[22] It also cut litigation costs by half.[23] The review of the Kentucky VA program also was positive.[17] **FIGURE 2** illustrates the key features of the Michigan program.[24]

Conclusions: Effective apologies

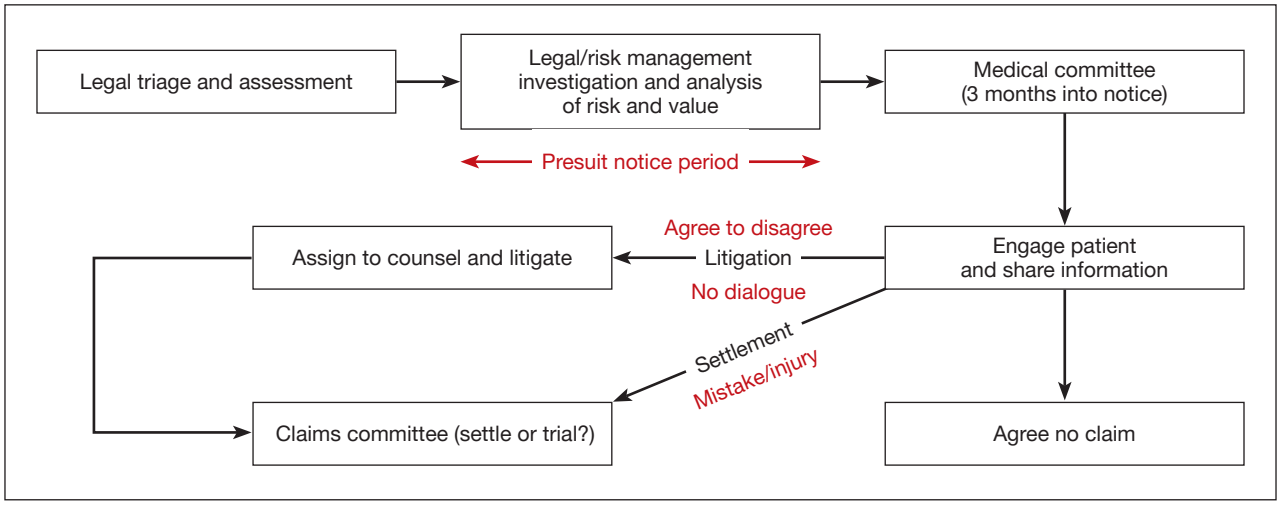
Our conclusions, first, are that apologies are important from all perspectives: ethical, medical, and legal. On the other hand, all of the attention given in recent years to apology statutes may have been misplaced, at least if they were intended to be malpractice reform.[17]

Institutional apology and response programs are likely successful because they are thoughtfully put together, generally based on the best understanding of how injured patients respond to apologies and what it takes to be sincere, and communicate that sincerity, in the apology. What is an effective apology?, "The acceptance of responsibility for having caused harm." It may, for example, mean accepting some financial responsibility for the harm. It is also important that the apology is conveyed in such a way that it includes an element of self-critical expression.[25] Although there are many formulations of the elements of an effective apology, one example is, "(1) acknowledging and accepting responsibility for the offense; (2) expressing remorse with forbearance, sincerity, and honesty;

FAST TRACK

Effective apologies accept responsibility for having caused harm, express remorse, and explain understanding of the offense and needed reparations

FIGURE 2 University of Michigan model addressing medical malpractice[24]



(3) explaining the understanding of the offense; and (4) willingness to make reparations."[26]

At the other extreme is a medical professional, after a bad event, trying to engage in a half-hearted, awkward, or insincere apology on an ad hoc and poorly planned basis. Worse still, "when victims perceive apologies to be insincere and designed simply to cool them off, they react with more rather than less indignation."[27] Of course, the "forced apology" may be the worst of all. An instance of this was addressed in a New Zealand study in which providers were "forced" to provide a written apology to a couple (Mr. and Mrs. B) and a separate written apology to Baby B when there was failure to discuss vitamin K administration during the antenatal period when it was indicated.[28] Rather than emphasizing required apology in such a case, which can seem hollow and disingenuous, emphasis was placed on the apology providing a "positive-physiological" effect for those harmed, and on strategies that "nurture the development of the moral maturity required for authentic apology."

The great advantage of institutional or practice-wide policies is that they can be developed in the calm of planning, with good foresight and careful consideration. This is much different from having to come up with some approach in the heat of something having gone wrong. Ultimately, however, apologies are not about liability. They are about caring for, respecting, and communicating with those who are harmed. Apologizing is often the right and professional thing to do. ●

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The role of hysteroscopy in diagnosing endometrial cancer

Certain hysteroscopic findings correlate with the likelihood of endometrial carcinoma—and the absence of pathology. Here is a breakdown of hysteroscopic morphologic findings and hysteroscopic-directed biopsy techniques.

Amy L. Garcia, MD

IN THIS ARTICLE

For more than 45 years, gynecologists have used hysteroscopy to diagnose endometrial carcinoma and to associate morphologic descriptive terms with visual findings.[1] Today, considerably more clinical evidence supports visual pattern recognition to assess the risk for and presence of endometrial carcinoma, improving observer-dependent biopsy of the most suspect lesions (**VIDEO 1**).

In this article, I discuss the clinical evolution of hysteroscopic pattern recognition of endometrial disease and review the visual findings that correlate with the likelihood of endometrial carcinoma. In addition, I have provided 9 short videos that show hysteroscopic views of various endometrial pathologies in the online version of this article at https://www.mdedge.com/obgyn.

The negative hysteroscopic view defined

In 1989, Dr. Frank Loffer confirmed the diagnostic superiority of visually directed biopsy. He demonstrated the advantages of using hysteroscopy and directed biopsy in the evaluation of abnormal uterine bleeding (AUB) to obtain a more accurate diagnosis compared with dilation and curettage (D&C) alone (sensitivity, 98% vs 65%, respectively).[2]

Also derived from this work is the clinical application of the "negative hysteroscopic view" (NHV). Loffer used the following criteria to define the NHV: good visualization of the entire uterine cavity, no structural abnormalities of the cavity, and a uniformly thin, homogeneous-appearing endometrium without variations in thickness (**TABLE 1**). The last criterion can be expected to occur only in the early proliferative phase or in postmenopausal women.

Use of hysteroscopy therefore can predict accurately the absence of intrauterine and endometrial pathology when visual findings are negative and tissue sampling is not warranted (**FIGURE 1, VIDEO 2**).

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The author reports being a consultant to Karl Storz Endoscopy and having a current financial relationship with Minerva Surgical.

Efforts in hysteroscopic classification of endometrial carcinoma

Lesion morphologic characteristics. Sugimoto was among the first to describe the hysteroscopic identification of visual morphologic features that are most likely to be associated with endometrial carcinoma.[1] Patients with AUB were evaluated with hysteroscopy as first-line management

to describe lesion morphology and confirm biopsy with histopathology. Sugimoto classified endometrial carcinoma as circumscribed or exophytic with distinct forms, such as polypoid, nodular, papillary, and ulcerated (**FIGURE 2**). Diffuse or endophytic carcinoma is defined by an ulcerated type of lesion that indicates necrosis; this is most likely to represent an undifferentiated tumor. Sugimoto also described abnormal vascularity that often is associated with carcinoma.[1]

Endometrial features. Valli and Zupi created a nomenclature and classification for hysteroscopic endometrial lesions by prospectively grading 4 features: thickness, surface, vascularization, and color.[3] Features were scored based on the degree of abnormality and could be considered to be of low or high risk for the presence of carcinoma. High-risk hysteroscopic features included endometrial thickness greater than 10 mm, polymorphous surface, irregular vascularization, and white-grayish color. The sensitivity for accurately diagnosing endometrial lesions was 86.9% for mild lesions and 96% for severe lesions.[3] Also, these investigators confirmed the clinical value of the NHV and associated overall risk of precancer or cancer of the endometrium.

Amount of endometrial involvement. A few years later, Garuti and colleagues retrospectively related the hysteroscopic tumor features of known endometrial adenocarcinoma to stage, grade, and overall survival.[4] In this system, they focused on classification of tumor morphology as nodular (bulging), polypoid (thin pedicles), or papillary (numerous dendritic projections), as well as whether the amount of abnormal tissue present was less than or more than half of the endometrium and if the lesion involved the cervix.

Several important findings associated with this system may improve visual diagnosis. First, hysteroscopic evaluation had a 100% negative predictive value for the cervical spread of disease (**FIGURE 3, VIDEO 3**). Second, the hysteroscopic morphologic tumor type did not relate to surgical stage or pathologic grade. Third, when less than half of the endometrium was involved, stage I disease was found (97%, 33 of 34). Last, when more than half of the endometrium was involved, advanced disease beyond stage I was found (9 of 26, 6 of whom had poorly differentiated disease).[4]

Structured pattern analysis. Recently, Dueholm and co-investigators published a prospective evaluation of women with postmenopausal bleeding and an endometrial thickness of 5 mm or greater.[5] They used a structured system of visual pattern analysis during hysteroscopy that they termed the

TABLE 1 Negative hysteroscopic view (NHV) indicates likelihood of a normal uterine cavity and normal endometrium[a,2,3,6]

Criteria for NHV
• Good visualization of the entire uterine cavity
• No structural abnormalities of the cavity
• Uniformly thin, homogeneous-appearing endometrium without variations in thickness (early proliferative phase or in postmenopausal patients)

[a]Tissue sampling is not recommended with NHV.

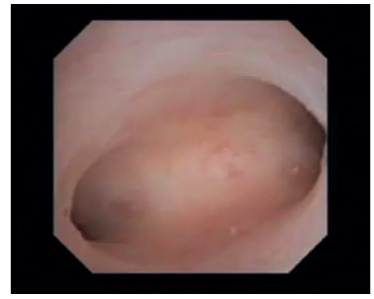

FIGURE 1 Negative hysteroscope view in a premenopausal woman
Image courtesy of Amy Garcia, MD.

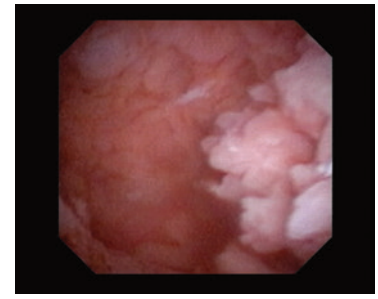

FIGURE 2 Papillary projections of adenocarcinoma
Image courtesy of Amy Garcia, MD.

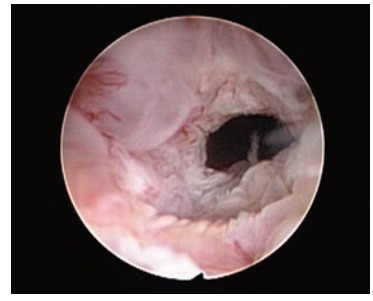

FIGURE 3 Adenocarcinoma with spread to the upper cervical canal near the internal os
Image courtesy of Amy Garcia, MD.

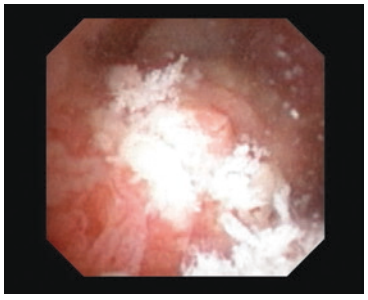

FIGURE 4 Cotton candy endometrium likely representing tissue necrosis
Image courtesy of Amy Garcia, MD.

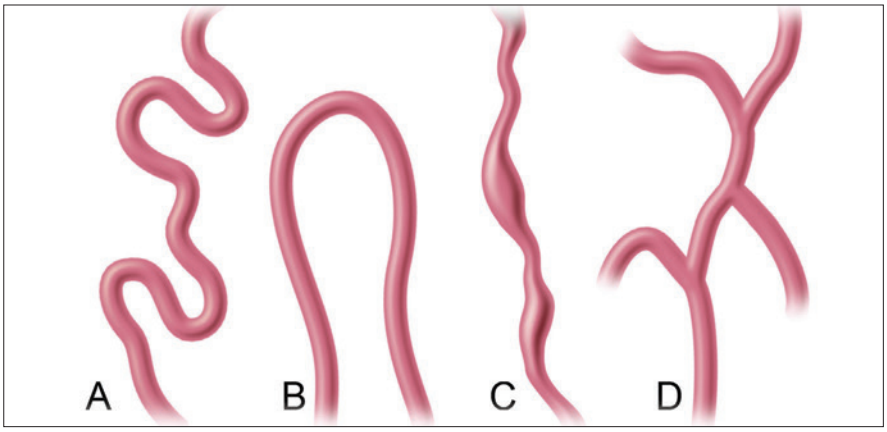

FIGURE 5 Hysteroscopic morphologic abnormal vessels of endometrial carcinoma (**A**) S-shaped; serpiginous. (**B**) Loop. (**C**) Irregular diameter. (**D**) Irregular branching.

hysteroscopic cancer (HYCA) scoring system. The HYCA scoring system is based on surface outline (uneven, polypoid, and papillary projections), necrosis (cotton candy endometrium [**FIGURE 4**], whitish-grayish areas without vessels on the surface), and vessel pattern (tortuous S-shaped, loops, irregular caliber, irregular branching, and irregular distribution [**FIGURE 5**]). Structured pattern analysis predicted cancer with higher accuracy than subjective evaluation.[5]

Morphologic variables as indicators. In 2016, Ianieri and colleagues published a retrospective study on a risk scoring system for diagnosing endometrial hyperplasia and adenocarcinoma via hysteroscopy.[6] They created a statistical risk model for development of the scoring system. A number of morphologic variables were prognostic indicators of atypical endometrial hyperplasia (AEH) and adenocarcinoma. These included widespread and irregular endometrial thickness, presence of multiple polyps with irregular aspects, dilated glandular orifices, irregular endometrial color (grey, white, or hyperemic), atypical vessels, crumbling of the endometrial neoplasms, and growth of cerebroid and arborescent aspects (**VIDEO 4**).

The scoring system for endometrial adenocarcinoma correctly classified 42 of 44 cancers (sensitivity, 95.4%; specificity, 98.2%), and AEH had a sensitivity of 63.3% and a specificity of 90.4%.[6] These investigators also showed a high negative predictive value of 99.5% for endometrial adenocarcinoma associated with a negative view at hysteroscopy. Similar to the Dueholm data, Ianieri and colleagues' morphologic pattern analysis predicted cancer with high accuracy.

Glomerular pattern association. Su and colleagues also showed that pattern recognition could aid in the accurate hysteroscopic diagnosis of endometrial adenocarcinoma.[7] They used the hysteroscopic presence of a glomerular pattern to predict the association with endometrial adenocarcinoma. A glomerular pattern was described as polypoid endometrium with a papillary-like feature, containing an abnormal neovascularization feature with "intertwined neovascular vessels covered by a thin layer of endometrial tissue" (**FIGURE 6,** page 40). The presence of a glomerular pattern indicated grade 2 or grade 3 disease in 25 of 26 women (96%; sensitivity, 84.6%, specificity, 81.8%)[7] (see video 4).

TABLE 2 summarizes significant morphologic findings relating to the presences of endometrial carcinoma.

Atypical endometrial hyperplasia: A difficult diagnosis

The most common type of endometrial cancer is endometrioid adenocarcinoma (type 1 endometrial carcinoma), and it accounts for

ILLUSTRATION: MARCIA HARTSOCK FOR OBG MANAGEMENT

TABLE 2 **Significant hysteroscopic morphologic findings relating to the presence of endometrial carcinoma or severity of disease**[1-7,9]

Authors	Hysteroscopic morphology associated with endometrial carcinoma
Sugimoto, 1975[1]	• Circumscribed (exophytic) —polypoid, nodular, papillary, ulcerated • Diffuse (endophytic) —ulcerated • Irregular vascularization
Loffer, 1989[2]	• NHV: —good visualization of the entire uterine cavity —no structural abnormalities of the cavity, and —uniformly thin, homogeneous-appearing endometrium without variations in thickness • NHV is predictive of normal endometrium
Valli and Zupi, 1995[3]	• Grading of 4 features: —thickness, surface, vascularization, and color • High-risk lesions: —endometrial thickness > 10 mm, polymorphous surface, irregular vascularization, and white-grayish color • Confirmed value of NHV
Garutti et al, 2001[4]	• Nodular, polypoid, or papillary lesion not associated with surgical stage or grade • 100% NPV for cervical spread • Less than half of endometrium involvement is more likely stage I disease • More than half of endometrium involvement is more likely stage II or III disease
Dueholm et al, 2015[5]	• Endometrial surface: —uneven surface texture pattern, polypoid surface, irregular surface, papillary projections • Necrosis: —cotton candy endometrium, whitish-grayish areas without vessels on the surface of a lesion • Vessel pattern: —irregular vessel pattern (tortuous S-formed, loops), irregular caliber, irregular branching, irregular distribution • Endometrial glands: —dilated glands and glands with irregular openings
Ianieri et al, 2016[6]	• Prognostic indicators: —widespread and irregular endometrial thickness —presence of multiple polyps with irregular aspects —dilated glandular orifices —irregular endometrial color (grey, white, hyperemic) —atypical vessels —crumbling of the endometrial neoplasms —growth of cerebroid and arborescent aspects • Confirmed value of NHV
Su et al, 2016[7]	• A glomerular pattern associated with grade 2 or grade 3 disease
De Franciscis et al, 2019[9]	• AEH: —focal or diffuse —papillary or polypoid —endometrial thickening —abnormal vascular patterns —evidence of glandular cysts —abnormal architecture features of the glandular outlets (thickening, irregular gland density, dilatation)

Abbreviations: AEH, atypical endometrial hyperplasia; NHV, negative hysteroscopic view; NPV, negative predictive value.

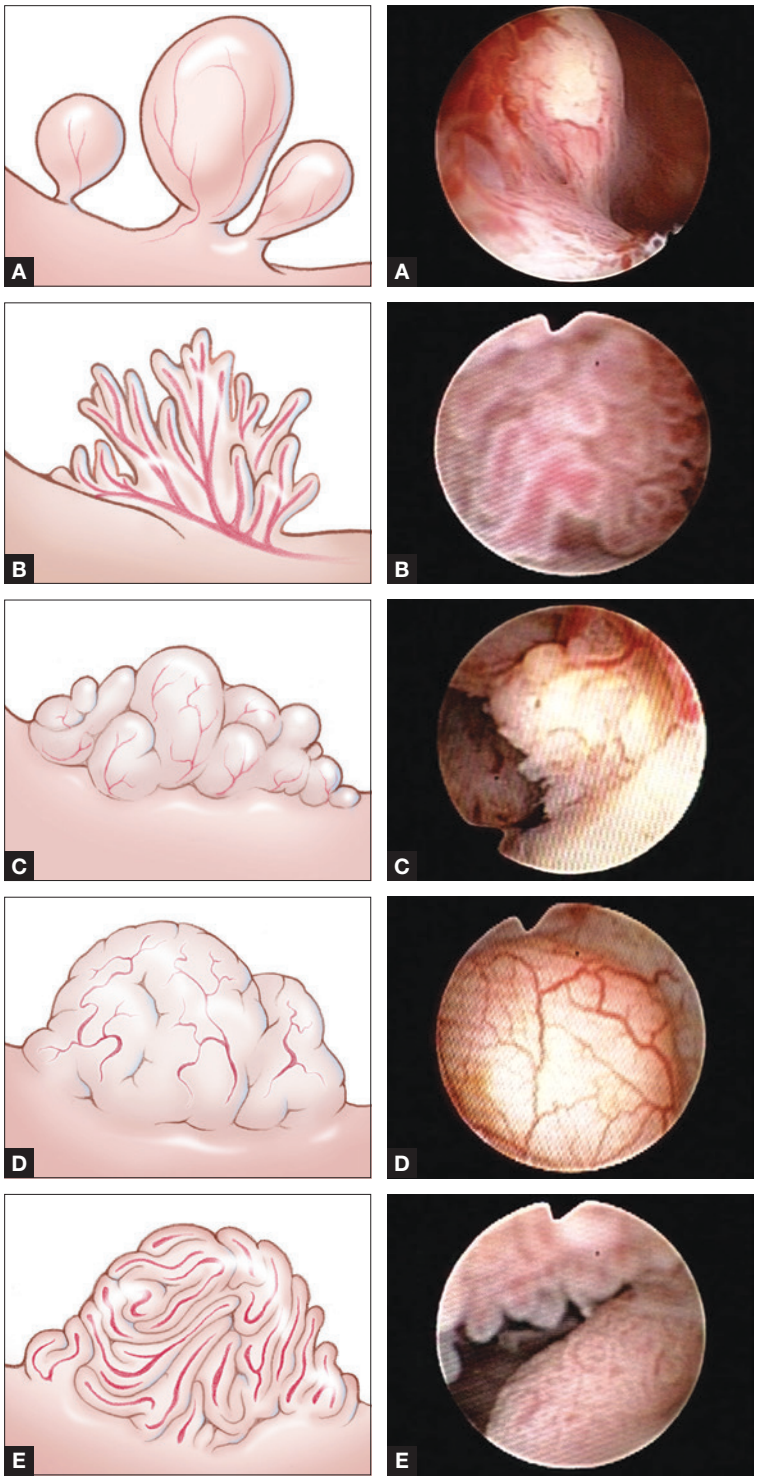

FIGURE 6 Hysteroscopic morphologic features of endometrial carcinoma (**A**) Polypoid; thin pedicles. (**B**) Papillary; numerous dendritic projections. (**C**) Nodular; bulging. (**D**) Cerebroid; nodular or polypoid with abnormal surface vessels. (**E**) Glomerular; polypoid with a papillary-like feature containing intertwined neovascular vessels covered by a thin layer of endometrial tissue. *Images courtesy of Amy Garcia, MD.*

approximately 75% to 80% of endometrial cancer diagnoses.[8] Risk factors include prolonged unopposed estrogen exposure, obesity, diabetes, and age. Type 1 endometrial carcinoma follows a progressive continuum of histopathologic change: from endometrial hyperplasia without atypia to endometrial hyperplasia with atypia (AEH) to well-differentiated endometrial cancer. Therefore, it is possible for endometrial carcinoma to be present simultaneously with AEH. The reported prevalence of concurrent endometrial carcinoma among patients with AEH on biopsy is between 17% and 52%.[8] Thus, the clinical consideration is for hysterectomy, especially in the postmenopausal patient with a diagnosis of AEH.

Hysteroscopic diagnosis of AEH, however, is more difficult than identification of endometrial carcinoma because a range of morphologic characteristics exist that resemble normal endometrium as well as more progressive disease (**VIDEO 5**). De Franciscis and colleagues based a hysteroscopic diagnosis of hyperplasia on one or more of the following findings: focal or diffuse, papillary or polypoid, endometrial thickening; abnormal vascular patterns; evidence of glandular cysts; and abnormal architecture features of the glandular outlets (thickening, irregular gland density, or dilatation)[9] (**VIDEO 6**).

Additional studies, including that from Ianieri and colleagues, also have determined that AEH is difficult to discern visually from normal endometrium and other endometrial pathologies.[6] In another investigation, Lasmar and coauthors reported a retrospective analysis of 4,054 hysteroscopic procedures with directed biopsies evaluating for concordance between the hysteroscopic view and histopathology.[10] Agreement was 56.3% for AEH versus 94% for endometrial carcinoma. Among those with a histologic diagnosis of AEH, in 35.4% benign disease was suspected; in 2.1%, endometrial carcinoma was suspected; and in 6%, normal findings were presumed.[10]

Because of the similarities in morphologic features between AEH and endometrial carcinoma, tissue biopsy under direct

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Don't miss the videos that accompany this article

Access them in the article online at mdedge.com/obgyn

Video 1. Endometrial carcinoma and visually directed biopsy

Nodular endometrioid adenocarcinoma grade 1 (type 1 endometrial carcinoma), benign endometrial polyps, and endometrial atrophy in a postmenopausal woman with bleeding. This video demonstrates visually directed biopsy to assure sampling of the most significant lesion.

Video 2. Negative hysteroscopic view

Digital flexible diagnostic hysteroscopy showing a negative hysteroscopic view in a premenopausal woman.

Video 3. Cervical spread of adenocarcinoma and visually directed biopsy

Diffuse endometrioid adenocarcinoma spread to the upper cervical canal near the internal cervical os. Hysteroscopic directed biopsy is performed.

Video 4. Endometrial adenocarcinoma

Fiberoptic flexible diagnostic hysteroscopy demonstrating diffuse endometrioid adenocarcinoma grade 3 with multiple morphologic features: polypoid, nodular, papillary, and glomerular with areas of necrosis.

Video 5. Endometrial polyp and atypical hyperplasia

Large benign endometrial polyp in an asymptomatic postmenopausal woman with enlarged endometrial stripe on pelvic ultrasound. The endometrium is atrophic except for a small whitish area on the anterior wall, which is atypical hyperplasia. This video highlights the need for visually directed biopsy to assure sampling of the most significant lesion.

Video 6. Nodular, polypoid atypical hyperplasia

Fiberoptic flexible diagnostic hysteroscopy showing diffuse nodular and polypoid atypical hyperplasia with abnormal glandular openings in a postmenopausal woman. Hysterectomy was performed secondary to the significant likelihood of concomitant endometrial carcinoma.

Video 7. Visually directed endometrial biopsy

Hysteroscopic-directed biopsy showing the technique of grasping and removing tissue of a benign adenomyosis cyst and proliferative endometrium.

Video 8. Carcinosarcoma

Carcinosarcoma (type 2 endometrial carcinoma) presents as a large intracavitary mass with soft, polypoid-like tissue in a symptomatic postmenopausal woman with bleeding.

Video 9. Carcinosarcoma

Carcinosarcoma (type 2 endometrial carcinoma) presents as a dense mass in a symptomatic postmenopausal woman with bleeding. This video shows the mass is nodular. These cancers typically grow into a spherical mass within the cavity.

visualization is warranted to assure sampling of the most significantly abnormal tissue and to confirm visual interpretation of findings.

Techniques for hysteroscopic-directed biopsy

Using a visual assessment of endometrial abnormalities allows the surgeon to examine the entire uterine cavity and to biopsy the most suspicious and concerning lesions. The directed biopsy technique can involve a simple grasping maneuver: With the jaws of a small grasper open, push slightly forward to accumulate tissue within the jaw, close the jaw, and remove the tissue carefully through the cervix (**VIDEO 7**). The size of the sample may be limited, and multiple samples may be needed, depending on the quantity of the tissue retrieved.

Another technique involves first creating a plane of tissue to be removed with scissors

and subsequently grasping and removing the tissue (see video 1 and video 3). This particular technique will yield more tissue with one pass of the hysteroscope into the cavity. Careful removal of tissue through the cervix is facilitated by withdrawing the sample in the grasper and the hysteroscope together at the same time, without pulling the sample through the operative channel of the hysteroscope. Also, by turning off the inflow port, the stream of saline does not wash the sample off the grasper at hysteroscope removal from the cervix.

Blind biopsy. If visual inspection reveals a diffuse process within the uterine cavity such that no normal endometrium is noted and the abnormality is of equal degree throughout the endometrial surface, a decision can be made to replace directed biopsy with a blind biopsy. In this scenario, the blind biopsy is certain to sample the representative disease process and not potentially miss significant lesions (see video 4 and video 6). Otherwise, the hysteroscope-directed biopsy would be preferable.

FAST TRACK

If visual inspection reveals a diffuse process within the uterine cavity such that no normal endometrium is noted and the abnormality is of equal degree throughout, a decision can be made to replace directed biopsy with blind biopsy

Potential for intraperitoneal dissemination of endometrial cancer

There is some concern about intraperitoneal dissemination of endometrial carcinoma at the time of hysteroscopy and effect on disease prognosis. Chang and colleagues conducted a large meta-analysis and found that hysteroscopy performed in the presence of type 1 endometrial carcinoma statistically significantly increased the likelihood of positive intraperitoneal cytology.[11] In the included studies that reported survival rates (6 of 19), positive cytology did not alter the clinical outcome. The investigators recommended that hysteroscopy not be avoided for this reason, as it helps in the diagnosis of endometrial carcinoma, especially in the early stages of disease.[11]

In a recent retrospective analysis, Namazov and colleagues included only stage I endometrial carcinoma (to exclude the adverse effect of advanced stage on survival) and evaluated the assumed isolated effect of hysteroscopy on survival.[12] They compared women in whom stage I endometrial carcinoma was diagnosed: 355 by hysteroscopy and 969 by a nonhysteroscopy method (D&C or office endometrial biopsy). Tumors were classified and grouped as low grade (endometrioid grade 1-2 and villoglandular) and high grade, consisting of endometrioid grade 3 and type 2 endometrial carcinoma (serous carcinoma, clear cell carcinoma, and carcinosarcoma) (**VIDEOS 8 AND 9**). Positive intraperitoneal cytology at the time of surgery was 2.3% and 2.1% (P = .832), with an average interval from diagnosis to surgery of 34.6 days (range, 7–43 days).

The authors proposed several explanations for the low rate of intraperitoneal cytology with hysteroscopy. One possibility is having lower mean intrauterine pressure below 100 mm Hg for saline uterine distension, although this was not standardized for all surgeons in the study but rather was a custom of the institution. In addition, the length of time between hysteroscopy and surgery may allow the immune-reactive peritoneum to respond to the cellular insult, thus decreasing the biologic burden at the time of surgery. The median follow-up was 52 months (range, 12–120 months), and there were no differences between the hysteroscopy and the nonhysteroscopy groups in the 5-year recurrence-free survival (90.2% vs 88.2%; P = .53), disease-specific survival (93.4% vs 91.7%; P = .5), and overall survival (86.2% vs 80.6%; P = .22). The authors concluded that hysteroscopy does not compromise the survival of patients with early-stage endometrial cancer.[12]

Retrospective data from Chen and colleagues regarding type 2 endometrial carcinoma indicated a statistically significant increase in positive intraperitoneal cytology for carcinomas evaluated by hysteroscopy versus D&C (30% vs 12%; P = .008).[13] Among the patients who died, there was no difference in disease-specific survival (53 months for hysteroscopy and 63.5 months for D&C; P = .34), and there was no difference in overall recurrence rates.[13] Compared with type 1 endometrial

carcinoma, type 2 endometrial carcinoma behaves more aggressively, with a higher incidence of extrauterine disease and an increased propensity for recurrence and poor outcome even in the early stages of the disease. This makes it difficult to determine the role of hysteroscopy in the prognosis of these carcinomas, especially in this study where most patients were diagnosed at a later stage.

Key takeaways

Hysteroscopy and directed biopsy are highly effective for visual and histopathologic diagnosis of atypical endometrial hyperplasia and endometrial carcinoma, and they are recommended in the evaluation of AUB, especially in the postmenopausal woman. When the hysteroscopic view is negative, there is a high correlation with the absence of uterine cavity and endometrial pathology. Hysteroscopic diagnostic accuracy is improved with structured use of visual grading scales, well-defined descriptors of endometrial pathology, and hysteroscopist experience.

Low operating intrauterine pressure may decrease the intraperitoneal spread of carcinoma cells during hysteroscopy, and current evidence suggests that there is no change in type 1 endometrial carcinoma prognosis and overall outcomes. Type 2 endometrial carcinoma is more aggressive and is associated with poor outcomes even in early stages, and the effect on disease progression by intraperitoneal spread of carcinoma cells at hysteroscopy is not yet known. Hysteroscopic evaluation of the uterine cavity and directed biopsy is easily and safely performed in the office and adds significantly to the evaluation and management of endometrial carcinoma. ●

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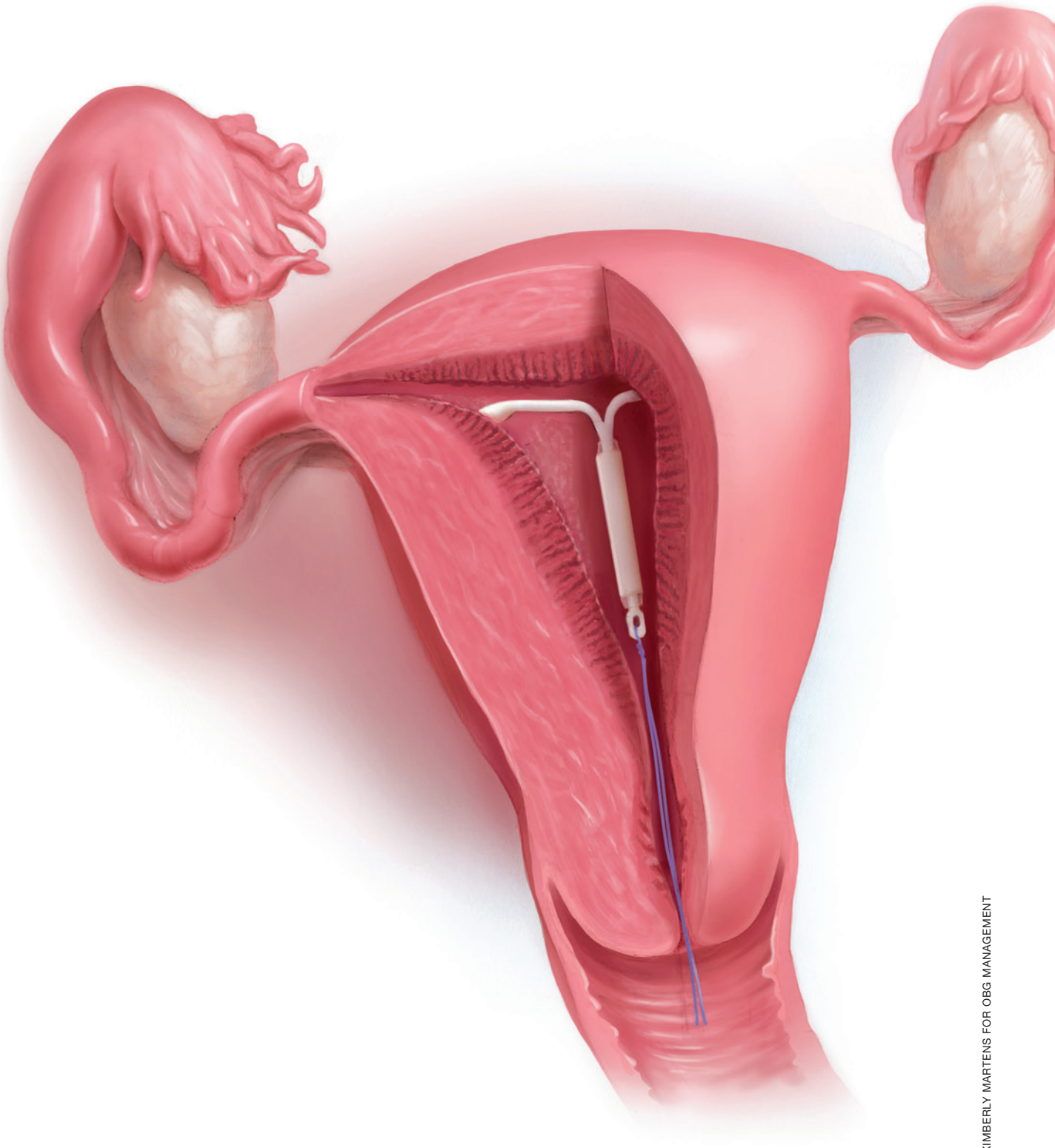

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

BREAK THIS PRACTICE HABIT

The IUD string check: Benefit or burden?

Routine office visits and patient self-checks for IUD strings are unsupported by data and are costly—it is time to discontinue them

Kathryn Fay, MD, and Lori Gawron, MD, MPH

CASE Patient experiences unnessary inconvenience, distress, and cost following IUD placement

Ms. J had a levonorgestrel intrauterine device (IUD) placed at her postpartum visit. Her physician asked her to return for a string check in 4 to 6 weeks. She was dismayed at the prospect of re-presenting for care, as she is losing the Medicaid coverage that paid for her pregnancy care. One month later, she arranged for a babysitter so she could obtain the recommended string check. The physician told her the strings seemed longer than expected and ordered ultrasonography. Ms. J is distressed because of the mounting cost of care but is anxious to ensure that the IUD will prevent future pregnancy.

Should the routine IUD string check be reconsidered?

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The string check dissension

Intrauterine devices offer reliable contraception with a high rate of satisfaction and a remarkably low rate of complications.[1-3] With the increased uptake of IUDs, the value of "string checks" is being debated, with myriad responses from professional groups, manufacturers, and individual clinicians. For many practicing ObGyns, the question remains: Should patients be counseled about presenting for or doing their own IUD string checks?

Indeed, all IUD manufacturers recommend monthly self-examination to evaluate string presence.[4-8] Manufacturers' websites prominently display this information in material directed toward current or potential users, so many patients may be familiar already with this recommendation before their clinician visit. Yet, the Centers for Disease Control and Prevention state that no routine follow-up or monitoring is needed.[9]

In our case scenario, follow-up is clearly burdensome and ultimately costly. Instead, clinicians can advise patients to return with rare but important to recognize complications (such as perforation, expulsion, infection), adverse effects, or desire for change. While no data are available to support in-office or at-home string checks, data do show that women reliably present when intervention is needed.

Here, we explore 5 questions relevant to IUD string checks and discuss why it is time to rethink this practice habit.

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FAST TRACK

A less than 0.1% risk of a non–life-threatening complication—unnoticed expulsion—does not warrant routine follow-up

What is the purpose of a string check?

String checks serve as a surrogate for assessing an IUD's position and function. A string check can be performed by a clinician, who observes the IUD strings on speculum exam or palpates the strings on bimanual exam, or by the patient doing a self-exam. A positive string check assures both the IUD user and the health care provider that an IUD remains in a fundal, intrauterine position, thus providing an ongoing reliable contraceptive effect.

However, string check reliability in detecting contraceptive effectiveness is uncertain. Strings that subjectively feel or appear longer than anticipated can lead to unnecessary additional evaluation and emotional distress: These are harms. By contrast, when an expulsion occurs, it often is a partial expulsion or displacement, with unclear effect on patient or physician perception of the strings on examination. One retrospective review identified women with a history of IUD placement and a positive pregnancy test; those with an intrauterine pregnancy (74%) frequently also had a malpositioned IUD (55%) and rarely identifiable string issues (16%).[10] Before asking patients and clinicians to use resources for performing string evaluations, the association between this action and outcomes of interest must be elucidated.

If not for assessing risk of expulsion, IUD follow-up allows the clinician to evaluate for other complications or adverse effects and to address patient concerns. This practice often is performed when the patient is starting a new medication or medical intervention. However, a systematic review involving 4 studies of IUD follow-up visits or phone calls after contraceptive initiation generated limited data, with no notable impact on contraceptive continuation or correct use.[11]

Most important, data show that patients present to their clinician when issues arise with IUD use. One prospective study of 280 women compared multiple follow-up visits with a single 6-week follow-up visit after IUD placement; 10 expulsions were identified, and 8 of these were noted at unscheduled visits when patients presented with symptoms.[12] This study suggests that there is little benefit in scheduled follow-up or set self-checks.

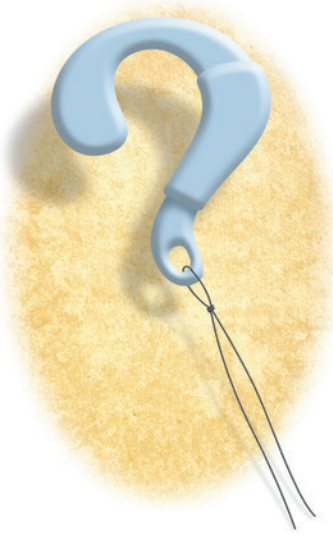
Furthermore, in a study in Finland of more than 17,000 IUD users, the rare participants who became pregnant during IUD use promptly presented for care because of a change in menses, pain, or symptoms of pregnancy.[13] While IUDs are touted as user independent, this overlooks the reality: Data show that device failure, although rare, is rapidly and appropriately addressed by the user.

Does the risk of IUD expulsion warrant string checks?

The risk of IUD expulsion is estimated to be 1% at 1 month and 4% at 1 year, with a contraceptive failure rate of 0.4% at 1 year. The risk of expulsion does not differ by age group, including adolescents, or parity, but it is higher with use of the copper IUD (2% at 1 month, 6% at 1 year) and with prior expulsion (14%, limited by small numbers).[1] Furthermore, risk of expulsion is higher with postplacental placement and second trimester abortion.[14,15] Despite this risk, the contraceptive failure rate of all types of IUDs remains consistently lower than all other reversible methods besides the contraceptive implant.[16]

Furthermore, while IUD expulsion is rare, unnoticed expulsion is even more rare. In one study with more than 58,000 person-years of use, 132 pregnancies were noted, and 7 of these occurred in the setting of an unnoticed expulsion.[13] Notably, a higher risk threshold is held for other medications. For example, statins are associated with a 3% risk of irreversible hepatic injury, yet serial liver function tests are not performed in patients without baseline liver dysfunction.[17] A less than 0.1% risk of a non–life-threatening complication—unnoticed expulsion—does not warrant routine follow-up. Instead, the patient gauges the tolerability of that risk in making a follow-up plan, particularly given the varied individual preferences in patients' management of the associated outcome of unintended pregnancy.

Are women interested in and able to perform their own string checks?



Recommendations to perform IUD string self-checks should consider whether women are willing and able to do so. In a study of 126 IUD users, 59% of women had attempted to check their IUD string at home, and one-third were unable to do so successfully; all participants had visible strings on subsequent speculum exam.[18] The women also were given the opportunity to perform a string self-check at the study visit. Overall, only 46% of participants found the exercise acceptable and were able to palpate the IUD strings.[18] The authors aptly stated, "A universal recommendation for practice that is meant to identify a rare complication has no clinical utility if at least half of the women are unable to follow it."

In which scenarios might a string check have clear utility?

The most important reason for follow-up after IUD placement or for patients to perform string self-checks is patient preference. At least anecdotally, some patients take comfort, particularly in the absence of menses, in palpating IUD strings regularly; these individuals should know that there is no necessity for but also no harm in this practice. In addition, patients may desire a string check or follow-up visit to discuss their new contraceptive's goodness-of-fit.

While limited data show that routinely scheduling such visits does not improve contraceptive continuation, it is difficult to extrapolate these data to the select individuals who independently desire follow-up. (In addition, contraceptive continuance is hardly a metric of success, as clinicians and patients can agree that discontinuation in the setting of patient dissatisfaction is always appropriate.)

Clinicians should share with patients differing risks of IUD expulsion, and this may prompt more nuanced decisions about string checks and/or follow-up. Patients with postplacental or postabortion (second trimester) IUD placement or placement following prior expulsion may opt to perform string checks given the relatively higher risk of expulsion despite the maintained, absolutely low risk that such an event is unnoticed.

If a patient does present for a string check and strings are not visualized on exam, reasonable attempts should be made to identify the strings at that time. A cytobrush can be used to liberate and identify strings within the cervical canal. If the clinician cannot identify the strings or the patient is unable to tolerate such attempts, ultrasonography should be performed to localize the IUD. The ultrasound scan can be done in the office, if available, which is more cost-effective for women than a referral to radiology. If ultrasonography does not identify an intrauterine IUD, an x-ray is the next step to determine if the IUD has expulsed or perforated.

Is a string check worth the cost?

Health care providers may not be aware of the cost of care from the patient perspective. While the Affordable Care Act of 2010 mandates contraception coverage for women with insurance, a string check often is coded as a problem-based visit and thus may require a significant copay or out-of-pocket cost for high-deductible plans—without a proven benefit.[19] Women who lack insurance coverage may forgo even necessary care due to the cost.[20]

The bottom line

The medical community and ObGyns specifically are familiar with a practice of patient self-examination falling by the wayside, as has been seen with breast self-examination.[21] While counseling on string checks can complement conversations about risks and patients' personal preferences regarding follow-up, no

FAST TRACK

The most important reason for follow-up after IUD placement or for patients to perform string self-checks is patient preference

ILLUSTRATION: JOHN J. DENAPOLI

data support routine string checks in the clinic or at home. One of the great benefits of IUD use is its lack of barriers and resources for ongoing use. Physicians need not reintroduce burdens without benefits to those who desire this contraception method. ●

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Daily calorie intake requirements during pregnancy: Does one size fit all?

Women with obesity can maintain their daily calorie intake during pregnancy, according to the results of a prospective observational study of 54 pregnant women with obesity. For women with obesity who gained the recommended 11 to 20 lb during pregnancy, mean (SD) daily energy intake was 2,698 (99) kcal/day and energy expenditure was 2,824 (105) kcal/day. Therefore, to meet the recommended amount of weight gain, women had a negative energy balance (-125 [52] kcal/day).

Most J, St Amant M, Hsia DS, et al. Evidence-based recommendations for energy intake in pregnant women with obesity. J Clin Invest. 2019;129:4682-4690.

EXPERT COMMENTARY
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In 2009, the Institute of Medicine, now known as the National Academy of Medicine, updated its gestational weight gain guideline. This guideline's major difference, compared with the 1990 guideline, is a specific weight gain range for women with obesity: 5 to 9 kg, or 11 to 20 lb.[1] This weight gain range was chosen in part because it allows for a minimum weight gain that supports the growth and development of tissues (fetus, placenta, breast, uterus) and fluids (blood volume, intracellular and extracellular fluid), also known as the "fat-free" mass.

Many studies have since shown not only associations between lower-than-guideline-recommended weight gain and improved pregnancy outcomes (for example, reductions in preeclampsia and cesarean deliveries), but also increases in low birth weight for infants of women with obesity.[2,3] Although the weight gain guideline differs based on a woman's prepregnancy body mass index, the energy requirements, or how many additional calories a woman should consume daily, are the same for all, regardless of weight prior to pregnancy: an increase by 340 to 452 kcal/day in the second and third trimesters.[1]

Recently, Most and colleagues challenged this recommendation for energy requirements with results from their prospective observational study of 54 women with obesity during pregnancy.[4] They aimed to evaluate energy intake with the energy intake-balance method (doubly labeled water and whole-room indirect calorimetry and body composition) according to tests done at 13 to 16 weeks' gestation and 35 to 37 weeks' gestation and according to the current National Academy of Medicine gestational weight gain guideline (inadequate, recommended, or excessive weight gain groups).[4]

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The 2009 guideline weight gain range (11-20 lb) was chosen in part because it allows for a minimum weight gain that supports the growth and development of tissues and fluids, also known as the "fat-free" mass

The author reports no financial relationships relevant to this article.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Most and colleagues' data suggest that maintaining energy balance can support obligatory growth and development of women and their fetuses during pregnancy (fat-free mass). In doing so, women with obesity meet the current gestational weight gain guideline. It is hoped that this important research will be used in future studies, with larger sample sizes, to evaluate energy requirements during pregnancy, especially in women with different classes of obesity. Ultimately, these new recommendations for energy requirements should be combined with studies of health behavior interventions for gestational weight gain.

The study by Most and colleagues supports the concept that energy requirements need to be individualized for women to meet the recommended amount of gestational weight gain. If women meet their gestational weight gain goals, they have the potential to improve their health and the health of their offspring.

MICHELLE A. KOMINIAREK, MD, MS

Details of the study

Women who participated in this study were recruited from the Pennington Biomedical Research Center in Louisiana and were mostly multiparas (57%); about half had a college degree or higher (52%) and 41% were African American. The investigators found that gestational weight gain in their participants was similar to that found in other large epidemiologic studies in that 67% of women had excessive gestational weight gain.[5]

Findings. For women who gained the recommended amount of weight (n = 8), mean (SD) daily energy intake was 2,698 (99) kcal/day and energy expenditure was 2,824 (105) kcal/day. Therefore, to meet the recommended amount of weight gain, these women had a negative energy balance (-125 [52] kcal/day). Women with inadequate weight gain (n = 10) also had a negative energy balance (-262 [32] kcal/day), but the difference was not significantly different compared with that in the recommended gestational weight gain group ($P = .08$). By contrast, women with excessive gestational weight gain (n = 36) had a mean (SD) positive energy balance of 186 (29) kcal/day.

Fat-free mass and fat mass weight gains. The body weight gains of the fat-free and fat mass compartments also were compared with linear mixed effect models among the 3 weight gain groups. There were no differences in the amount of fat-free mass gained among the 3 weight gain groups ($P>.05$), but women with excessive gestational weight gain had significantly higher increases in fat mass compared with the other 2 weight gain groups ($P<.001$).

Pregnancy outcomes. Although there were no differences in cesarean deliveries or birth weight among the 3 weight gain groups, the study was not powered to detect these differences.

Study strengths and limitations

It is important to note that this study by Most and colleagues was not a health behavior intervention for gestational weight gain. Women who participated in the study did not receive specific directions or advice on diet or physical activity. Furthermore, the study used the current gestational weight gain guideline as a reference to determine energy intake. As such, findings from this study alone cannot be used to adapt the current gestational weight gain guideline for women with obesity.

The study methods were rigorous in terms of the energy intake measurements, but a larger and more diverse sample size is needed to confirm the study findings. ●

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