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OBG MANAGEMENT

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Society of Gynecologic Surgeons Annual Meeting Highlights Issue

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Hysteroscopy and COVID-19

Have recommended techniques changed?

Laura Florez, MD; Jose Carugno, MD

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Safeguarding outpatient practices against COVID-19

Mifepristone restrictions lifted during COVID-19

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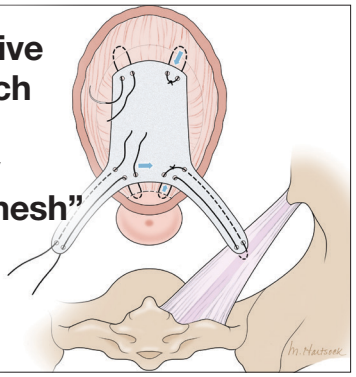
Innovative approach to POP surgery "post-mesh"

p. SS3



*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

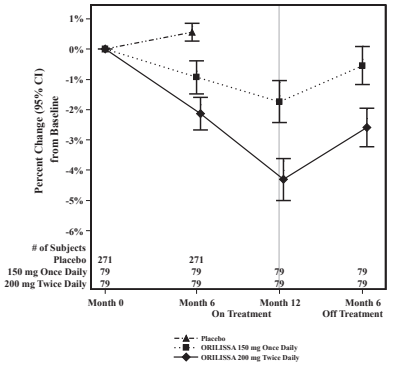
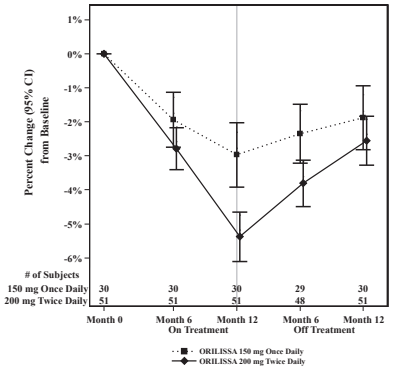


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



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

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

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

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

Hepatic Transaminase Elevations

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

Changes in Lipid Parameters

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

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

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

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

Hypersensitivity Reactions

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

Endometrial Effects

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

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

Effects on menstrual bleeding patterns

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

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

	ORILISSA 150mg Once Daily		ORILISSA 200mg Twice Daily		Placebo	
	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.

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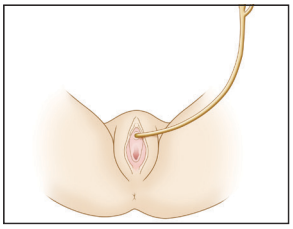
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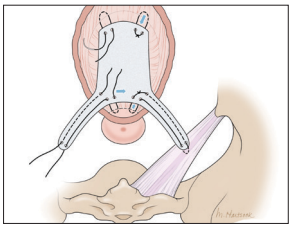
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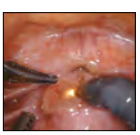

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Major changes in Medicare billing are planned for January 2021: Some specialties fare better than others

The changes decrease Medicare payments for procedural services but increase valuation of office-based services

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The Centers for Medicare and Medicaid Services (CMS) finalized an increase in the relative value of evaluation and management (E/M) service codes effective January 1, 2021, which results in an overall decrease in the payment for procedural services in the Medicare program. (Due to the mandate for budget neutrality, an increase in relative value units [RVUs] for E/M resulted in a large decrease in the conversion factor—the number of dollars per RVU). This has increased payments for endocrinologists, rheumatologists, and family medicine clinicians and decreased payments for radiologists, pathologists, and surgeons.

In a major win for physicians, CMS proposes to simplify documentation requirements for billing and focus on the complexity of the medical decision making (MDM) or the total time needed to care for the patient on the date of the service as the foundation for determining the relative value of the service. Therefore, there is **no more counting bullets**—ie, we don't have to perform a comprehensive physical exam or review of systems to achieve a high level code! Prior to this change, time was only available for coding purposes when counseling and coordination of care was the predominant service (>50%), and only face-to-face time with the patient was considered. Effective January 1, for office and other outpatient services, **total** time on the calendar date of the encounter will be used. This acknowledges the intensity and value of non–face-to-face work.

Acting through CMS, the federal government influences greatly the US health care system. CMS is an agency in the Department of Health and Human Services that administers the Medicare program and partners with state governments to administer the Health Insurance Exchanges, Medicaid, and the Children's Health Insurance programs (CHIP).[1] In addition, CMS is responsible for enforcing quality care standards in long-term care facilities and clinical laboratories and the implementation of the Health Insurance Portability and Accountability Act.[1]

In January, CMS plans the following major changes to coding and documentation[2,3]:

1. Selection of the level of E/M service will no longer require documentation of bullet points in the history, physical exam, and MDM. The simplified system allows physicians and qualified health care professionals to code either by total time (both face-to-face and non–face-to-face) on the date of the encounter or by level of MDM.
2. For established office patients, 5 levels of office-based evaluation and management services will be retained. CMS had initially proposed to reduce the number of office-based E/M codes from 5 to 3, combining code levels 2, 3, and 4 into 1 code.[4] However, after receiving feedback from professional societies and the public, CMS abandoned the plan for radical simplification of coding levels.[2,3] Implementation of their proposal would have resulted in the same payment for treatment of a hang nail as for a complex gyn patient with multiple medical problems. Both patient advocacy groups and professional societies argued

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that incentives originally were misaligned.

3. For new office patients, since both 99201 and 99202 require straightforward MDM, the level 1 code (99201) has been eliminated, reducing the number of code levels from 5 to 4.
4. History and physical exam will **no longer be used** to determine code level for office E/M codes. **These elements will be required only as medically appropriate.** This means that documentation review will no longer focus on "bean counting" the elements in the history and physical exam.
5. Following a reassessment of the actual time required to provide E/M services in real-life practice, CMS plans to markedly increase the relative value of office visits for established patients and modestly increase the relative value of office visits for new patients. CMS operates under the principle of "neutral budgeting," meaning that an increase of the relative value of E/M codes will result in a decrease in the payment for procedural codes. The actual RVUs for procedural services do not change; however, budget neutrality requires a decrease in the dollar conversion factor. The proposed changes will increase the payment for E/M services and decrease payments for procedural services.

Refocusing practice on MDM complexity

The practice of medicine is a calling with great rewards. Prominent among those rewards are improving the health of women, children, and the community, developing deep and trusting relationships with patients, families, and clinical colleagues. The practice of medicine is also replete with a host of punishing administrative burdens, including prior authorizations, clunky electronic medical records, poorly designed quality metrics that are applied to clinicians, and billing compliance rules that emphasize the repetitive documentation of clinical information with minimal value.

Some of the most irritating aspects of medical practice are the CMS rules governing medical record documentation required for billing ambulatory office visits. Current coding compliance focuses on counting the number of systems reviewed in the review of systems; the documentation of past history, social history, and family history; the number of organs and organ elements examined during the physical examination; and the complexity of MDM.

In January 2021, CMS plans to adopt new Current Procedural Terminology (CPT) code descriptors for the office and other outpatient E/M services that sunset most of the "bean-counting" metrics and emphasize the importance of the complexity of MDM in guiding selection of a correct code.[2] Beginning in January 2021, clinicians will have the option of selecting an E/M code level based on the **total** amount of **time** required to provide the office visit service or the complexity of MDM. When selecting a code level based on MDM the new guidance emphasizes the importance of reviewing notes from other clinicians, reviewing test results, ordering of tests, and discussing and coordinating the care of the patient with other treating physicians. These changes reflect a better understanding of what is most important in good medical practice, promoting better patient care. **TABLES 1** (page 12) **AND 2** (page 14) provide the initial guidance from CMS concerning selection of E/M code level based on time and MDM, respectively.[2] The guidance for using MDM to select an E/M code level is likely to evolve following implementation, so stay tuned. When using MDM to select a code, 2 of the 3 general categories are required to select that level of service.

Increase in the valuation of office-based E/M services

The Medicare Physician Fee Schedule uses a resource-based relative value system to determine time and intensity of the work of clinical practice. This system recognizes 3 major factors that influence the resources required to provide a service:

- work of the clinician
- practice expense for technical components
- cost of professional liability insurance.

Many primary care professional associations have long contended that CMS has undervalued office-based E/M services relative to procedures, resulting in the devaluing of primary care practice. After the CPT code descriptors were updated by the CPT editorial panel, 52 specialty societies surveyed their members to provide inputs to CMS on the time and intensity of the office and other outpatient E/M codes as currently practiced. The American Medical Association's Specialty Society Resource-Based Relative Value Scale Update Committee (RUC) reviewed the surveys and provided new inputs via open comment to CMS. CMS has responded to this feedback with a review of the intensity of clinical work required to provide an ambulatory visit service. In response to the review, CMS proposes to accept the recommendations of the RUC representing the house of medicine and increase the work and practice expense relative value assigned

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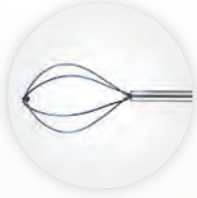

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to new and established office visit codes. Overall, the combination of changes in relative values assigned for the work of the clinician and the expense of practice, increases the total value of office-based E/M codes for new patients by 7% to 14% and for established patients from 28% to 46% (see supplemental table with the online version of this article).

Decreased payments for procedural services

Medicare is required to offset increased payment in one arena of health care delivery with decreased payment in other arenas of care, thereby achieving "budget-neutrality." As detailed above, CMS plans to increase Medicare payments for office-based E/M services. Payment for services is calculated by multiplying the total RVUs for a particular service by a "conversion factor" (ie, number of dollars per RVU). To achieve budget-neutrality, CMS has proposed substantially reducing the conversion factor for 2021 (from $36.09 to $32.26), which will effectively decrease Medicare payments for procedural services since their RVUs have not changed. While the AMA RUC and many specialty societies continue to strongly advocate for the E/M work RVU increases to be included in the E/M components of 10- and 90-day global services, CMS has proposed to implement them only for "stand alone" E/M services.

Organizations are lobbying to delay or prevent the planned decrease in conversion factor, which results in substantial declines in payment for procedural services. (See "What do the Medicare billing changes mean for the Obstetrical Bundled services?" with the online version of this article.) Due to the economic and clinical practice challenges caused by the coronavirus disease 2019 (COVID-19) pandemic it would be best if CMS did not reduce payments to physicians who are experts in procedural health care, thereby avoiding the risk of reduced access to these vital services.

If the current CMS changes in payment are implemented, endocrinologists, rheumatologists, and family physicians will have an increase in payment, and radiologists, pathologists, and surgeons will have a decrease in payment (**TABLE 3**, page 43).[6] Obstetrics and gynecology is projected to have an 8% increase in Medicare payment. However, if an obstetrician-gynecologist derives most of their Medicare payments from surgical procedures, they are likely to have a decrease in payment from Medicare. Other payers will be incorporating the new coding structure for 2021; however, their payment structures and conversion factors are likely to vary. It is important to note that the RVUs for procedures have not changed. The budget neutrality adjustment resulted in a much lower conversion factor and therefore a decrease in payment for those specialties whose RVUs did not increase.

TABLE 1 **Current Procedural Terminology code descriptors for selecting office-based evaluation and management level based on time**[2]

New patients—Code levels	Time
99202	15 to 29 minutes
99203	30 to 44 minutes
99204	45 to 59 minutes
99205	60 to 74 minutes
Established patients—Code levels	**Time**
99211	Presenting problem is minimal, <10 minutes
99212	10 to 19 minutes
99213	20 to 29 minutes
99214	30 to 39 minutes
99215	40 to 54 minutes

Bottom line

Working through the Medicare, Medicaid, and CHIP programs, CMS can influence greatly the practice of medicine including medical record documentation practices and payment rates for every clinical service. CMS proposes to end the onerous "bean counting" approach to billing compliance and refocus on the complexity of MDM as the foundation for selecting a billing code level. This change is long overdue, valuing the effective management of complex patients in office practice. Hopefully, CMS will reverse the planned reduction in the payment for procedural services, preserving patient access to important health care services. ●

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The authors report no financial relationships relevant to this article.

CONTINUED ON PAGE 14

Mindy H.
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TABLE 2 Centers for Medicare and Medicaid Services guidance for selecting office-based evaluation and management level–based medical decision making (MDM)[2]

Code	Level of MDM	Number and complexity of problems addressed	Amount and complexity of data to be reviewed and analyzed	Risk of complications and morbidity or mortality
99202 99212	Straightforward	Minimal: self-limited or minor problem	Minimal or none	Minimal risk of morbidity from testing or treatment
99203 99213	Low	• 2 or more self-limited or minor problems • Or 1 stable chronic illness • Or 1 acute uncomplicated illness or injury	• Must meet criteria in either category • Category 1: Any combination of 2: • Review of external note(s), • Review of result(s) of tests, • Ordering of tests • Category 2: Assessment requiring an independent historian	Low risk of morbidity from additional diagnostic testing or treatment
99204 99214	Moderate	• 1 or more chronic illnesses with exacerbation or side effects of treatment • Or 2 or more stable chronic illnesses • Or 1 undiagnosed new problem with uncertain prognosis • Or 1 acute illness with systemic symptoms • Or 1 acute complicated injury	• Must meet criteria in one of the 3 categories below: • Category 1: Meets 3 of 4: review of external notes, review of results, ordering of tests, assessment requiring an independent historian. • Category 2: Independent interpretation of a test. • Category 3: Discussion of management or test interpretation with external physician or other clinician	• Moderate risk of morbidity from additional diagnostic testing or treatment. • Examples: • Prescription drug management • Decisions regarding minor surgery with identified patient or procedure risk factors • Decision regarding elective major surgery without documented risk factors • Diagnosis or treatment significantly limited by social determinants of health
99205 99215	High	• 1 or more chronic illnesses with severe exacerbation, progression or side effects of treatment • Or 1 acute or chronic illness or injury that poses a threat to life or bodily function	• Must meet criteria in one category • Category 1: Meets 3 of 4: review of external notes, review of results, ordering of tests, assessment requiring an independent historian. • Category 2: Independent interpretation of a test. • Category 3: Discussion of management or test interpretation with external physician or other clinician	• High risk of morbidity from additional diagnostic testing or treatment. • Examples: • Drug therapy requiring intensive monitoring for toxicity • Decision regarding elective major surgery with documented risk factors • Decision regarding emergency major surgery • Decision regarding hospitalization • Decision not to resuscitate

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Pelvic floor dysfunction UPDATE

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While evidence-based guidelines regarding postoperative voiding dysfunction are lacking, several studies add to the growing literature. Two experts provide recommendations to promote safe, efficient care of patients.

Postoperative voiding dysfunction refers to the acute inability to spontaneously and adequately empty the bladder after surgery. Postoperative voiding dysfunction occurs in 21% to 42% of pelvic reconstructive surgeries, as well as 7% to 21% of benign gynecologic surgeries.[1-4] While much of its peril lies in patient discomfort or dissatisfaction with temporary bladder drainage, serious consequences of the disorder include bladder overdistension injury with inadequate drainage and urinary tract infection (UTI) associated with prolonged catheterization.[4-6]

Although transient postoperative voiding dysfunction is associated with anti-incontinence surgery, tricyclic antidepressant use, diabetes, preoperative voiding dysfunction, and postoperative narcotic use, it also may occur in patients without risk factors.[4,7,8] Thus, all gynecologic surgeons should be prepared to assess and manage the patient with postoperative voiding dysfunction.

Diagnosis of postoperative voiding dysfunction can be approached in myriad ways, including spontaneous (or natural) bladder filling or bladder backfill followed by spontaneous void. When compared with spontaneous void trials, backfill-assisted void trial is associated with improved accuracy in predicting voiding dysfunction in patients who undergo urogynecologic surgery, leading to widespread adoption of the procedure following pelvic reconstructive surgeries.[9,10]

Criteria for "passing" a void trial may include the patient's subjective feeling of having emptied her bladder; having a near-baseline force of stream; or commonly by objective parameters of voided volume and postvoid residual (PVR), assessed via catheterization or bladder scan.[3,6,10] Completing a postoperative void trial typically requires significant nursing effort because of the technical demands of backfilling the bladder, obtaining the voided volume and PVR, or assessing subjective emptying.

Management of postoperative voiding dysfunction typically consists of continuous drainage with a transurethral catheter or clean intermittent self-catheterization (CISC). Patients discharged home with a bladder drainage method also may be prescribed various medications, such as antibiotics, anticholinergics, and bladder analgesics, which often depends on provider practice.

Given the minimal universal guidance available for gynecologic surgeons on postoperative voiding dysfunction, we review several articles that contribute new evidence on the assessment and management of this condition.

IN THIS ARTICLE

CONTINUED ON PAGE 19

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Few cases (0.36%) of adverse reactions of cystitis, pyelonephritis and other upper urinary tract infection (UTI) have been reported in Phexxi™ clinical studies. Of these, one case of pyelonephritis was considered serious and required hospitalization. Avoid use of Phexxi™ in females of reproductive potential with history of recurrent urinary tract infection or urinary tract abnormalities.

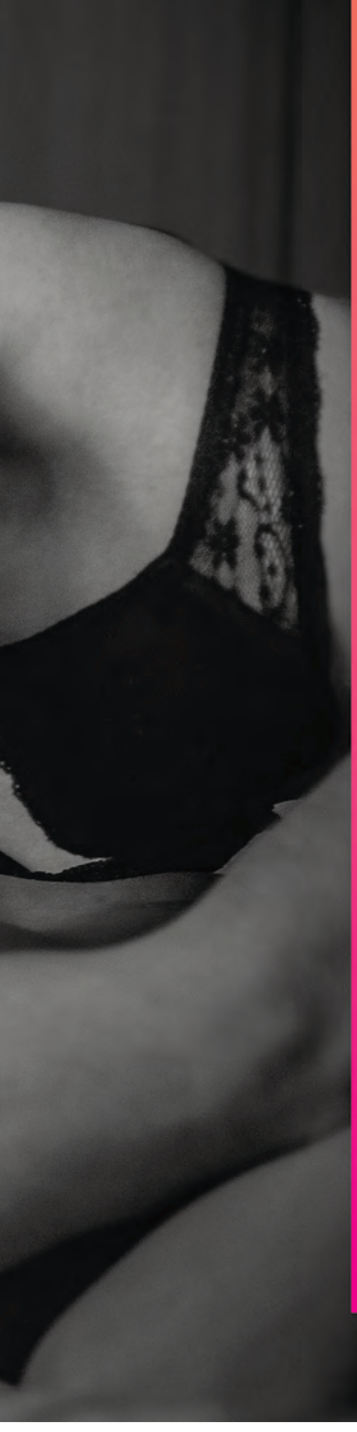
ADVERSE REACTIONS

Most common adverse reactions were vulvovaginal burning sensation, vulvovaginal pruritus, vulvovaginal mycotic infection, urinary tract infection, vulvovaginal discomfort, bacterial vaginosis, vaginal discharge, genital discomfort, dysuria, and vulvovaginal pain.

Patients should be counseled on the following:

- **To contact and consult with their healthcare provider for severe or prolonged genital irritation or experiencing urinary tract symptoms.**
- **To discontinue Phexxi™ if they develop a local hypersensitivity reaction.**
- **That Phexxi™ does not protect against HIV infection or other sexually transmitted infections.**

To report SUSPECTED ADVERSE REACTIONS, contact Evofem at toll-free phone 1-833-EVFMBIO or you may contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.



INTRODUCING

phexxi™
(lactic acid, citric acid, and potassium bitartrate) Vaginal Gel 1.8%, 1%, 0.4%

A non-hormonal, in-the-moment contraceptive

pHinally! There's Phexxi™

An FDA-approved contraceptive vaginal gel designed to meet her needs

- **NON-HORMONAL**
- **WOMAN CONTROLLED**
- **WORKS IMMEDIATELY**

Phexxi™ is a **vaginal pH modulator (VPM)**—a first-in-class, **non-hormonal** prescription contraceptive that works immediately to maintain the vagina's acidic pH in the presence of semen.[1-4]

Discover
why Phexxi™ may be an option for your patients by visiting
HCP-Phexxi.com/contraception

INDICATIONS AND USAGE
Phexxi™ is indicated for the prevention of pregnancy in females of reproductive potential for use as an on-demand method of contraception.

LIMITATIONS OF USE
Phexxi™ is not effective for the prevention of pregnancy when administered after intercourse.

Please see full Prescribing Information for Phexxi™.
Please see Brief Summary on the following page.

REFERENCES: 1. Phexxi™ [Prescribing Information]. Evofem Biosciences, Inc: San Diego, CA; May 2020. **2.** Phexxi™ Vaginal Gel. Medi-Span®; June 8, 2020. **3.** Bayer LL, Jensen JT. ACIDFORM: a review of evidence. *Contraception*. 2014;90:11-18. **4.** Nayak S, Avery A, McLeod Griffiss J, Charles CD, Culwell KR. A randomized placebo-controlled pilot study of the effect and duration of Amphora, a multipurpose vaginal pH regulator, on vaginal pH. *Clin Exp Obstet Gynecol*. 2019;46(5):736-742.

EVOFEM BIOSCIENCES®

EVFM-US-000071 • August 2020 • Produced in USA.

phexxi™

(lactic acid, citric acid, and potassium bitartrate) Vaginal Gel 1.8%, 1%, 0.4%

BRIEF SUMMARY: Consult the Package Insert for complete Prescribing Information

INDICATIONS AND USAGE

PHEXXI™ is indicated for the prevention of pregnancy in females of reproductive potential for use as an on-demand method of contraception.

LIMITATIONS OF USE

PHEXXI is not effective for the prevention of pregnancy when administered after intercourse.

WARNINGS AND PRECAUTIONS

Cystitis and Pyelonephritis

Among 2804 subjects who received PHEXXI in Studies 1 and 2, 0.36% (n=10) reported adverse reactions of cystitis, pyelonephritis, or other upper urinary tract infection (UTI). Of these, one case of pyelonephritis was considered serious and required hospitalization. Avoid use of PHEXXI in females of reproductive potential with a history of recurrent urinary tract infection or urinary tract abnormalities.

ADVERSE REACTIONS

Clinical Trials Experience

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

The safety of PHEXXI (pre-filled applicator with 5-gram dose) has been evaluated in two clinical trials (Study 1 and Study 2) in 2804 subjects (over 19,000 cycles of exposure). The racial/ethnic distribution was 66% White, 27% Black or African American, 2% Asian, 1% American Indian or Alaska Native, 0.3% Native Hawaiian or Pacific Islander, and 5% other; 32% of the study population was Hispanic. Study 1 included a one-year extension phase where 342 U.S. subjects were exposed to PHEXXI for 13 cycles.

Hypersensitivity Reaction:

Of the 2804 PHEXXI-treated subjects in Studies 1 and 2, one subject reported a suspected drug hypersensitivity. Avoid PHEXXI use in females of reproductive potential with suspected hypersensitivity to the ingredients in PHEXXI.

The most common adverse reactions (≥10%) in the U.S. population in Studies 1 and 2 (n = 2480) were: vulvovaginal burning sensation (18.0%) and vulvovaginal pruritus (14.5%). The majority of these adverse reactions were mild and few led to discontinuation. Table 1 summarizes the most common adverse reactions (≥ 2%) reported by subjects using PHEXXI in the U.S.

Table 1. Adverse Reactions that Occurred in ≥ 2% of Subjects Who Used PHEXXI to Prevent Pregnancy (Studies 1 and 2 – U.S. population only)

Adverse Reaction	PHEXXI (N=2480) (%)
Vulvovaginal Burning Sensation	18.0
Vulvovaginal Pruritus	14.5
Vulvovaginal Mycotic Infection*	9.1
Urinary Tract Infection†,‡	9.0
Vulvovaginal Discomfort	9.0
Bacterial Vaginosis	8.4
Vaginal Discharge	5.5
Genital Discomfort	4.1
Dysuria	3.1
Vulvovaginal pain	2.1

*Includes preferred terms (PT) vulvovaginal mycotic infection and vulvovaginal candidiasis.
†Includes PTs urinary tract infection, streptococcal urinary tract infection, Escherichia urinary tract infection, and urinary tract infection bacterial.
‡Does not include PTs cystitis, kidney infection, and pyelonephritis [see *Warnings and Precautions (5.1) of PHEXXI Full Prescribing Information*].

Among subjects who used PHEXXI in Studies 1 and 2, 1.6% discontinued from the clinical trials due to an adverse reaction. The most common adverse reactions leading to study discontinuation were vulvovaginal burning sensation (0.7%); and vulvovaginal pruritus and vulvovaginal discomfort (0.1% each).

Adverse Reactions in Male Partners:

Among male partners of subjects who used PHEXXI for contraception in Study 2, 9.8% (131 of 1330) reported symptoms of local discomfort (burning, itching, pain, and "other"). Of these local discomfort symptoms, 74.7% were mild, 21.4% were moderate, and 3.9% were severe. Two subjects discontinued participation in the study due to male partner symptoms.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There is no use for PHEXXI in pregnancy; therefore, discontinue PHEXXI during pregnancy. There are no data with the use of PHEXXI in pregnant women or animals. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

Lactation

Risk Summary

There are no data on the presence of lactic acid, citric acid, and potassium bitartrate or their metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

Pediatric Use

The safety and effectiveness of PHEXXI have been established in females of reproductive potential.

Efficacy is expected to be the same for post-menarchal females under the age of 17 as for users 17 years and older. The use of PHEXXI before menarche is not indicated.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Advise the patient to read the Patient Information and FDA-approved patient labeling (Instructions for Use).

Advise the patient:

- To intravaginally administer the contents of one pre-filled single-dose applicator of PHEXXI before **each** episode of vaginal intercourse and to administer an additional dose if intercourse does not occur within one hour of administration [*see Dosage and Administration (2.1) of PHEXXI Full Prescribing Information*].
- To consult their healthcare provider for severe or prolonged genital irritation [*see Adverse Reactions (6.1) of PHEXXI Full Prescribing Information*].
- To discontinue PHEXXI if they develop a local hypersensitivity reaction [*see Adverse Reactions (6.1) of PHEXXI Full Prescribing Information*].
- To contact their health care provider if experiencing urinary tract symptoms [*see Warnings and Precautions (5.1) of PHEXXI Full Prescribing Information*].
- That PHEXXI does not protect against HIV infection and other sexually transmitted infections.

Manufactured for Evofem, Inc.,
a wholly owned subsidiary of Evofem Biosciences, Inc.,
12400 High Bluff Drive, Suite 600, San Diego, CA 92130

U.S. Patent 6,706,276

REFDOC-000554

To report SUSPECTED ADVERSE REACTIONS, contact Evofem at toll-free phone 1-833-EVFMBIO or you may contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

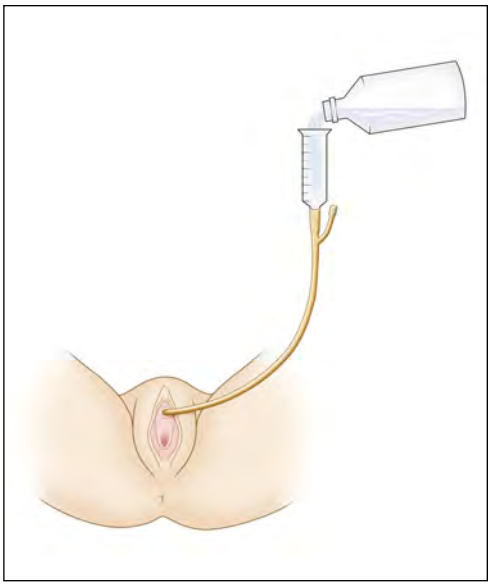
EVOFEM BIOSCIENCES®

CONTINUED FROM PAGE 15

How can we efficiently approach the postoperative void trial for pelvic floor surgery?

Chao L, Mansuria S. Postoperative bladder filling after outpatient laparoscopic hysterectomy and time to discharge: a randomized controlled trial. Obstet Gynecol. 2019;133:879-887.

Despite efforts to implement and promote enhanced recovery after surgery pathways, waiting for spontaneous void can be a barrier to efficient same-day discharge. Chao and Mansuria conducted a randomized controlled trial (RCT) to determine whether backfilling the bladder intraoperatively, compared with spontaneous (physiologic) filling, would reduce time to discharge in patients undergoing total laparoscopic hysterectomy (TLH) or supracervical hysterectomy (SCH).



Backfill-assisted void trial with instillation of sterile fluid filled to gravity using a 50-mL syringe attached to a Foley catheter

Study details

Women undergoing TLH or laparoscopic SCH for benign indications were randomly assigned to undergo either a backfill-assisted void trial in the operating room with 200 mL of sterile normal saline (n = 75) or Foley catheter removal with spontaneous fill in the postanesthesia care unit (PACU) (n = 78).

For both groups, the maximum time allowed for spontaneous void was 5 hours. A successful void trial was defined as a voided volume of at least 200 mL. If a patient was unable to void at least 200 mL, a bladder scan was performed, and the patient was considered to have failed the void trial if a PVR of 200 mL or greater was noted. If the PVR was less than 200 mL, the patient was given an additional 1 hour to spontaneously void 200 mL by 6 hours after the surgery. Patients who failed the void trial were discharged home with a transurethral catheter.

The primary outcome was time to discharge, and the sample size (153 participants included in the analysis) allowed 80% power to detect a 30-minute difference in time to discharge. Participant baseline characteristics, concomitant procedures, and indication for hysterectomy were similar for both groups.

Results. The mean time to discharge was 273.4 minutes for the backfill-assisted void trial group and 283.2 minutes for the spontaneous fill group, a difference of 9.8 minutes that was not statistically significant ($P = .45$).

Although it was not a primary outcome, time to spontaneous void was 24.9 minutes shorter in the backfill group ($P = .04$). Rates of postoperative voiding dysfunction did not differ between the 2 groups (6.7% for the backfill group and 12.8% for the spontaneous fill group; $P = .2$). There were no significant differences in emergency department visits, UTI rates, or readmissions.

FAST TRACK

The mean time to discharge was 273.4 minutes for the backfill-assisted void trial group and 283.2 minutes for the spontaneous fill group, a 9.8-minute difference that was not statistically significant (P = .45)

CONTINUED ON PAGE 20

ILLUSTRATION: MARCIA HARTSOCK FOR OBG MANAGEMENT

CONTINUED FROM PAGE 19

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Backfilling the bladder in the operating room prior to catheter discontinuation can reduce time to first spontaneous void, but not the overall time to discharge.

Bladder backfill is safe, simple, and may reduce time to spontaneous void

Strengths of the study included its prospective randomized design, blinded outcome assessors, and diversity in benign gynecologic surgeries performed. Although this study found a reduced time to spontaneous void in the backfill group, it was not powered to assess this difference, limiting ability to draw conclusions from those data. Data on postoperative nausea and pain scores also were not collected, which likely influenced the overall time to discharge.

Void trial completion is one of many criteria to fulfill prior to patient discharge, and a reduced time to first void may not decrease the overall length of PACU stay if other factors, such as nausea or pain, are not controlled. Nonetheless, backfilling the bladder intraoperatively is a safe alternative that may decrease the time to first spontaneous void, and it is a relatively simple alteration in the surgical workflow that could significantly lessen PACU nursing demands.

Algorithm assesses need for PVR, although further study required

FAST TRACK

A void trial was considered to be passed when a PVR was less than 100 mL or less than 50% of the total bladder volume, with a minimum voided volume of 200 mL

Meekins AR, Siddiqui N, Amundsen CL, et al. Improving postoperative efficiency: an algorithm for expedited void trials after urogynecologic surgery. South Med J. 2017;110:785-790.

To determine ways to further maximize postoperative efficiency, Meekins and colleagues sought to determine whether certain voided volumes during backfill-assisted void trials could obviate the need for PVR assessment.

Void trial results calculated to develop algorithm

The study was a secondary analysis of a previously conducted RCT that assessed antibiotics for the prevention of UTI after urogynecologic surgery. Void trials from the parent RCT were performed via the backfill-assisted method in which the bladder was backfilled in the PACU with 300 mL of normal saline or until the patient reported urgency to void, after which the catheter was removed and the patient was prompted to void immediately.

Postvoid residual levels were assessed via ultrasonography or catheterization. A void trial was considered to be passed when a PVR was less than 100 mL or less than 50% of the total bladder volume, with a minimum voided volume of 200 mL.

In the follow-up study, the authors analyzed the void trial results of 255 women of the original 264 in the parent RCT. A total of 69% of patients passed their void trial. The authors assessed the optimal positive predictive value (PPV) and negative predictive value (NPV) combinations, which were then used to create lower and upper voided volume thresholds that would best predict a failed or passed trial, thus obviating PVR measurement.

Results. When patients voided less than 100 mL, the NPV was 96.7% (meaning that they had a 96.7% chance of failing the void trial).

CONTINUED ON PAGE 24

FOR THE TREATMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS DUE TO MENOPAUSE IN WOMEN WITH A UTERUS

OFFER THE CONVENIENCE OF ONE

BIJUVA IS AN ORAL COMBINATION OF ESTRADIOL AND MICRONIZED PROGESTERONE[1,2]

Bijuva® 1mg/100mg
(estradiol and progesterone) capsules

ONE CAPSULE

BIJUVA is a once-daily oral capsule—taken each evening with food—that fits easily into her daily routine and may improve compliance[1,3-5]

ONE PRESCRIPTION

BIJUVA combines 2 bio-identical* hormones in 1 capsule—with just 1 prescription[1,2]

ONE AFFORDABLE TREATMENT

Patients pay as little as $35†

*Bio-identical hormones are structurally identical to the hormones produced within a woman's body. The relevance of risks associated with the use of synthetic hormones compared to bio-identical hormones is not known but cannot be excluded.

†Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state healthcare programs (including any state pharmaceutical assistance programs). Please see Program Terms, Conditions, and Eligibility Criteria at **savings.bijuva.com.**

TO REQUEST SAMPLES, VISIT BIJUVAINFO.COM

INDICATION

BIJUVA is a combination of estradiol and progesterone indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

Estrogen Plus Progestin Therapy

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

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 WHI estrogen-alone substudy reported increased risks of stroke and DVT**
- **The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older**

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should these occur or be suspected, therapy should be discontinued immediately. Risk factors for arterial vascular disease and/or venous thromboembolism (VTE) should be managed appropriately.
- The WHI substudy of daily estrogen plus progestin after a mean follow-up of 5.6 years reported an increased risk of invasive breast cancer. Observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy after several years of use. The risk increased with duration of use and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). The use of estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.
- Endometrial hyperplasia (a possible precursor to endometrial cancer) has been reported to occur at a rate of approximately less than one percent with BIJUVA. Clinical surveillance of all women using estrogen plus progestin therapy is important. Adequate diagnostic measures should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.
- 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.
- In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin when compared to placebo. It is unknown whether these findings apply to younger postmenopausal women.
- Estrogens increase the risk of gallbladder disease.
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs.
- Monitor thyroid function in women on thyroid replacement hormone therapy.

ADVERSE REACTIONS

The most common adverse reactions (≥3%) for BIJUVA are breast tenderness (10.4%), headache (3.4%), vaginal bleeding (3.4%), vaginal discharge (3.4%) and pelvic pain (3.1%).

Please note that this information is not comprehensive. Please see Brief Summary of the Full Prescribing Information, including BOXED WARNING, on the following pages.

References: 1. BIJUVA [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2019. **2.** Lobo RA, Liu J, Stanczyk FZ, et al. Estradiol and progesterone bioavailability for moderate to severe vasomotor symptom treatment and endometrial protection with the continuous-combined regimen of TX-001HR (oral estradiol and progesterone capsules). *Menopause*. 2019;26(7):720-727. **3.** Lobo RA, Archer DF, Kagan R, et al. A 17ß-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. *Obstet Gynecol*. 2018;132(1):161-170. **4.** Sutton SS, Hardin JW, Bramley TJ, D'Souza AO, Bennett CL. Single- versus multiple-tablet HIV regimens: adherence and hospitalization risks. *Am J Manag Care*. 2016;22(4):242-248. **5.** Coca A, Agabiti-Rosei E, Cifkova R, Manolis AJ, Redón J, Mancia G. The polypill in cardiovascular prevention: evidence, limitations and perspective - position paper of the European Society of Hypertension. *J Hypertens*. 2017;35(8):1546-1553.

TherapeuticsMD®
For Her. For Life.

BIJUVA® (estradiol and progesterone) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use **BIJUVA** safely and effectively. Please visit BIJUVAHCP.com for Full Prescribing Information.

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

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 (5.1, 5.3), and Clinical Studies (14.4, 14.5) in full prescribing information].*

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of deep vein thrombosis (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 conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.4) in full prescribing information].*

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or 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 (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].*

Breast Cancer

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer*[see Warnings and Precautions (5.2), and Clinical Studies (14.4) 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.

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 (5.2) 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 (5.1, 5.3), and Clinical Studies (14.4, 14.5) in full prescribing information].*

The WHI estrogen-alone substudy reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral CE (0.625 mg)-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.4) in full prescribing information].*

The 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 (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.5) 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.

INDICATIONS AND USAGE

Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

DOSAGE AND ADMINISTRATION

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

Take a single BIJUVA (estradiol and progesterone) capsule, 1 mg/100 mg, orally each evening with food.

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should these occur or be suspected, therapy should be discontinued immediately. Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the Women's Health Initiative estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.4) in full prescribing information].* The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.4) in full prescribing information].* Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.4) in full prescribing information].*

In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo *[see Clinical Studies (14.4) in full prescribing information].*

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

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

Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated.

The increase in VTE risk was demonstrated during the first year and persisted *[see Clinical Studies (14.4) in full prescribing information].* Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years [*see Clinical Studies (14.4) in full prescribing information].* Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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

Malignant Neoplasms

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups *[see Clinical Studies (14.4) in full prescribing information].*

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80] *[see Clinical Studies (14.4) in full prescribing information].*

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

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

In a one-year trial, among 1,684 women who received a combination of estradiol plus progesterone (1 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 50 mg progesterone or 0.25 mg estradiol plus 50 mg progesterone) or placebo (n=151), six new cases of breast cancer were diagnosed, two of which occurred among the group of 415 women treated with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg. No new cases of breast cancer were diagnosed in the group of 151 women treated with placebo.

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

(continued on next page)

Endometrial Cancer

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg.

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-fold 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 progestogen 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 progestogen to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Ovarian Cancer

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

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

Probable Dementia

In the WHIMS estrogen 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% CI, 1.21 to 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years *[see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].*

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% CI, 0.83 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years *[see Use in Specific Populations (8.5), and Clinical Studies (14.5) 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% CI, 1.19 to 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 *[see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].*

Gallbladder Disease

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

Hypercalcemia

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

Visual Abnormalities

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

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

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestogen with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

Elevated Blood Pressure

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

Hypertriglyceridemia

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

Hepatic Impairment and/or Past History of Cholestatic Jaundice

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

Hypothyroidism

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

Fluid Retention

Estrogens and progestins may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens plus progestins are prescribed.

Hypocalcemia

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

Exacerbation of Endometriosis

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

Hereditary Angioedema

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

Exacerbation of Other Conditions

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

Laboratory Tests

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

Drug Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS

In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reactions with BIJUVA (incidence ≥ 3% of women and greater than placebo) were breast tenderness (10.4%), headache (3.4%), vaginal bleeding (3.4%), vaginal discharge (3.4%) and pelvic pain (3.1%).

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

BIJUVA is not indicated for use in pregnancy. There are no data with the use of BIJUVA in pregnant women, however, epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogen and progestins) before conception or during early pregnancy.

Lactation

BIJUVA is not indicated for use in females of reproductive potential. Estrogens are present in human milk and can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established.

Pediatric Use

BIJUVA is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use

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

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Manufactured for: TherapeuticsMD, Inc. Boca Raton, FL 33431
Based on BJVA-LAB-20003.4 Revised: 11/2019

TherapeuticsMD®

BJVA-20054.3 12/2019

CONTINUED FROM PAGE 20

TABLE 1 Proposed algorithm for backfill-assisted void trial in the PACU

Void volume	Void trial status	PVR assessment
≥ 200 mL	Successful	Unnecessary
100–199 mL	Indeterminate	Recommended
< 100 mL	Unsuccessful	Unnecessary

Abbreviations: PACU, postanesthesia care unit; PVR, postvoid residual.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Application of the algorithm proposed by the study investigators has the potential to eliminate the need for a PVR assessment in most patients following a backfill-assisted void trial.

When patients voided 200 mL or more, the PPV was 97% (meaning that they had a 97% chance of passing the void trial). Receiver operating characteristic analysis confirmed that voided volume alone was an excellent predictor of final void trial results, with area under the curve of 0.97. The authors estimated that applying this algorithm to their study population would have eliminated the need for assessing PVR in 85% of patients. Ultimately, they proposed the algorithm shown in **TABLE 1**.

A potential alternative for assessing PVR

This study's strengths include the use of prospectively and systematically collected void trial data in a large patient population undergoing various urogynecologic procedures. By contrast, the generalizability of the results is limited regarding other void trial methods, such as spontaneous filling and void, as well as populations outside of the studied institution.

With the algorithm, the authors estimated that the majority of postoperative patients would no longer require a PVR assessment in the PACU. This could have beneficial downstream implications, including decreasing the nursing workload, reducing total time in the PACU, and minimizing patient discomfort with PVR assessment.

While further studies are needed to validate the proposed algorithm in larger populations, this study provides evidence of an efficient alternative to the traditional approach to PVR assessment in the PACU.

FAST TRACK

Applying the proposed algorithm to the study population would have eliminated the need for assessing PVR in an estimated 85% of patients

An alternative to Foley use if a patient does not know CISC

Boyd SS, O'Sullivan DM, Tunitsky-Bitton E. A comparison of two methods of catheter management after pelvic reconstructive surgery: a randomized controlled trial. Obstet Gynecol. 2019;134:1037-1045.

The traditional indwelling catheter as a postoperative bladder drainage method has a number of drawbacks, including an increased rate of UTI, patient discomfort, and potential limitations in mobility due to the presence of a drainage bag.[5]

Boyd and colleagues reported on a variation of traditional transurethral catheterization that hypothetically allows for improved mobility. With this method, the transurethral catheter is occluded with a plastic plug that is intermittently plugged and unplugged (plug-unplug method) for bladder drainage. To test whether activity levels are improved with the plug-unplug method versus the continuous drainage approach, the authors conducted an RCT in women undergoing pelvic

TABLE 2 Selected outcomes between postoperative days 5 and 7

Outcome	Plug-unplug (n = 32)	Continuous drainage (n = 31)	Reference (n = 30)	*P* value
Total AAS score (preoperative)[a]	90.8 [12.3]	88.5 [14.3]	91.4 [13.3]	.67
Total AAS score (postoperative)[a]	70.3 [16.9]	67.7 [21.4]	79.4 [23.6]	.09
Overall level of pain (0–10)	5.8 [2.3]	5.7 [2.2]	4.4 [2.9]	.07
"Very satisfied with surgery"	25 (78.1)	25 (80)	20 (66.7)	.20
"Catheter is easy to use at all times"[b]	3.9 [1.1]	3.8 [1.1]	N/A	.63
"Catheter is preventing me from doing some activities I feel I could otherwise do"[b]	2.5 [1.5]	3.4 [1.2]	N/A	.01
Passed void trial at 5–7 days	23 (71.9)	18 (58.1)	N/A	.25
Time to passed void trial[c]	7 (5–13)	7 (6–15)	N/A	.20
UTI treatment[c]	24 (75)	16 (51.6)	2 (6.7)	< .001

Data are mean [SD], n (%), or median (interquartile range).

Abbreviations: AAS, Activity Assessment Scale; N/A, not applicable; UTI, urinary tract infection.

[a]AAS: Scale 0–100; higher scores reflect better functional activity.

[b]Catheter effect questions, with the following scale: 0, strongly disagree; 1, disagree; 2, neither agree nor disagree; 3, agree; 4, strongly agree.

[c]Data collected from time of surgery until 3 months postoperatively.

reconstructive surgery to compare the plug-unplug method with transurethral catheterization (with a continuous drainage bag) and a reference group of freely voiding women.

Study particulars and outcomes

The trial's primary outcome was the patients' activity score as measured by the Activity Assessment Scale (AAS) at 5 to 7 days postoperatively. Because of the theoretically increased risk of a UTI with opening and closing a closed drainage system, secondary outcomes included the UTI rate, the time to pass an outpatient void trial, postoperative pain, patient satisfaction, and catheter effect. To detect an effect size of 0.33 in the primary outcome between the 3 groups, 90 participants were needed along with a difference in proportions of 0.3 between the catheterized and noncatheterized groups.

The participants were randomly assigned 1:1 preoperatively to the continuous drainage or plug-unplug method. All patients underwent a backfill-assisted void trial prior to hospital discharge; the first 30 randomly assigned patients to pass their void trial comprised the reference group. Patients in the plug-unplug arm were instructed to uncap the plastic plug to drain their bladder when they felt the urge to void or at least every 4 hours. All catheterized patients were provided with a large drainage bag for gravity-based drainage for overnight use.

Participants who were discharged home with a catheter underwent an outpatient void trial between postoperative days 5 and 7. A urinalysis was performed at that time and a urine culture was done if a patient reported UTI symptoms. All patients underwent routine follow-up until they passed the office void trial.

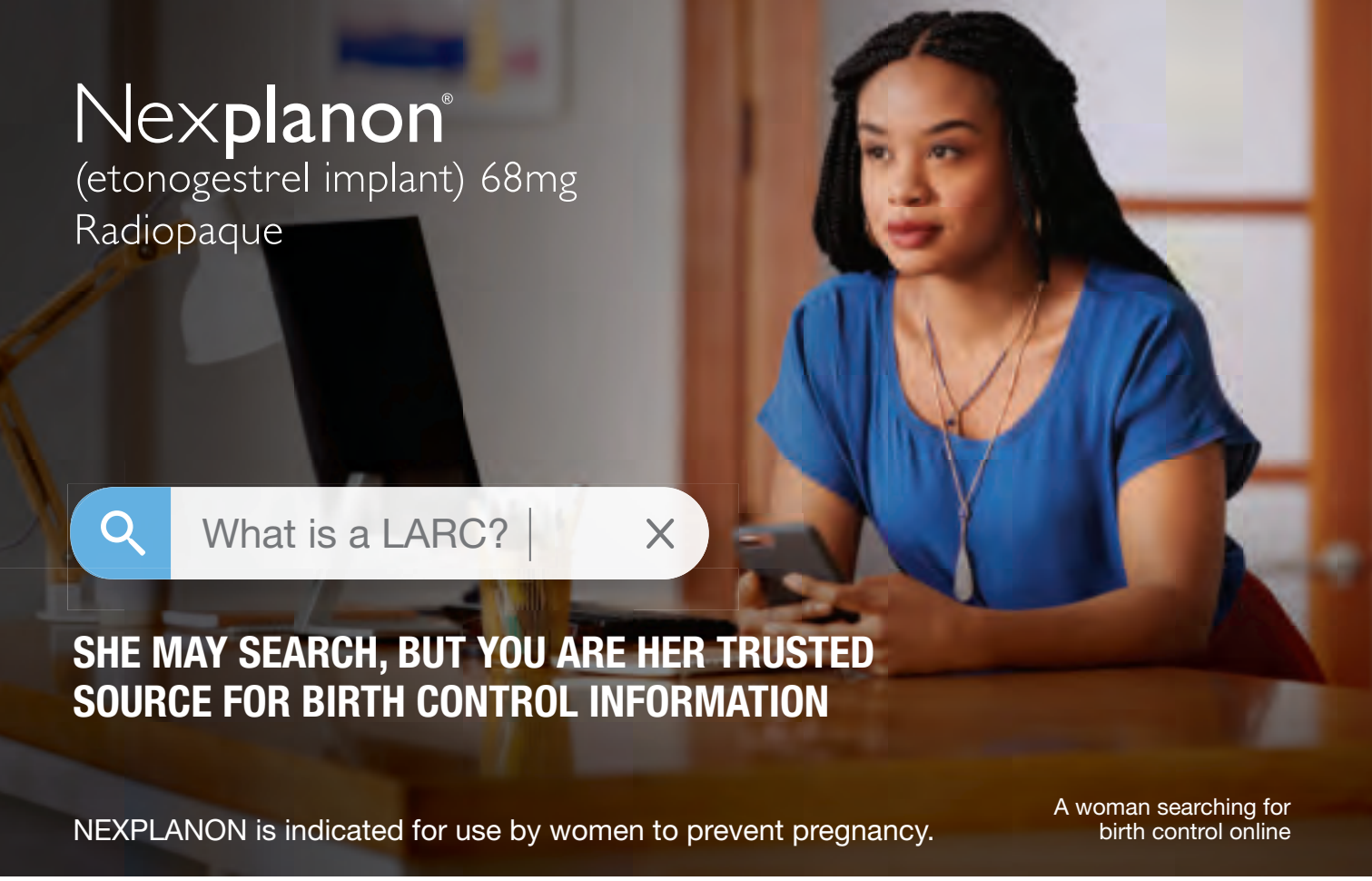
Results. Ninety-three women were included in the primary analysis. There were no differences in baseline characteristics between groups. No difference was detected in activity by AAS scores between all 3 groups (scores: plug-unplug, 70.3; continuous drainage, 67.7;

FAST TRACK

No difference was found in AAS scores between the 3 groups; scores: plug-unplug, 70.3; continuous drainage, 67.7; reference arm, 79.4 (P = .09)

CONTINUED ON PAGE 30

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque



SHE MAY SEARCH, BUT YOU ARE HER TRUSTED SOURCE FOR BIRTH CONTROL INFORMATION

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.

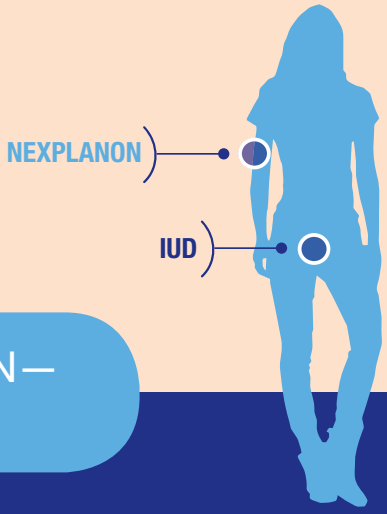
NEXPLANON and pregnancy

- 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
INVENTING FOR LIFE

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.

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Practice points on postoperative voiding dysfunction

- Bladder backfill in the operating room followed by spontaneous void in the postanesthesia care unit (PACU) is a safe and efficient way to assess for postoperative voiding dysfunction.
- Voids of 200 mL or more (following a 300-mL backfill) may not require a PACU postvoid residual assessment.
- Postoperative activity does not appear to be impacted by the presence of an indwelling catheter.

reference arm, 79.4; $P = .09$). The 2 treatment arms had no overall difference in culture-positive UTI (plug-unplug, 68.8%; continuous drainage, 48.4%; $P = .625$). No significant difference was found in the percentage of patients who passed their initial outpatient void trial (plug-unplug, 71.9%, vs continuous drainage, 58.1%; $P = .25$) (**TABLE 2**, page 25).

FAST TRACK

The concern that opening and closing a transurethral drainage system would increase UTI rates was not substantiated, but the study was not powered specifically for this outcome

Catheter impact on postoperative activity considered

Strengths of the study include the prospective randomized design, the inclusion of a noncatheterized reference arm, and use of a validated questionnaire to assess activity. The study was limited, however, by the inability to blind patients to treatment and the lack of power to assess other important outcomes, such as UTI rates.

Although the authors did not find a difference in activity scores between the 2 catheterization methods, no significant difference was found between the catheterized and noncatheterized groups, which suggests that catheters in general may not significantly impact postoperative activity. The theoretical concern that opening and closing a transurethral drainage system would increase UTI rates was not substantiated, although the study was not powered specifically for this outcome.

Ultimately, the plug-unplug method may be a safe alternative for patients who desire to avoid attachment to a drainage bag postoperatively.

For a review of antibiotic prophylaxis for UTI in postoperative catheter-managed women, read the online version of this article at mdedge.com/obgyn. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Based on the results of an RCT that compared 2 methods of catheter management after pelvic reconstructive surgery, the plug-unplug catheterization method may be an acceptable alternative to traditional catheterization.

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COVID-SAFE: Strategies for safeguarding your outpatient clinical practice against COVID-19

Rethinking—and revamping—your ObGyn clinical practice in the era of the COVID-19 public health emergency

Mary L. Rosser, MD, PhD

No question, the COVID-19 pandemic has been a challenging time for medical practices across the United States. Uncertainty remains regarding bringing patients and services back into our offices. One factor that distinguishes many ObGyn practices from other specialties is that our practices have remained open—in some form—since the beginning of the pandemic. In various parts of the country, gynecologic surgeries and routine office visits have been significantly reduced; however, deliveries and gynecologic emergencies have continued.

In this article, I suggest a framework of strategies and resources to provide insight for outpatient operations. Individual practices will vary across the nation depending on local conditions. Full practice capacity may take on a different look than it had prior to the pandemic, and there is opportunity to change the way we operate.

Strategy 1: Consult regulatory requirements frequently

As the local status of COVID-19 evolves quickly, it is essential to examine the frequently updated recommendations from regulatory agencies at the federal, state, and local levels. Clinical practices that function within health systems need to demonstrate alignment with hospital or university policies and procedures. The Centers for Disease Control and Prevention (CDC), Occupational Safety and Health Administration (OSHA), Centers for Medicare and Medicaid Services (CMS), and individual state departments of health provide dynamic resources that are easily accessible online.[1-3]

The American College of Obstetricians and Gynecologists (ACOG) continues to be an excellent medical society resource.[4] Subspecialty organizations that provide up-to-date guidance include the Society for Maternal-Fetal Medicine (SMFM), Society of Gynecologic Surgeons (SGS), AAGL (American Association of Gynecologic Laparoscopists), American Society for Reproductive Medicine (ASRM), and Society of Gynecologic Oncology (SGO).[5-9] These resources are updated as more information about COVID-19 emerges, and they may be modified to different local-regional conditions.

The professional liability insurance carrier is an important source of insight for a number of circumstances, including modifications to your office practice, such as returning to full-scope or part-time practice; operating outside normal clinical service arrangements (for example, assisting with emergency care); offering telehealth services; and adding extra hours or employees to accommodate the patient backlog. Business insurance coverage is a separate issue to consider.

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Reviewing the practice policy may protect your business from COVID-related liabilities.

Consulting with legal counselors can be helpful. They can assist with navigating various practice and personnel COVID-related changes, as well as developing a viable plan for patients who were previously insured pre–COVID-19 who are currently uninsured.

Strategy 2: Reimagine schedule capacity

The waxing and waning of the COVID-19 crisis presents an opportunity to evaluate our office practices and make necessary and positive changes. The question becomes, do we operate our practices as usual or do we rethink our strategy for seeing patients and integrate lessons learned from the pandemic? Patients are deciding when they are comfortable to schedule elective surgeries and routine office encounters. This gives us the chance to break from the tradition of 100% in-person visits and change the way we care for women.

FAST TRACK

Telehealth does not replace the in-person visit but can be viewed as a complementary and supplementary service

The coronavirus has accelerated the rise of telehealth/telemedicine and is, perhaps, a silver lining of the pandemic. Telehealth is a valuable tool for accessing health services when in-person visits are not possible. Evaluating and triaging patients for in-person versus telehealth visits is now a viable option for clinical practice and reduces exposure to COVID-19 infection.

Telemedicine is convenient, and clinicians can use it to counsel and screen for various health issues as well as to extend their reach to rural communities. Appropriate consent should be documented in the patient chart. As some areas continue to be without adequate access to WiFi, telephone contact also is currently acceptable. Telehealth does not replace the in-person visit but can be viewed as a complementary and supplementary service.

Consider a balance between telehealth and in-person visits by evaluating which visits can continue remotely and which can alternate with in-person visits. This offers tremendous flexibility and will expand delivery of essential health care to patients.[10] Integrating telemedicine into clinical practice provides an additional benefit: It minimizes the exposure and transmission of COVID-19 to health care workers and patients and preserves supplies, including personal protective equipment (PPE).

Prioritize the backlog of patients who require follow-up testing, procedures, and surgeries. Communicate with patients that it is safe to be seen and important to not avoid routine and preventative visits that might reveal concerns or conditions that require treatment.

Strategy 3: Institute infection prevention and control measures

The importance of instituting and ensuring safety measures for office personnel and patients cannot be underestimated. Recently, a study from King's College in London found that frontline health care workers with PPE still have 3 to 4 times the risk of contracting coronavirus compared with the general public.[11] Health care systems should ensure adequate PPE availability and develop additional strategies to protect health care workers from COVID-19. We have to be fanatical about cleanliness and PPE. We have to be diligent about how we space ourselves and our patients. Consider adjusting workflows to ensure that visits can be conducted as quickly and safely as possible.

Communicating updated safety plans and processes are invaluable for both patients and health care workers. Patients want to be reassured that safety precautions are in place to keep the environment safe and clean. Additionally, privacy and confidentiality concerns should be addressed.

Consider a modified office schedule that can reduce the number of people in the office, person-to-person contact, and COVID-19 transmission. Social distancing is improved and PPE and other supplies are preserved.

- Employees can work on alternating days or during different parts of the day.
- Administrative staff who do not need to be physically present in the office might work remotely.
- Expanding office hours (early morning, evening, and weekends) spreads patient visits throughout the day and minimizes high-volume in-person visits.

Institute a daily COVID-19 symptom attestation and temperature check for employees on arrival at work.

Health care personnel with symptoms of COVID-19 should be prioritized for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) RNA testing with an approved nucleic acid or antigen detection assay. A negative result indicates that the person most likely did not have an active SARS-CoV-2 infection at the time the sample was collected. A second test for SARS-CoV-2 RNA may be performed at the discretion of the evaluating health care provider, particularly when a higher level of clinical suspicion for infection exists.

The return to work decision should be determined by an agreed on symptom-based approach to clearance. If needed on a case-by-case basis, a review can be performed with the individual's health care provider.[12]

Require universal masking and appropriate protective equipment.

- All staff members, patients, and visitors must wear masks correctly in the facilities (except children under age 2).
- All clinical staff members must wear masks correctly and eye protection during every patient encounter.

Reconfigure the waiting room and patient flow.

- Configure waiting room furniture to reinforce 6 feet of physical distancing.
- Remove all books, magazines, and toys from all waiting areas.
- Laminate signage for display.
- Install plexiglass at the check-in desk to minimize virus transmission.
- If possible, ask patients to wait in their car until their appointment time or to go directly to their exam room on arrival if it is available.
- Implement virtual check-in and check-out so that patients reduce unnecessary contact with surfaces and staff.
- Limit a high volume of patients to maintain social distancing etiquette, avoid delays, and allow adequate cleaning time between patients.
- Permit visitors to accompany adult patients to their ambulatory appointments only if special assistance is required.
- Limit the number of staff members in the exam and treatment rooms and maintain at least 6 feet between people except during medical care activities.
- Consider patient flow in a one-way traffic pattern.

Focus on keeping the clinical practice clean. (Follow the instructions and disinfect with a registered disinfectant product that meets the US Environmental Protection Agency criteria for use against COVID-19.[13])

- Clean waiting rooms and restrooms frequently.
- Coordinate patient appointments to allow for infection control measures.
- Frequently clean high-touch surfaces, including tables, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, and sinks.
- Clinicians and all medical staff members should wash their hands before and after interacting with patients.
- Clean and disinfect the exam and treatment rooms before and after each patient.
- Use products that are effective against a range of organisms and viruses, including the coronavirus that causes COVID-19.
- Place signs indicating that rooms have been cleaned; this will assure and comfort patients. Take credit for your infection control processes.

Keep abreast of isolation and precaution guidelines. Based on data available at the time of this article's publication, the CDC recommends ending isolation and transmission-based precautions for most people with COVID-19 using a symptom-based strategy.[14] This limits unnecessary prolonged isolation and use of laboratory testing resources.

Generally, repeat SARS-CoV-2 polymerase chain reaction (PCR) testing is not recommended for "COVID-19 recovered" patients. Specifically, those patients with a prior positive SARS-CoV-2 PCR test result and who have met criteria for isolation discontinuation do not need a follow-up PCR test. A *test-based* strategy to discontinue isolation and transmission-based precautions is required only for severely immunocompromised patients.[15]

FAST TRACK

Configure waiting room furniture to reinforce 6 feet of physical distancing

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Prepare for a future COVID-19 surge and review your emergency plan and responses and revise as needed. Review handling of the current pandemic and best practices plus areas of improvement.

Symptom-based criteria for discontinuing transmission-based precautions include the following:

Patients with mild to moderate illness, not severely immunocompromised:

- at least 10 days have passed *since symptoms first appeared* and
- at least 24 hours have passed *since last fever* without fever-reducing medications and
- symptoms (cough, shortness of breath) have improved.

Note: For patients who are not severely immunocompromised and are asymptomatic throughout their infection, transmission-based precautions may be discontinued when at least 10 days have passed since the date of their first positive viral diagnostic test.

Patients with severe to critical illness, severely immunocompromised:

- at least 20 days have passed *since symptoms first appeared* and
- at least 24 hours have passed *since last* fever without fever-reducing medications and
- symptoms (cough, shortness of breath) have improved.

Note: For patients who are severely immunocompromised and are asymptomatic throughout their infection, transmission-based precautions may be discontinued when at least 20 days have passed since the date of their first positive viral diagnostic test.

FAST TRACK

Continue to communicate the message that the safety and well-being of our health care workers and patients in our clinical practices is paramount

Strategy 4: Implement frequent employee communication and care

The safety and well-being of our health care workers and patients in our clinical practices is paramount. Continuing to communicate this message and developing and sharing a plan may ameliorate the obvious toll on mental and emotional well-being. Frequent and effective communication with your clinical team is vital to reinforce policies and protocols, eliminate silos, and reduce errors.

Practice communication and care with these approaches:

- Offer regular employee COVID-19 testing.
- Re-educate staff about infection control protocols to ensure buy-in.
- Communicate with staff about the plan to address staffing shortages.
- Implement regular employee team huddles that can address accomplishments, challenges, areas for improvement, and top priorities.
- Perform regular celebrations for staff appreciation.
- Address mental health and chronic stress and offer empathy and coping resources and services to staff and clinicians. This will have a valuable, long-term benefit.

Patient communication. As the COVID-19 pandemic continues and stay-at-home policies are in place, patients should be encouraged to seek medical care if they are ill or have acute or chronic conditions. Communicate regularly with patients and let them know that their safety and well-being is the top priority. Prior to in-person visits, inform them of the safety processes that are in place to protect them.

Fostering an honest clinician-patient relationship enhances communication. Despite these efforts, some patients may not be forthcoming about their COVID-19 symptoms, illness, exposure, or travel. Health care staff can be encouraged to set a tone of tolerance and compassion and treat everyone with universal precautions.

Rising to the challenges

During the coronavirus pandemic, ObGyns continue to safely care for pregnant women and also triage and treat women who require timely office care as well as emergency and cancer-related surgeries.

The COVID-19 environment rapidly changes depending on the practice location. The strategies described represent a compilation of resources from key organizations that hopefully will prove useful and can be shaped to fit your practice. Local and regional recommendations vary, and no one can predict the course of the virus.

Consider reviewing your contingency plans regularly. As we have learned over

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OBG MANAGEMENT

SPECIAL SECTION

THE 2020 SCIENTIFIC MEETING OF THE SOCIETY OF GYNECOLOGIC SURGEONS

HIGHLIGHTS ISSUE, PART 1

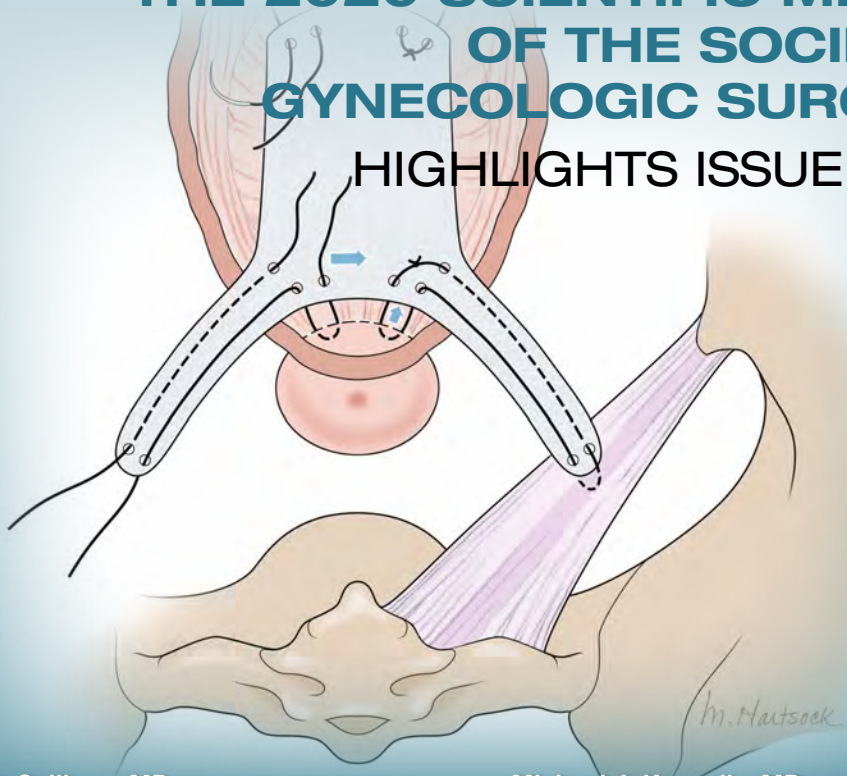

ILLUSTRATION: MARCIA HARTSOCK

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Even in a virtual environment, the Society of Gynecologic Surgeons delivers without a "glitch"

The events typical of in-person meetings, such as abstracts, videos, postgraduate courses, and keynote addresses, were offered, with much interaction between participants

Patrick J. Culligan, MD

Earlier this year, I was honored to serve as the Scientific Program Chair for the 46th Annual Scientific Meeting of the Society of Gynecologic Surgeons (SGS). This year's meeting was the first ever (and hopefully last) "virtual" scientific meeting, which consisted of a hybrid of prerecorded and live presentations. Although faculty and attendees were not able to be together physically, the essence of the lively SGS meetings came through loud and clear. We still had "discussants" comment on the oral presentations and ask questions of the presenters. These questions and answers were all done live—without a glitch! Many thanks to all who made this meeting possible.

In addition to the outstanding abstract and video presentations, there were 4 superb postgraduate courses:

- Mikio Nihira, MD, chaired "Enhanced recovery after surgery: Overcoming barriers to implementation."
- Charles Hanes, MD, headed up "It's all about the apex: The key to successful POP surgery."
- Cara King, DO, MS, led "Total laparoscopic hysterectomy: Pushing the envelope."
- Vincent Lucente, MD, chaired "Transvaginal reconstructive pelvic surgery using graft augmentation post-FDA."

Many special thanks to Dr. Lucente who transformed his course into a wonderful article for this special section of OBG Management (see next page). These courses were well attended and quite interactive despite the virtual format.

One of our exceptional keynote speakers was Marc Beer (a serial entrepreneur and cofounder, chairman, and CEO of Renovia, Inc.), whose talk was entitled "A primer on medical device innovation—How to avoid common pitfalls while realizing your vision." Mr. Beer has turned this topic into a unique article for this special section (see next month's issue for Part 2).

Our TeLinde Lecture, entitled "Artificial intelligence in surgery," was delivered by the dynamic Vicente Gracias, MD, professor of surgery at Robert Wood Johnson University Hospital, New Brunswick, New Jersey. We also held 2 live panel discussions that were very popular. The first, "Work-life balance and gynecologic surgery," featured various perspectives from Drs. Kristie Green, Sally Huber, Catherine Matthews, and Charles Rardin. The second panel discussion, entitled "Understanding, managing, and benefiting from your e-presence," by experts Heather Schueppert; Chief Marketing Officer at Unified Physician Management, Brad Bowman, MD; and Peter Lotze, MD. Both of these panel discussions are included in this special section as well (with the latter on page SS8).

I hope you enjoy the content of this special section of OBG Management highlighting the 2020 SGS meeting. Watch for part 2 in the next issue, and I hope to see you at our 47th Annual Scientific Meeting in Palm Springs, California, in March 2021. ■

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Transvaginal reconstructive surgery for POP: Innovative approach to graft augmentation in the post-mesh era

These surgeons describe a novel technique for transvaginal reconstruction using a biologic allograft product

Jessica Sosa-Stanley, MD; Vincent R. Lucente, MD, MBA; Michael J. Kennelly, MD; and Sachin B. Shenoy, MD

Pelvic organ prolapse (POP) is a common occurrence over the course of a woman's lifetime, especially in parous women (up to 50% of women who have given birth).[1] The anterior vaginal wall is the most common site of POP and has the highest recurrence rate of up to 70%.[2] The risk of developing POP increases with age, obesity, White race, family history, and prior pelvic surgery, such as hysterectomy. It affects more than 3 million women in the United States alone, often negatively impacting sexual function and overall quality of life.[3,4]

Because women are living longer than ever before and are more active in their senior years, a long-lasting, durable surgical repair is desirable, if not necessary. To be cost-effective and to avoid general anesthesia, the surgical approach ideally should be vaginal.

Biologic and synthetic grafts to augment transvaginal repair traditionally are used to improve on the well-recognized high failure rate of native-tissue repair that is often seen at both short-term and medium-term follow-up.[5] The failure rate is commonly referenced as 30% to 40% at 2-year follow-up and 61% to 70% at 5-year follow-up, well-established by the results of the OPTIMAL randomized clinical trial.[6] The more recent Descent trial likewise demonstrates a higher failure rate of native-tissue repair versus transvaginal mesh repair at a shorter term of 30 to 42 months.[7] Furthermore, the use of permanent versus absorbable suture in suspension of the vaginal apex is associated with lower short-term failure rates.[8]

Despite this Level I evidence that demonstrates a clear advantage for obtaining a longer or more durable repair with permanent materials, native-tissue repairs with absorbable suture are still performed routinely. Since the US Food and Drug Administration (FDA) ordered that the use of transvaginal surgical mesh augmentation for pelvic reconstructive surgery be discontinued, it is more important than ever to explore evolving alternative native-tissue augmentation repair techniques that hopefully can preserve the advantages and merits of vaginal surgery and achieve longer durability.[9]

Biologic graft augmentation use in transvaginal reconstruction

All biologic grafts, including allografts derived from human tissue and xenografts derived from animal tissue, are acellular constructs composed of extracellular matrix (ECM) that acts as scaffolding for the host tissue. The ECM is predominantly composed of collagen (types I and III) and noncollagenous fibronectin, laminin, and glycosaminoglycans in various amounts depending on

Dr. Lucente reports that he has received grant or research support from Advanced Tactile Imaging, Boston Scientific, Coloplast, FemSelect, and Valencia; serves as a consultant to Coloplast and Contura; and is a speaker for Allergan, Boston Scientific, Coloplast, Duchesnay, FemSelect, and Neomedic. Dr. Kennelly reports that he has received grant or research support from Coloplast and Boston Scientific and serves as a consultant to Coloplast and Boston Scientific. Dr. Sosa-Stanley and Dr. Shenoy report no financial relationships relevant to this article.

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the source tissue. The 3D presentation of ECM's complex molecules allows for rapid repopulation of host cells and revascularization with eventual regeneration.

Once a biologic graft is placed surgically, the body's response to the scaffold ECM mimics the normal wound-healing process, beginning with fibrin-rich matrix hemostasis and the subsequent innate immune response of neutrophil and M1 macrophage infiltration. M1 macrophages are proinflammatory and clear cellular debris and begin the process of graft scaffold degradation. The host tissue then begins the process of remodeling through pro-remodeling M2 macrophages and stem cell recruitment, proliferation, and differentiation.[10] As the biologic graft provides initial structure and strength for pelvic repairs, the ideal ECM scaffold would not degrade before the host is able to fully undergo regeneration and maintain its structure and strength.

Biologic grafts differ in source (allograft or xenograft), type (pericardium, dermis, or bladder), developmental stage (fetal or adult), decellularization processing, and sterilization techniques. These 5 aspects determine the distinct 3D ECM scaffold structure, strength, and longevity. If the ECM scaffold is damaged or retains noncollagenous proteins during the preparation process, an inflammatory response is triggered in which the graft is degraded, resorbed, and replaced with scar tissue. Furthermore, certain processing techniques aimed at extending the ECM's durability—that is, cross-linking collagen—results in the foreign body response in which there is no vascular infiltration or cellular penetration of the graft and a collagen capsule is created around the empty matrix.[11] To avoid resorption or encapsulation of the graft, the ECM scaffolds of biologic grafts must be optimized to induce regeneration.

Choosing surgical POP repair

The decision to undergo surgical treatment for prolapse is a shared decision-making process between the patient and surgeon and always should be individualized. The type of procedure and the surgical approach will depend on the patient's goals, the degree of prolapse, clinical history, risk tolerance, the surgeon's skill set, and whether or not there is an indication or relative contraindication for uterine removal at the time of prolapse repair.

While the FDA's order does not apply to transabdominally placed surgical mesh, such as sacrocolpopexy, not all patients are ideal candidates for an abdominal sacrocolpopexy. Most notable are women with a history of multiple prior abdominal surgeries with higher rates of intraperitoneal adhesions. Ideally, to be cost-effective and to avoid general anesthesia, the surgical approach should be vaginal whenever possible.

Biologic versus native-tissue grafts

Currently, only low-quality evidence exists that compares the outcomes of biologic grafts with traditional native-tissue repairs in POP. Studies have been limited by poor reporting of methods, inconsistency in technique and materials used, and imprecise definitions. One Cochrane Review on the surgical management of POP concluded that biologic graft augmentation was associated with a lower failure rate (18%) within 1 to 2 years when compared with a traditional anterior colporrhaphy (28%).[12]

Based on consideration of all Cochrane Database Reviews and recent large systematic reviews, there clearly is a paucity of information on which to draw well-defined conclusions regarding the advantage of biomaterials in prolapse surgery.[12-14] This is due in part to the variation in graft material used and the surgical technique employed.

Similarly, evidence is lacking regarding the superiority of one type of biologic graft over another. Furthermore, some of the grafts previously studied are no longer on the market.[15] With the FDA's removal of all transvaginal mesh, including xenografts, only allografts are available for pelvic floor reconstruction. Currently, only 3 commercial manufacturers market allografts for pelvic floor reconstruction. Each allograft is available in various sizes and all can be trimmed at the time of the surgical procedure to customize both the size and shape to fit the individual patient.

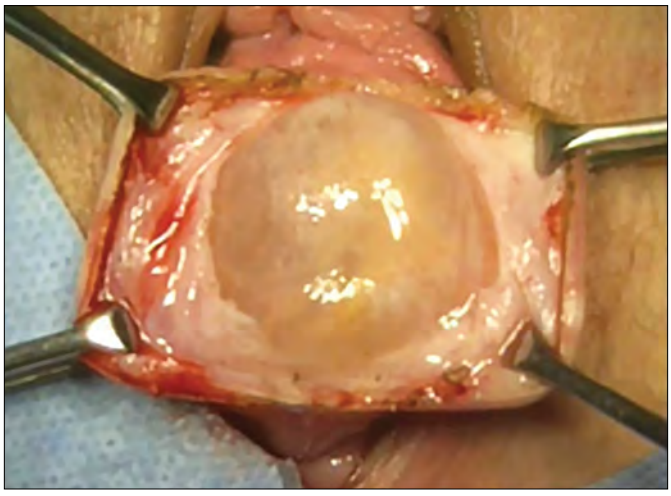
A novel technique using Axis Dermis and polypropylene suture

One of the commercially available allografts, Axis Dermis (Coloplast), is non–cross-linked and is

derived from human cadaveric dermal tissue from the back and dorsum of the upper leg. It is sterilized by a proprietary Tutoplast sterilization process that uses gamma irradiation to inactivate and prevent the transmission of pathogens. This unique technique involving solvent dehydration means the graft is never freeze dried; thus, the natural tissue matrix is preserved.

Additionally, the allograft is antigen-free, which decreases the risk of tissue reaction (scarring/fibrosis) and aids in the process of host tissue remodeling; invasion by growth factors, blood cells, collagen, elastin, and neovascularization. This natural tissue remodeling facilitates the anticipated "reabsorption" of the graft by the host tissue, leaving the patient with a tissue scaffold, that is, a stronger layer of "fascia" beneath the muscularis.[16] As a result of this "biocompatible" graft, the host tissue remodeling has been shown in the rat model to involve early cellular infiltration and angiogenesis (in the first week after implantation), that leads to an organized cellular architecture with greater tensile strength by week 4, and ultimately inability to distinguish host collagen from the implant by 8 to 12 weeks.[17,18]

FIGURE 1 Hydrodissection of the vesicovaginal space



Steps in performing the technique

To ensure that the graft is placed adjacent to the vaginal serosa, a full-thickness dissection is carried out to enter the true vesicovaginal space, which lies below all 4 histologic layers of the vagina (nonkeratinized stratified squamous epithelium, lamina propria, muscularis, and serosa). For the anterior dissection, a Tuohy epidural needle is used to achieve an accurate and consistent depth when injecting fluid (hydrodissection) to enter this true pelvic space (**FIGURE 1**). Correct entry into the vesicovaginal space can be confirmed visually by the presence of adipose tissue.

Many pelvic surgeons use the sacrospinous ligament (SSL) as a strong and reliable point of attachment for vaginal prolapse repair. It can be approached either anteriorly or posteriorly with careful dissection. Permanent suture (0-Prolene) is used to "bridge" the attachment between the SSL, the Axis Dermis graft, and the cervix (or vaginal apex). The suture is placed in the middle third and lower half of the ligament to avoid injury to nearby neurovascular structures.

While the surgeon may use any suture-capturing device, we prefer the Anchosure System (Neomedic). This device delivers a small anchor securely into the ligament through a single point of entry, minimizing the risk of postoperative pain for the patient. A 6 cm x 8 cm size Axis Dermis graft is then trimmed to meet the specifications of the patient's anatomy.

Most commonly, we measure, mark, and trim the body of the graft to 5.5 cm in length with a width of 3 cm. The bilateral arms are approximately 1 cm in width and comprise the remaining length of the 8 cm graft (**FIGURE 2**, page SS6). As shown in Figure 2, pre-made holes are marked and punched out using a large hollow needle. These serve as the points of attachment for the permanent suture to be "weaved" into the graft arms and delayed absorbable "tacking suture" to be attached from the pubocervical fascia at the bladder neck to the distal end of the graft. This facilitates fixation of the graft in the midline of the anterior vaginal wall, overlying any central distention-type defect.

Finally, following attachment of the SSL permanent suture to the distal graft arm, this suture is then attached to the proximal U-shaped end of the graft body (in the midline), followed by a deep and secure bite through the cervix (or vaginal vault apex) and back through the proximal graft. These

FIGURE 2 Biologic allograft augmentation use in transvaginal reconstruction

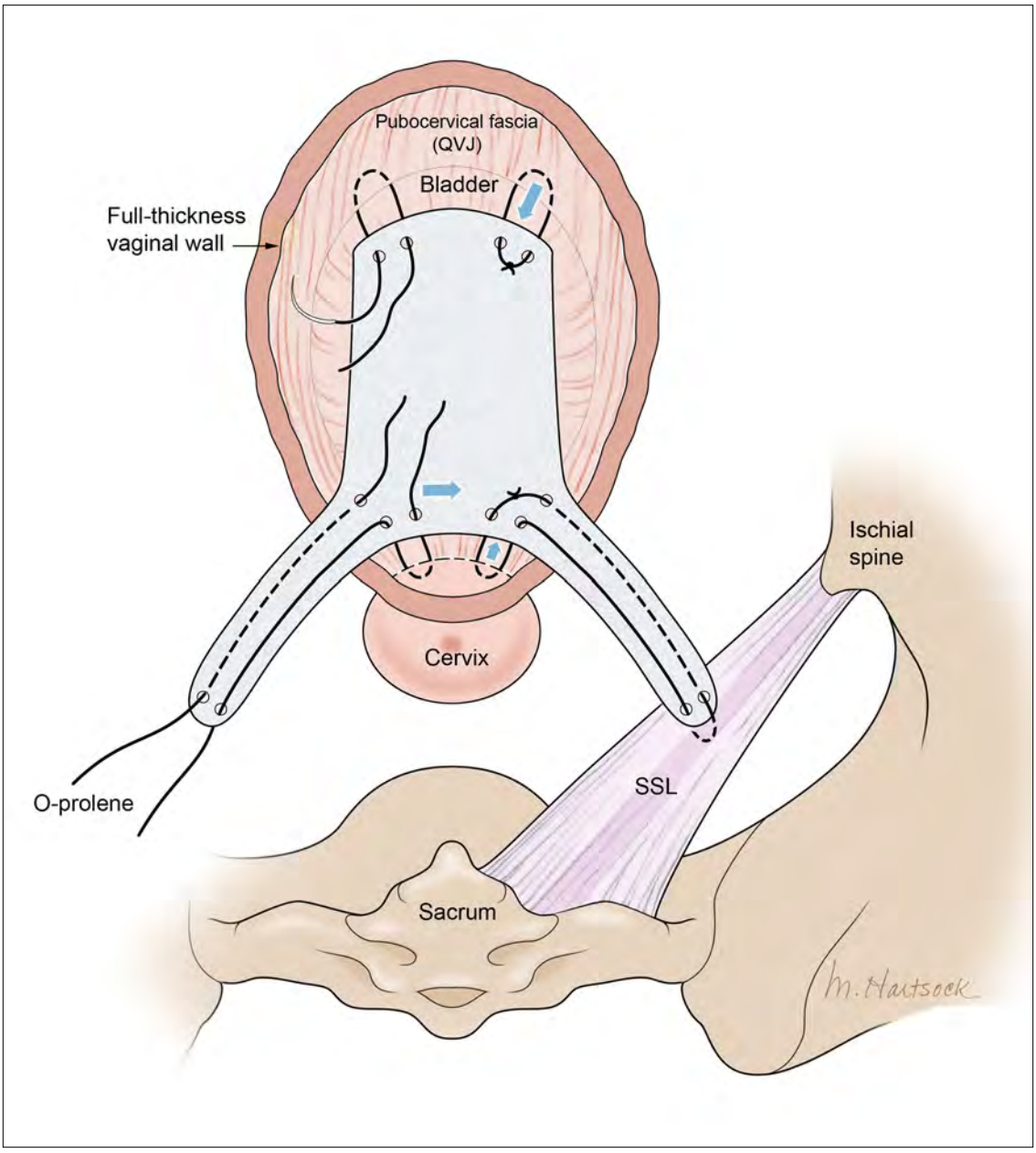


ILLUSTRATION: MARCIA HARTSOCK FOR OBG MANAGEMENT

SSL suspension sutures are then tied such that the distal arms of the graft advance down to the ligament. Care is taken not to tie down to the SSL itself, rather until the cervix (or apex) is reduced to its normal anatomical location.

After the graft is secured in place, the full-thickness vaginal wall is closed with delayed absorbable suture. Sterile 1-inch ribbon packing is placed in the vagina immediately to close any dead space between the vagina and the graft to decrease the risk of seroma or hematoma formation.

This newly developed technique, like many surgeries for POP, requires extensive knowledge of pelvic anatomy and skill in vaginal surgery, and we recommend referral to a subspecialist in Female Pelvic Medicine and Reconstructive Surgery.

Upcoming plans to share outcomes data

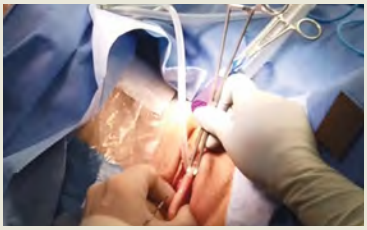
We are in the process of performing a retrospective review of all of the cases we have performed at our institution using this technique of permanent suture bridging to the SSL within the arm of the biograft. Given the relatively recent FDA announcement, we have yet to establish any long-term outcomes data. However, the preliminary results at 6-month follow-up are promising and demonstrate a low (2.6%) failure rate, without significant safety concerns. We hope to publish these data as well as more data on longitudinal outcomes in the future.

In summary

Many women are at risk for native-tissue repair failure or are not well suited for an abdominal procedure to correct their pelvic support defect and restore their quality of life. As expert pelvic surgeons, we play an important role in the search for innovative solutions for these women. There is ample opportunity for future research and clinical trials to determine the best biologic materials and their optimal use in pelvic reconstructive surgery.

Originally, polypropylene mesh was designed for use in augmenting abdominal hernia repairs and later was adapted by manufacturers for use in POP repair. The FDA removal from the market of existing transvaginal synthetic mesh kits was a unique catalyst that challenged our community to develop transvaginal repairs using biologic grafts that are genuinely tailored to the unique needs of the female pelvic anatomy. ■

WATCH THE VIDEO



See the online version of this article at http://www.mdedge.com/obgyn

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ROUNDTABLE

How to build your identity as a physician online

With the right know-how you can maximize your e-presence, optimizing your website, growing your patient base, and managing your reputation at the same time

Expert panel featuring Patrick J. Culligan, MD; Brad Bowman, MD; Peter M. Lotze, MD; and Heather Schueppert

To have a thriving business in today's world, a functioning website is crucial to the overall business health. For a medical practice in general, and for its physicians specifically, it is one of the first steps for maintaining a practice. But to grow that practice, it is crucial to take the steps beyond just having a website. Growth requires website optimization for search engines, an expanding referral base, and the knowledge to use web tools and social media at your disposal to promote the practice and its physicians. In this roundtable, several marketing experts and web-savvy physicians discuss using available tools to best position and grow a practice.

Choosing a web upgrade

Patrick J. Culligan, MD: Peter, can you start us off by describing your relationship with Heather, and how your practice benefitted from her expertise?

Peter M. Lotze, MD: Sure. I am a urogynecologist in the competitive market of pelvic reconstructive surgery in Houston, Texas. Within that market, my main approach was to reach out to other physicians to refer patients to my practice. It generally would work, but took increasingly greater amounts of time to call these physicians up, write them letters, and maintain relationships. I felt that the large, national practice group that I am in did not have a significant web presence optimized to promote my practice, which makes it difficult for patients seeking your services to find you in their search for a doctor. It is helpful for patients to be able to understand from your website who you are, what you do, and what their experience may be like.

Glaring to me was that a web search specific for me or things that I do, would not produce our company's results until page 2 or more on Google. This can be devastating for a practice because most people don't go past the first page, and you can end up with fewer self-referrals, which should be a significant portion of new patients to your practice. I knew I needed guidance; I knew of Heather's expertise given her exceptional past work building marketing strategies.

Digital go-tos for marketing

Heather Schueppert: Yes, I was pleased to work with Dr. Lotze, and at the time was a marketing consultant for practices such as his. But gone are the days of printed material—brochures, pamphlets, or even billboards—to effectively promote a business, or in this case, a practice. What still withstands the test of time, however, as the number 1 marketing referral source is word of mouth—from your trusted friend, family member, or coworker.

It is now proven that the number 2 most trusted form of advertising, the most persuasive and the most motivating, is online marketing.[1] It is the "digital word of mouth"—the review. Patients are actively online, and a strong digital presence is critical to provide that direct value to retain and grow your patient base.

Foundations of private practice reach out

There are 3 important areas that I consider the foundation of any private practice marketing strategy (**TABLE**). First is an updated website that is search engine optimized (SEO). You can't just set it and forget it, it needs to be an updated website. The algorithms for search engines are changing constantly to try to make it as fair and

TABLE Checklist for building and maintaining your e-presence

- Local search audit and completion
- Updated, SEO-optimized website
- Review management with focus on patient satisfaction questions
- Regular and relevant social media

relevant as possible for patients or consumers to find the businesses they are searching for online.

The second area is review management, and for a physician, or even a care center, to do this on your own is a daunting task. It is a critical component, however, to making sure that your reputation out there, that online word of mouth, is as high a star rating as possible.

The third component is local search, which is basically a form of SEO that helps businesses show up in relevant local searches. We are all familiar with the search, "find a restaurant near me," anything that pushes those search engines to find something local.

Those are what I call the effective triad: that updated website, the review management, and the local search, and all of these are tied together. I think Dr. Lotze and his practice did these effectively well, and I believe that he achieved his goals for the longer term.

Review/reputation management

Dr. Culligan: Brad, is there something that doctors may not know about Healthgrades, and are there opportunities to take full advantage of this physician-rating site?

Brad Bowman, MD: I agree with everything that Dr. Lotze and Heather have said. Start with yourself—what is it that you want to be, the one thing you want to stand for? Get your own marketing, your website right, then, the point is, once you do all that and you are number 1 in SEO, you are still only going to get about 25% of the people looking for you by name to come to your website. The other 75% are going to look at all the other different sites that are out there to provide information to consumers. So the question becomes what do you do with all these other third-party sites? Healthgrades is the most comprehensive and has the highest traffic of the third-party "find a doctor" sites. In 2020, half of all Americans who go to a doctor will use Healthgrades at some point to help select and connect with that doctor.

Physicians have their focus on the quality of the care they provide. Patients, however, focus on the quality of the entire health care experience. Did I get better? How long did I have to wait? Was the office staff helpful? Scarily enough, we still spend more time shopping for a refrigerator or mattress than we do shopping for a doctor. We still tend to think that all doctors are the same. It is the reality of how we have been trained by our insurance companies and by the health care system. That is why getting your marketing right and getting what is it that you want to be known for out there is important, so that you can get the types of patients you want.

Listings management is very important. Make sure that you are findable everywhere. There are services that will do this: Doctor.com, Reputation.com, and many others. They can help you make sure you get all your basic materials right: addresses, phone numbers, your picture. Because 75% of people are going to end up on third-party websites, if your phone number is wrong there, you could lose that patient.

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Then the second piece of working with third-party sites is reputation management. Physician reviews are not a bad thing, they are the new word of mouth, as Heather pointed out. Most (80%) of the reviews are going to be positive. The others will be negative, and that is okay. It is important that you get at least 1 or 2 reviews on all the different sites. We know from Healthgrades.com that going from zero reviews to 1 review will increase your call volume by 60%. If you have the choice between 2 physicians and one practice looks like people have been there before, you will go to that one.

You can learn from reviews as well, consumers provide valid feedback. Best practice is to respond to every positive and negative review. Thank them, indicate that you have listened to them, and address any concerns as necessary.

Dr. Lotze: As an example, one of the paramount things that Heather introduced me to was the third party I use to run my website. That company sends a HIPAA-compliant review out to each patient we have seen that day and gives them the opportunity to rate our services and leave comments. If a patient brings up a concern, we can respond immediately, which is important. Patients appreciate feeling that they have been heard. Typically, communicating with a patient will turn the 3-star review into a 5-star as she follows up with the practice.

Ms. Schueppert: Timeliness is important. And just to mention, there certainly is a time commitment to this (and it is a marathon versus a sprint) and there is some financial investment to get it going, but it could truly be detrimental to a practice if you decide not to do anything at all.

Dr. Bowman: Agencies can really help with the time commitment.

Handling bad reviews

Dr. Culligan: What about that person who seems to have it out for you, perhaps giving you multiple bad reviews?

Dr. Bowman: I have seen this before. At Healthgrades, we recently analyzed 8.4 million patient reviews to see what people wrote about.[2] The first thing they will talk about is quality of care as they see it. Did I get better or not? You can't "fix" every patient; there will be some that you cannot help. The next thing patients comment on is bedside manner. With negative reviews, you will see more comments about the office staff.[2]

A single negative review actually helps make the positive ones look more credible. But if you do believe someone is trolling you, we can flag it and will investigate to the best of our ability. (Different sites likely have different editorial policies.) For example, we look at the IP addresses of all reviews, and if multiple reviews are coming from the same location, we would only let one through, overwriting the previous review from that address.

Patients just want to be heard. We have seen people change their views, based on how their review is handled and responded to.

Dr. Lotze: Is there a response by the physician that you think tends to work better in terms of resolving the issue that can minimize a perceived caustic reaction to a patient's criticism?

Dr. Bowman: First, just like with any stressful situation, take a deep breath and respond when you feel like you can be constructive. When you do respond, be gracious. Thank them for their feedback. Make sure you reference something about their concern: "I understand that you had to wait longer than you would have liked." Acknowledge the problem they reference, and then just apologize: "I'm sorry we didn't meet your expectations." Then, if they waited too long for example, "We have a new system where no one should have to wait more than 30 minutes…." You can respond privately or publically. Generally, public responses are better as it shows other consumers that you are willing to listen and consider their point of view.

The next phase at Healthgrades

Dr. Culligan: Do you see changes to the way physician-rating sites are working now? Are we going to stay status quo over the next 10 years, or do you see frontiers in how your site is going to develop?

Dr. Bowman: For Healthgrades, we rely on quantitative and objective measures, not just the qualitative. We are investing heavily right now in trying to help consumers understand what are the relative volumes of different procedures or different patient types that each individual doctor sees. Orthopedics is an easy example—if you have a knee problem, you want to go to someone who specializes in knees. Our job is to help consumers easily identify, "This is a shoulder doctor, this is a knee doctor, and this is why that matters."

In the meantime, as a physician, you can always go into our site and state your care philosophy,

identifying what is the sort of patient that you like to treat. Transparency is good for everyone, and especially physicians. It helps the right patient show up for you, and it helps you do a better job providing referrals.

Social media: Avoid pitfalls, and use it to your benefit

Dr. Lotze: Branding was one of the things that I was confused about, and Heather really helped me out. As physicians, we put ourselves out there on our websites, which we try to make professional sources of information for patients. But patients often want to see what else they can find out about us, including Healthgrades and social media. I think the thing that is important to know with social media is that it is a place where people learn about you as a person. Your social media should be another avenue of promotion. Whether it is your personal or professional Facebook page, people are going to see those sites. You have an opportunity to promote yourself as a good physician and a good person with a wholesome practice that you want people to come to. If a physician is posting questionable things about themselves on any kind of social media, it could be perceived as inappropriate by the patient. That can impact how patients think of you as a person, and how they are going to grade you. If people lose sight of who you are due to a questionable social media posting, everything else (SEO, the website) can be for naught.

Dr. Culligan: What are the most important social media tools to invest your time in?

Ms. Schueppert: Before anybody jumps into social media, I firmly recommend that you make sure your local search and your Google 3-pack is set up—which is basically a method Google uses to display the top 3 results on its listings page. Then make sure you have a review management system in place. Make sure you have that updated website. Those are the foundational elements. Once you have that going, social media is the next added layer to that digital presence.

I usually recommend LinkedIn. It is huge because you are staying in contact with your colleagues, that business-to-business type of connection. It remains a way for physicians to set themselves up as experts in their level of specialty.

From there, it's either Instagram or Facebook. If you are serving more of the younger generations, the millennials and younger, then Instagram is the way to go. If you are focusing on your 40+, 50+, they are going to be far more on Facebook.

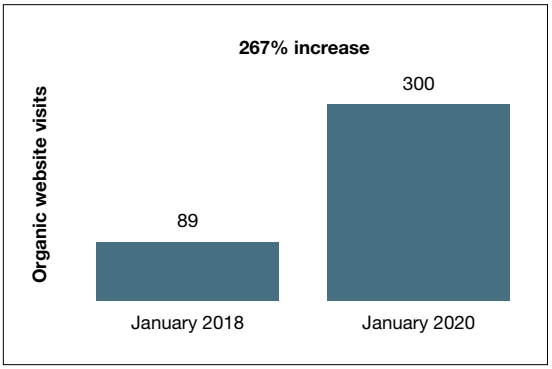
Dr. Lotze: For me, a Facebook page was a great place to start. The cost of those Google ads—the first things we see at the top of a Google search in their own separate box—is significant. If a practice has that kind of money to invest, great; it is an instant way to be first on the page during a search. But there are more cost-effective ways of doing that, especially as you are getting your name out. Facebook provides, at a smaller cost, promotion of whatever it is that you are seeking to promote. You can find people within a certain zip code, for instance, and use a Facebook ad campaign that can drive people to your Facebook page—which should have both routinely updated new posts and a link to your website. The posts should be interesting topics relevant to the patients you wish to treat (avoiding personal stories or controversial discussions). You can put a post together, or you can have a third-party service do this. People who follow your page will get reminders of you and your practice with each new post. As your page followers increase, your Facebook rank will improve, and your page will more likely be discovered by Facebook searches for your services. With an added link to your office practice website, those patients go straight to your site without getting lost in the noise of Google search results.

For Instagram, a short video or an interesting picture, along with a brief statement, are the essentials. You can add a single link. Marketing here is by direct messaging or having patients going to your website through a link. Instagram, like Facebook, offers analytics to help show you what your audience likes to read about, improving the quality of your posts and increasing number of followers.

YouTube is the number 2 search engine behind Google. A Google search for your field of medicine may be filled with pages of competitors. However, YouTube has a much lower volume of competing practices, making it easier for patients to find you. The only downside to YouTube is that it will list your video along with other competing videos, which can draw attention away from your practice.

If you want to promote your website or practice with video, using a company such as Vimeo is a better choice compared with YouTube, as YouTube gets credit for video views—which improves YouTube's SEO and not your own website. Vimeo allows for your website to get credit each time the

FIGURE Web traffic before and after hiring a webmaster



video is watched. Regardless of where you place your videos, make them short and to the point, with links to your website. Videos only need to be long enough to get your message across and stimulate interest in your practice.

If you can have a blog on your website, it also will help with SEO. What a search engine like Google wants to see is that a patient is on your web page and looking at something for at least 60 seconds. If so, the website is deemed to have information that is relevant, improving your SEO ranking. Finally, Twitter also can be used for getting messaging out and for branding. The problem with it is that many people go to Twitter to follow a Hollywood celebrity, a sports star, or are looking for mass communication. There is less interest on Twitter for physician outreach.

Measuring ROI

Dr. Culligan: What's the best way to track your return on investment?

Dr. Lotze: First for me was to find out what didn't work in the office and fix that before really promoting my practice. It's about the global experience for a patient, as Brad mentioned. As a marketing expert, Heather met with me to understand my goals. She then called my office as a patient to set up an appointment and went through that entire office experience. We identified issues needing improvement.

The next step was to develop a working relationship with my webmaster—someone who can help manage Internet image and SEO. Together, you will develop goals for what the SEO should promote specific to your practice. Once a good SEO program is in place, your website's ranking will go up—although it can take a minimum of 6 months to see a significant increase. To help understand your website's performance, your webmaster should provide you with reports on your site's analytics.

As you go through this process, it is great to have a marketing expert to be the point person. You will work closely together for a while, but eventually you can back off over time. The time and expense you invest on the front end have huge rewards on the back end. Currently, I still spend a reasonable amount of money every month. I have a high self-referral base because of these efforts, however, which results in more patient surgeries and easily covers my expenses. It is money well invested. My website traffic increased by 268% over 2 years (**FIGURE**). I'll propose that currently more than half of my patients are self-referrals due to online marketing.

Ms. Schueppert: The only thing I would add is training your front staff. They are checking people in, taking appointments, checking your patients out. Have them be mindful that there are campaigns going on, whether it is a social media push, or a new video that went on the website. They can ask, "How did you hear about us?" when a new patient calls.

Dr. Bowman: Unless you are a large university hospital, where the analytics get significantly more advanced in terms of measuring return on investment (ROI), I think you should just be looking at your schedule and looking at your monthly billings and seeing how they change over time. You can calculate how much a new patient is worth because you can figure out how many patients you have and how much you bill and what your profits are.

Dr. Culligan: For those of us who are hospital employees, you can try to convince the hospital that you can do a detailed ROI analysis, or you can just look at it like (say it's $3,000 per month), how many surgeries does this project have to generate before the hospital makes that back? The answer is a fraction of 1 case.

Thank you to all of you for your expertise on this roundtable. ■

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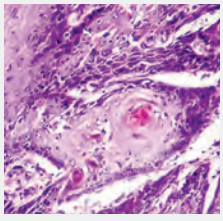

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Hysteroscopy and COVID-19: Have recommended techniques changed due to the pandemic?

Be cognizant to follow these recommendations for minimizing the risk of viral spread during hysteroscopic procedures

Laura Florez, MD, and Jose Carugno, MD

IN THIS ARTICLE

The emergence of the coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) in December 2019, has resulted in a global pandemic that has challenged the medical community and will continue to represent a public health emergency for the next several months.[1] It has rapidly spread globally, infecting many individuals in an unprecedented rate of infection and worldwide reach. On March 11, 2020, the World Health Organization designated COVID-19 as a pandemic. While the majority of infected individuals are asymptomatic or develop only mild symptoms, some have an unfortunate clinical course resulting in multi-organ failure and death.[2]

It is accepted that the virus mainly spreads during close contact and via respiratory droplets.[3] The average time from infection to onset of symptoms ranges from 2 to 14 days, with an average of 5 days.[4] Recommended measures to prevent the spread of the infection include social distancing (at least 6 feet from others), meticulous hand hygiene, and wearing a mask covering the mouth and nose when in public.[5] Aiming to mitigate the risk of viral dissemination for patients and health care providers, and to preserve hospital resources, all nonessential medical interventions were initially suspended. Recently, the American College of Surgeons in a joint statement with 9 women's health care societies have provided recommendations on how to resume clinical activities as we recover from the pandemic.[6]

As we reinitiate clinical activities, gynecologists have been alerted of the potential risk of viral dissemination during gynecologic minimally invasive surgical procedures due to the presence of the virus in blood, stool, and the potential risk of aerosolization of the virus, especially when using smoke-generating devices.[7,8] This risk is not limited to intubation and extubation of the airway during anesthesia; the risk also presents itself during other aerosol-generating procedures, such as laparoscopy or robotic surgery.[9,10]

Hysteroscopy is considered the gold standard procedure for the diagnosis and management of intrauterine pathologies.[11] It is frequently performed in an office setting without the use of anesthesia.[11,12] It is usually well tolerated, with only a few patients

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reporting discomfort.[12] It allows for immediate treatment (using the "see and treat" approach) while avoiding not only the risk of anesthesia, as stated, but also the need for intubation—which has a high risk of droplet contamination in COVID-19–infected individuals.[13]

Is there risk of viral dissemination during hysteroscopic procedures?

The novel and rapidly changing nature of the COVID-19 pandemic present many challenges to the gynecologist. Significant concerns have been raised regarding potential risk of viral dissemination during laparoscopic surgery due to aerosolization of viral particles and the presence of the virus in blood and the gastrointestinal tract of infected patients.[7] Diagnostic, and some simple, hysteroscopic procedures are commonly performed in an outpatient setting, with the patient awake. Complex hysteroscopic interventions, however, are generally performed in the operating room, typically with the use of general anesthesia. Hysteroscopy has the theoretical risks of viral dissemination when performed in COVID-19–positive patients. Two important questions must be addressed to better understand the potential risk of COVID-19 viral dissemination during hysteroscopic procedures.

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Hysteroscopy and COVID-19

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FAST TRACK

Although the smoke generated during hysteroscopy is not released into the air, necessary precautions should be undertaken to minimize COVID-19 transmission risk

1. Is the virus present in the vaginal fluid of women infected with COVID-19?

Recent studies have confirmed the presence of viral particles in urine, feces, blood, and tears in addition to the respiratory tract in patients infected with COVID-19.[3,14,15] The presence of the SARS-CoV-2 virus in the female genital system is currently unknown. Previous studies, of other epidemic viral infections, have demonstrated the presence of the virus in the female genital tract in affected patients of Zika virus and Ebola.[16,17] However, 2 recent studies have failed to demonstrate the presence of the SARS-CoV-2 virus in the vaginal fluid of pregnant[14] and not pregnant[18] women with severe COVID-19 infection.

2. Is there risk of viral dissemination during hysteroscopy if using electrosurgery?

There are significant concerns with possible risk of COVID-19 transmission to health care providers in direct contact with infected patients during minimally invasive gynecologic procedures due to direct contamination and aerosolization of the virus.[10,19] Current data on COVID-19 transmission during surgery are limited. However, it is important to recognize that viral aerosolization has been documented with other viral diseases, such as human papillomavirus and hepatitis B.[20] A recent report called for awareness in the surgical community about the potential risks of COVID-19 viral dissemination during laparoscopic surgery. Among other recommendations, international experts advised minimizing the use of electrosurgery to reduce the creation of surgical plume, decreasing the pneumoperitoneum pressure to minimum levels, and using suction devices in a closed system.[21] Although these preventive measures apply to laparoscopic surgery, it is important to consider that hysteroscopy is performed in a unique environment.

During hysteroscopy the uterine cavity is distended with a liquid medium (normal saline or electrolyte-free solutions); this is opposed to gynecologic laparoscopy, in which the peritoneal cavity is distended with carbon dioxide.[22] The smoke produced with the use of hysteroscopic electrosurgical instruments generates bubbles that are immediately cooled down to the temperature of the distention media and subsequently dissolve into it. Therefore, there are no bubbles generated during hysteroscopic surgery that are subsequently released into the air. This results in a low risk for viral dissemination during hysteroscopic procedures. Nevertheless, the necessary precautions to minimize the risk of COVID-19 transmission during hysteroscopic intervention are extremely important.

Recommendations for hysteroscopic procedures during the COVID-19 pandemic

We provide our overall recommendations for hysteroscopy, as well as those specific to the office and hospital setting.

Recommendations: General

Limit hysteroscopic procedures to COVID-19–negative patients and to those patients in whom delaying the procedure could result in adverse clinical outcomes.[23]

Universally screen for potential COVID-19 infection. When possible, a phone interview to triage patients based on their symptoms and infection exposure status should take place before the patient arrives to the health care center. Patients with suspected or confirmed COVID-19 infection who require immediate evaluation should be directed to COVID-19–designated emergency areas.

Universally test for SARS-CoV-2 before procedures performed in the operating room (OR). Using nasopharyngeal swabs for the detection of viral RNA, employing molecular methods such as polymerase chain reaction (PCR), within 48 to 72 hours prior to all OR hysteroscopic procedures is strongly recommended. Adopting this testing strategy will aid to identify asymptomatic SARS-CoV-2-infected patients, allowing to defer the procedure, if possible, among patients testing positive. If tests are limited, testing only patients scheduled for hysteroscopic procedures in which general or regional anesthesia will be required is acceptable.

Universal SARS-CoV-2 testing of patients undergoing in-office hysteroscopic diagnostic

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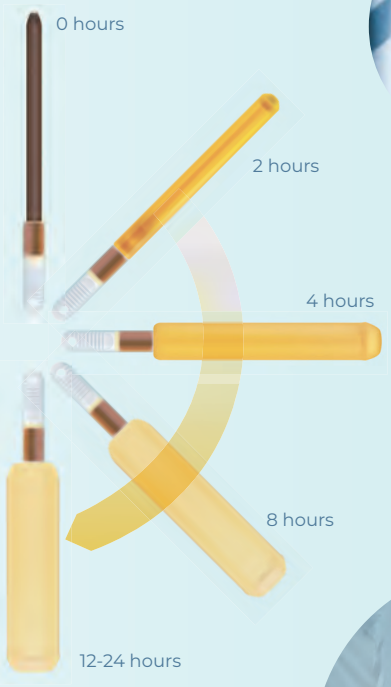

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Hysteroscopy and COVID-19

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or minor operative procedures without the use of anesthesia is not required.

Limit the presence of a companion. It is understood that visitor policies may vary at the discretion of each institution's guidelines. Children and individuals over the age of 60 years should not be granted access to the center. Companions will be subjected to the same screening criteria as patients.

Provide for social distancing and other precautionary measures. If more than one patient is scheduled to be at the facility at the same time, ensure that the facility provides adequate space to allow the appropriate social distancing recommendations between patients. Hand sanitizers and facemasks should be available for patients and companions.

Provide PPE for clinicians. All health care providers in close contact with the patient must wear personal protective equipment (PPE), which includes an apron and gown, a surgical mask, eye protection, and gloves. Health care providers should wear PPE deemed appropriate by their regulatory institutions following their local and national guidelines during clinical patient interactions.

Restrict surgical attendees to vital personnel. The participation of learners by physical presence in the office or operating room should be restricted.

FAST TRACK

For office procedures, minimize accompanying companions to one person under the age of 60; For OR procedures, limit the number of personnel in the procedure room

Recommendations: Office setting

Preprocedural recommendations

- Advise patients to come to the office alone. If the patient requires a companion, a maximum of one adult companion under the age of 60 should be accepted.
- Limit the number of health care team members present in the procedure room.

Intraprocedural recommendations

- Choose the appropriate device(s) that will allow for an effective and fast procedure.
- Use the recommended PPE for all clinicians.
- Limit the movement of staff members in and out of the procedure room.

Postprocedure recommendations

- When more than one case is scheduled to be performed in the same procedure room, allow enough time in between cases to grant a thorough OR decontamination.
- Allow for patients to recover from the procedure in the same room as the procedure took place in order to avoid potential contamination of multiple rooms.
- Expedite patient discharge.
- Follow up after the procedure by phone or telemedicine.
- Use standard endoscope disinfection procedures, as they are effective and should not be modified.

Recommendations: Operating room setting

Preprocedural recommendations

- Perform adequate patient screening for potential COVID-19 infection. (Screening should be independent of symptoms and not be limited to those with clinical symptoms.)
- Limit the number of health care team members in the operating procedure room.
- To minimize unnecessary staff exposure, have surgeons and staff not needed for intubation remain outside the OR until intubation is completed and leave the OR before extubation.

Intraprocedure recommendations

- Limit personnel in the OR to a minimum.
- Staff should not enter or leave the room during the procedure.
- When possible, use conscious sedation or regional anesthesia to avoid the risk of viral dissemination at the time of intubation/extubation.
- Choose the device that will allow an effective and fast procedure.
- Favor non–smoke-generating devices, such as hysteroscopic scissors, graspers, and tissue retrieval systems.
- Connect active suction to the outflow, especially when using smoke-generating instruments, to facilitate the extraction of surgical smoke.

Postprocedure recommendations

- When more than one case is scheduled to be performed in the same room, allow enough time in between cases to grant a thorough OR decontamination.
- Expedite postprocedure recovery and patient discharge.

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Hysteroscopy and COVID-19

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- After completion of the procedure, staff should remove scrubs and change into clean clothing.
- Use standard endoscope disinfection procedures, as they are effective and should not be modified.

Conclusions

The COVID-19 pandemic has caused a global health emergency. Our knowledge of this devastating virus is constantly evolving as we continue to fight this overwhelming disease. Theoretical risk of "viral" dissemination is considered extremely low, or negligible, during hysterosocopy. Hysteroscopic procedures in COVID-19–positive patients with life-threatening conditions or in patients in whom delaying the procedure could worsen outcomes should be performed taking appropriate measures. Patients who test negative for COVID-19 (confirmed by PCR) and require hysteroscopic procedures, should be treated using universal precautions. ●

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the last several months, there is a science to maintaining a COVID-SAFE environment.

Practice operations likely will change to adapt to new conditions. The pandemic has challenged us to evolve, and we have responded with new capabilities and resilience while we continue to deliver superior and compassionate care for women.

For additional strategies on how to safeguard your practice against COVID-19, read the online version of this article at mdedge.com/obgyn. ●

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TABLE 3 Projected changes in Medicare payments with the new CMS rules in January 2021[5,a]

Specialties with greatest payment increase	Percent increase
Endocrinology	+ 17%
Rheumatology	+ 16%
Hematology/Oncology	+ 14%
Family Practice	+ 13%
Allergy/Immunology	+ 9%
Obstetrics and Gynecology	+ 8%
Psychiatry	+ 8%
Specialties with greatest payment decrease	**Percent decrease**
Radiology	- 11%
Pathology	- 9%
Cardiac Surgery	- 9%
Interventional Radiology	- 9%
Anesthesiology	- 8%
Thoracic Surgery	- 8%
General Surgery	- 7%

[a]The estimated changes are based on the summation of changes in the assigned relative value for clinical work, practice expense, and professional liability expense.

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* A positive HPV screening result may lead to further evaluation with cytology and/or colposcopy.

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