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OBG MANAGEMENT

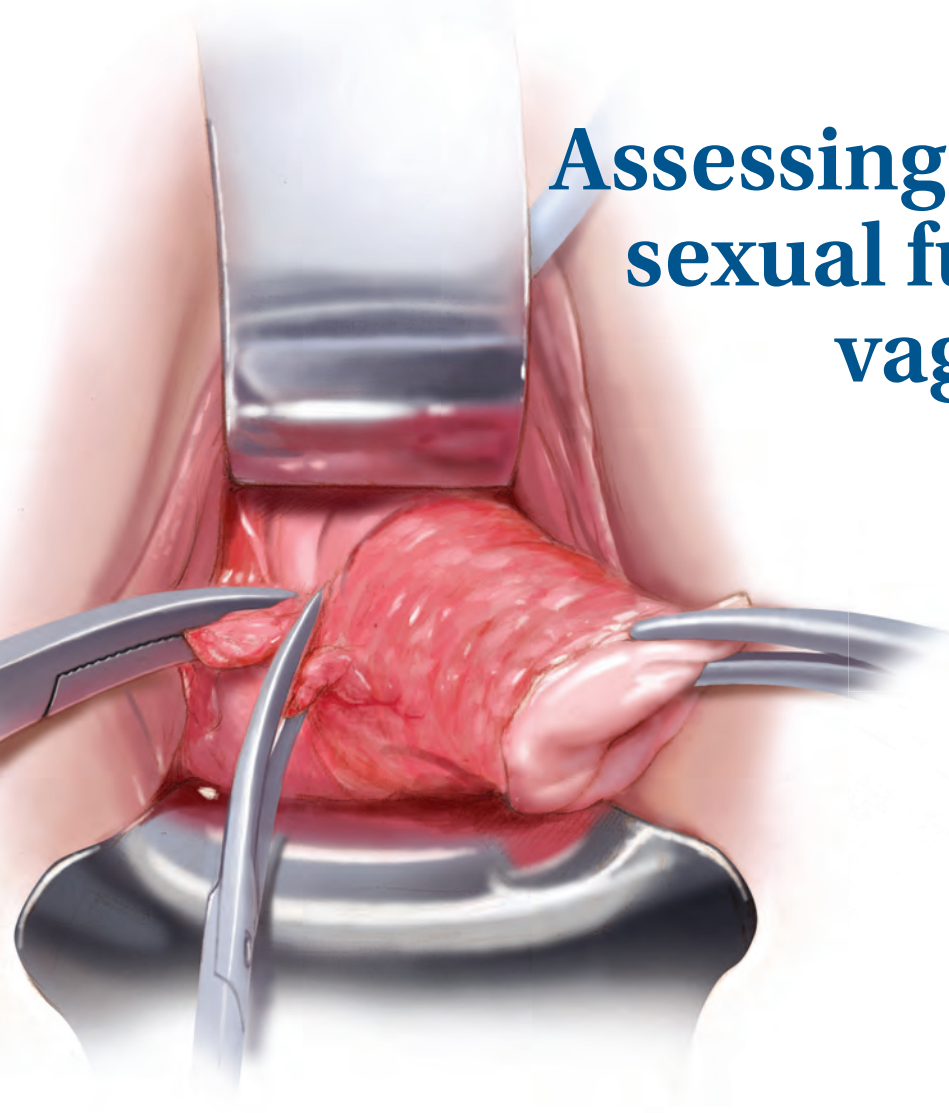
A member of the MDedge Network

Society of Gynecologic Surgeons Annual Meeting Highlights Issue

Laser and RFE device use in genital cosmetic surgery: A way forward

Sarah Ward, MD; Cheryl B. Iglesia, MD

Should long-held practices be discarded based on ARRIVE?



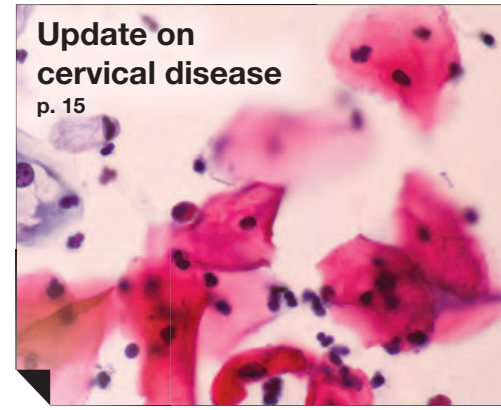
Assessing and treating sexual function after vaginal surgery

ObGyn liability claims resulting in payment are decreasing!

Robert L. Barbieri, MD

Treating the pregnant patient with opioid addiction

Can primary CD rates be reduced safely?



TAKE A NEXT STEP IN MODERATE TO SEVERE ENDOMETRIOSIS PAIN[1]

Dysmenorrhea
(150 mg or 200 mg)

Non-menstrual Pelvic Pain (NMPP)
(150 mg or 200 mg)

Dyspareunia*
(200 mg only)

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

Orilissa
elagolix tablets 150 mg 200 mg

Clinical study design: Two robust, similar, multicenter, double-blind, prospective, placebo-controlled phase 3 trials of 6-month treatment at 2 doses as compared with placebo in premenopausal women (18 to 49 years of age) with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain (N=1686).[1,2]

- Co-primary efficacy endpoints (independently evaluated): proportion of responders for dysmenorrhea at month 3 and proportion of responders for NMPP at month 3[1]

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

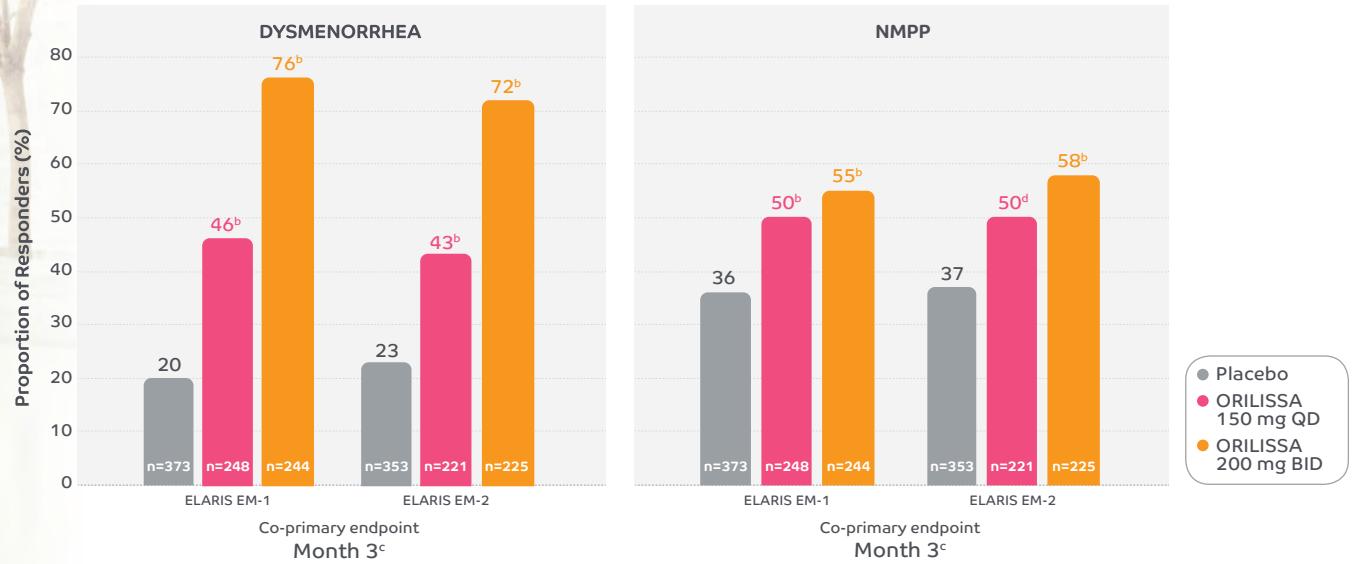
- Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials.
- ORILISSA users had a higher incidence of depression and mood changes compared to placebo and ORILISSA users with a history of suicidality or depression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

abbvie

PROVEN PAIN RELIEF IN 2 ORAL DOSING OPTIONS

EM-1 and EM-2: Response Rates vs Placebo[1,2,a-f]

Women were defined as responders only if they experienced clinically meaningful[a] pain reduction and stable or decreased rescue analgesic use for endometriosis-associated pain, as recorded in a daily electronic diary.



EM=ELARIS ENDOMETRIOSIS.

[a]Clinically meaningful reduction in pain was defined as a calculated threshold of improvement in pain score in each study. The threshold was determined based on an analysis of the change in pain score that corresponded to "much improved" or "very much improved" on the Patient Global Impression of Change questionnaire.

[b]*P*≤0.001 vs placebo.

[c]The co-primary efficacy endpoints were the proportion of responders for dysmenorrhea and pelvic pain not related to menses (NMPP) at month 3 compared with placebo.

[d]*P*≤0.01 vs placebo.

[e]Study EM-1—Dysmenorrhea responder threshold: at least 0.81-point decrease from baseline in dysmenorrhea score; NMPP responder threshold: at least 0.36-point decrease from baseline in NMPP score.

[f]Study EM-2—Dysmenorrhea responder threshold: at least 0.85-point decrease from baseline in dysmenorrhea score; NMPP responder threshold: at least 0.43-point decrease from baseline in NMPP score.

- 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[1]

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

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

These are not all the possible side effects of ORILISSA.

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

References: 1. Orilissa [package insert]. North Chicago, IL: AbbVie Inc; 2018. **2.** 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.

Consider ORILISSA for your patients with moderate to severe endometriosis pain.
Take a next step at ORILISSA.com/hcp

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

Orilissa®
elagolix tablets 150 mg 200 mg

ORILISSA™ (elagolix) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Important Dosing Information

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

Table 1. Recommended Dosage and Duration of Use

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

Hepatic Impairment

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

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

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

Missed Dose

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

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

CONTRAINDICATIONS

ORILISSA is contraindicated in women:

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

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

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

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

Clinical Trials Experience

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

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

Serious Adverse Events

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

Adverse Reactions Leading to Study Discontinuation

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

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

Common Adverse Reactions:

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

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

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

Less Common Adverse Reactions:

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

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

Bone Loss

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

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

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

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

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

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

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

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

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

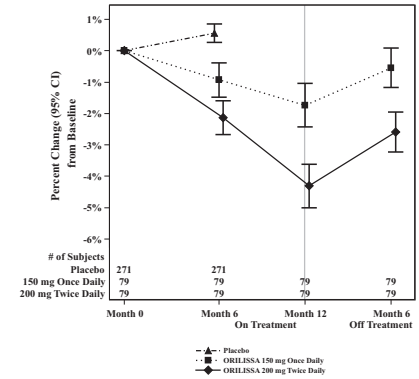
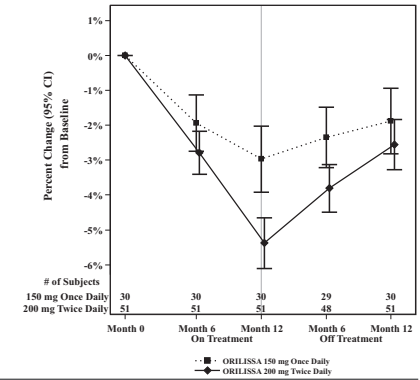


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

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

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

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

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

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

Hepatic Transaminase Elevations

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

Changes in Lipid Parameters

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

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

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

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

Hypersensitivity Reactions

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

Endometrial Effects

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

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

Effects on menstrual bleeding patterns

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

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

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

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

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

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

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

DRUG INTERACTIONS

Potential for ORILISSA to Affect Other Drugs

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

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

Potential for Other Drugs to Affect ORILISSA

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

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

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

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

Drug Interactions - Examples and Clinical Management

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

Table 7. Established Drug Interactions Based on Drug Interaction Trials

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

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

Data

Human Data

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

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

Animal Data

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

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

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

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

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

Lactation

Risk Summary

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

Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Renal Impairment

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

Hepatic Impairment

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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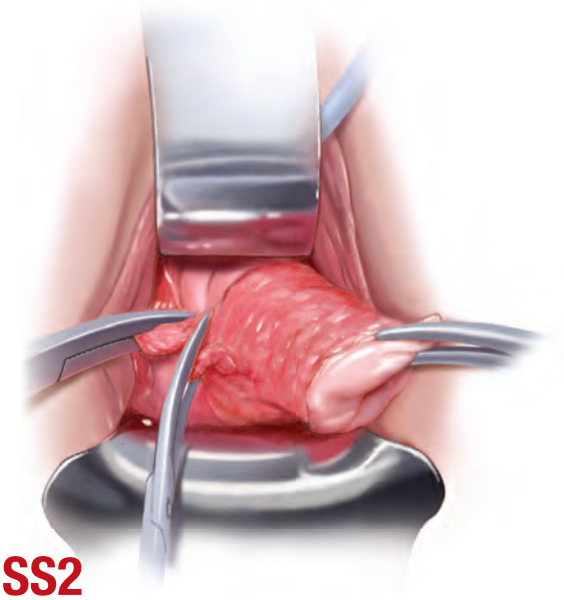

SS2 Assessing and treating sexual function after vaginal surgery

Keys to treatment include knowing the patient's preoperative history of any dysfunction; understanding her concerns, needs, and expectations; and starting conservatively

CASSANDRA L. CARBERRY, MD; DANIELLE ANTOSH, MD; AND REBECCA G. ROGERS, MD

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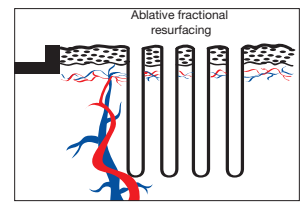
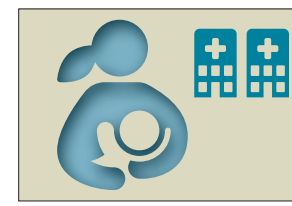


Energy-based technologies
SS9



Breastfeeding policies
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KERRIE G. SATCHER, MD; STEPHANIE J. CARSTENS, MD; AND ANDREW M. KAUNITZ, MD, NCMP

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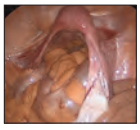
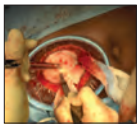


Laparoscopic bilateral salpingo-oophorectomy via minilaparotomy assistance for the massively enlarged adnexal mass

ROSA CUI, MD; ARIEL K. DUBIN, MD; AND ARNOLD P. ADVINCULA, MD



Minilaparotomy: Minimally invasive approach to abdominal myomectomy

SIERRA J. SEAMAN, MD; PATRICIA J. MATTINGLY, MD; AND ARNOLD P. ADVINCULA, MD

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EDITORIAL

Good news for ObGyns: Medical liability claims resulting in payment are decreasing!

Not as good news: Claims settling for a payment of greater than $1 million are increasing

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Medical professional liability claims (claims) are a major cause of worry and agony for physicians who are dedicated to optimizing the health of all their patients. Among physicians, those who practice neurosurgery, thoracic surgery, plastic surgery, and obstetrics and gynecology have the greatest rate of making a payment on a claim per year of practice.[1] Physicians who practice psychiatry, pediatrics, pathology, and internal medicine have the lowest rate of making a payment on a claim. Among the physicians in high-risk specialties, greater than 90% will have a claim filed against them during their career.[2] Although professional liability exposure reached a crisis during the 1980s and 1990s, recent data have shown a decrease in overall professional liability risk.

The good news: Paid claims per 1,000 ObGyns have decreased greatly

In a review of all paid claims reported to the National Practitioner Data Bank from 1992 to 2014, the annual rate of paid claims per 1,000 ObGyn physician-years was determined.[1] For the time periods 1992–1996, 1997–2002, 2003–2008, and 2009–2014, the annual rate of paid claims per 1,000 ObGyn physician-years was 57.6, 51.5, 40.0, and 25.9, representing an astounding 55% decrease in paid claims from 1992 to 2014 (**FIGURE**, page 12).[1]

The majority of claims result in no payment

In a review of the experience of a nationwide professional liability insurer from 1991 to 2005, only 22% of claims resulted in a payment.[2] In this study, for obstetrics and gynecology and gynecologic surgery, only 11% and 8% of claims, respectively, resulted in a payment.[2] However, being named in a malpractice claim results in significant stress for a physician and requires a great deal of work and time to defend.

In another study using data from the Physician Insurer's Association of America, among 10,915 claims closed from 2005 to 2014, 59.5% were dropped, withdrawn, or dismissed; 27.7% were settled; 2.5% were resolved using an alternative dispute

CONTINUED ON PAGE 12

Instant Poll

1. From CY14 to CY19, have your professional liability insurance premiums:
   - ❍ decreased
   - ❍ remained stable
   - ❍ increased
2. In which region do you practice?
   - ❍ Northeast
   - ❍ Southeast
   - ❍ Midwest
   - ❍ Southwest
   - ❍ West

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CONTINUED FROM PAGE 10

resolution process; 1.8% were uncategorized; and 8.6% went to trial.[3] Of the cases that went to trial, 87% resulted in a verdict for the physician and 13% resulted in a verdict for the plaintiff.[3]

Not as good news: Payments per claim and claims settling for a payment > $1 million are increasing

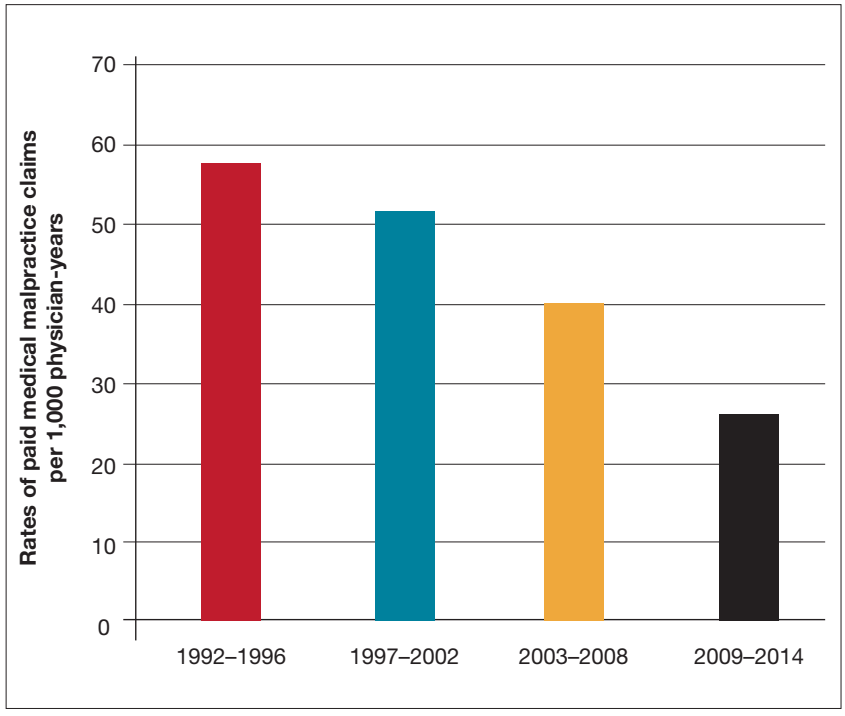
In the period 1992–1996, the average payment per paid claim in the field of obstetrics and gynecology was $387,186, rising to $447,034 in 2009–2014—a 16% increase.[1] From 2004 to 2010, million dollar payments occurred in about 8% of cases of paid claims, but they represent 36% of the total of all paid claims.[4] In the time periods 1992–1996 and 2009–2014, payments greater than $1 million occurred in 6% and 8% of paid claims, respectively.[1]

Claims settled for much more than $1 million are of great concern to physicians because the payment may exceed their policy limit, creating a complex legal problem that may take time to resolve. In some cases, where the award is greater than the insurance policy limit, aggressive plaintiff attorneys have obtained a lien on the defendant physician's home pending settlement of the case. When a multimillion dollar payment is made to settle a professional liability claim, it can greatly influence physician practice and change hospital policies. Frequently, following a multimillion dollar payment a physician may decide to limit their practice to low-risk cases or retire from the practice of medicine.

Liability premiums are stable or decreasing

From 2014 to 2019, my ObGyn professional liability insurance premiums decreased by 18%. During the same time period, my colleagues who practice surgical gynecology (no obstetrics) had a premium decrease of 22%. Insurers use a complex algorithm to determine annual liability insurance premiums, and premiums for ObGyns may not have stabilized or decreased in all regions (see Instant Poll on page 10).

FIGURE Annual rates of paid ObGyn medical malpractice claims per 1,000 physician-years[1]



Reform of the liability tort system

Litigation policies and practices that reduce liability risk reduce total medical liability losses. Policies that have helped to constrain medical liability risk include state constitutional amendments limiting payments for pain and suffering, caps on compensation to plaintiff attorneys, increased early resolution programs that compensate patients who experience an adverse event and no-fault conflict resolution programs.[5] In 2003, Texas implemented a comprehensive package of tort reform laws. Experts believe the reforms decreased the financial burden of professional liability insurance[6] and led to less defensive medical practices, reducing excessive use of imaging and laboratory tests.

Medical factors contributing to a decrease in claims

In 1999, the Institute of Medicine released the report, "To Err is Human," which galvanized health care systems to deploy systems of care that reduce the rate of adverse patient outcomes.[7] Over the past 20 years, health systems have implemented quality improvement programs in obstetrics and gynecology that have contributed to a reduction in the rate of adverse patient outcomes. This may have contributed to the decrease in the rate of paid claims.

In a quasi-experimental study

performed in 13 health systems, 7 interventions were implemented with the goal of improving outcomes and reducing medical liability. The 7 interventions included[8]:

1. an elective induction bundle focused on the safe use of oxytocin
2. an augmentation bundle focused on early intervention for possible fetal metabolic acidosis
3. an operative vaginal delivery bundle
4. TeamSTEPPS teamwork training to improve the quality of communication
5. best practices education with a focus on electronic fetal monitoring
6. regular performance feedback to hospitals and clinicians
7. implementation of a quality improvement collaboration to support implementation of the interventions.

During the two-year baseline period prior to the intervention there were 185,373 deliveries with 6.7 perinatal claims made per 10,000 deliveries and 1.3 claims paid per 10,000 deliveries. Following the intervention, the rate of claims made and claims paid per 10,000 deliveries decreased by 22% and 37%, respectively. In addition there was a marked decrease in claims over $1 million paid, greatly limiting total financial liability losses.

Experts with vast experience in obstetrics and obstetric liability litigation have identified 4 priority interventions that may improve outcomes and mitigate liability risk, including: 1) 24-hour in-house physician coverage of an obstetrics service, 2) a conservative approach to trial of labor after a prior cesarean delivery, 3) utilization of a comprehensive, standardized event note in cases of a shoulder dystocia, and 4) judicious use of oxytocin, misoprostol, and magnesium sulfate.[9]

Other health system interventions that may contribute to a reduction in claims include:

- systematic improvement in the quality of communication among physicians and nurses through the use of team training, preprocedure huddles, and time-out processes[10]
- rapid response systems to rescue hospital patients with worrisome vital signs[11]
- standardized responses to a worrisome category 2 or 3 fetal heart-rate tracing[12]
- rapid recognition, evaluation, and treatment of women with hemorrhage, severe hypertension, sepsis, and venous thromboembolism[13]
- identification and referral of high-risk patients to tertiary centers[14]
- closed loop communication of critical imaging and laboratory results[15]
- universal insurance coverage for health care including contraception, obstetrics, and pediatric care.

Medical liability risk is an important practice issue because it causes excessive use of imaging and laboratory tests and often traumatizes clinicians, which can result in burnout. In the 1980s and 1990s, medical liability litigation reached a crescendo and was a prominent concern among obstetrician-gynecologists. The good news is that, for ObGyns, liability risk has stabilized. Hopefully our resolute efforts to continuously improve the quality of care will result in a long-term reduction in medical liability risk. ●

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

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Are sweeping efforts to reduce primary CD rates associated with an increase in maternal or neonatal AEs?

Not measurably, according to this analysis of cross-sectional data from 56 hospitals with more than 119,000 deliveries as part of the California Maternal Quality Care Collaborative (CMQCC) statewide effort to reduce primary cesarean delivery (CD) rates. No significant difference in maternal or neonatal adverse events (AEs) were reported before (2015), compared with after (2017), implementation of the program, suggesting that introduction of this quality improvement bundle did not measurably compromise patient safety.

FAST TRACK

California's statewide collaborative to reduce NTSV CD included education on ACOG/SMFM guidelines, introduction of a toolkit, increased labor support, and shared best practices

Main EK, Chang SC, Cape V, et al. Safety assessment of a large-scale improvement collaborative to reduce nulliparous cesarean delivery rates. Obstet Gynecol. 2019;133:613-623.

EXPERT COMMENTARY

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Cesarean delivery can be lifesaving for both mother and infant. When compared with successful vaginal delivery, however, CD is associated with higher maternal complication rates (including excessive blood loss requiring blood product transfusion, infectious morbidity, and venous thromboembolic events), longer hospital length of stay, and higher cost. While the optimal CD rate is not well defined, it is generally accepted that the CD rate in the United States is excessively high. As such, efforts to reduce the CD rate should be encouraged, but not at the expense of patient safety.

The authors report no financial relationships related to this article.

Details about the study

In keeping with the dictum that the most important CD to prevent is the first one, the California Maternal Quality Care Collaborative (CMQCC) in 2016 introduced a large-scale quality improvement project designed to reduce nulliparous, term, singleton, vertex (NTSV) CDs across the state. This bundle included education around joint guidelines issued by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine on reducing primary CDs,[1] introduction of a CMQCC

CONTINUED ON PAGE 34

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Dr. Einstein has advised or participated in educational speaking activities, but he does not receive an honorarium from any companies. In specific cases, Rutgers has received payment for his time spent for these activities from Photocure, Papivax, Cynvec, Merck, Hologic, and PDS Biotechnology. If travel is required for meetings with industry, the company pays for Dr. Einstein's travel expenses. Rutgers has received grant funding for research-related costs of clinical trials that Dr. Einstein has been the overall or local principal investigator within the past 12 months from J&J, Pfizer, and Inovio. Rutgers has received payment for Dr. Einstein's time from Photocure, Papivax, Cynvec, and PDS Biotechnology. Dr. Novetsky is the overall principal investigator of an investigator-initiated grant sponsored by Roche. His institution, Rutgers, has received funding for the clinical costs of this trial. Dr. Marcus reports no financial relationships relevant to this article.

A promising technology for predicting cervical dysplasia, cervical cancer outcomes and surgical technique, and updated USPSTF guidance on cervical cancer screening

Cervical cancer rates remain low in the United States, with the incidence having plateaued for decades. And yet, in 2019, more than 13,000 US women will be diagnosed with cervical cancer.[1] Globally, in 2018 almost 600,000 women were diagnosed with cervical cancer[2]; it is the fourth most frequent cancer in women. This is despite the fact that we have adequate primary and secondary prevention tools available to minimize—and almost eliminate—cervical cancer. We must continue to raise the bar for preventing, screening for, and managing this disease.

Human papillomavirus (HPV) vaccines provide a highly effective primary prevention strategy, but we need to improve our ability to identify and diagnose dysplastic lesions prior to the development of cervical cancer. Highly sensitive HPV testing and cytology is a powerful secondary prevention approach that enables us to assess a woman's risk of having precancerous cells both now and in the near future. These modalities have been very successful in decreasing the incidence of cervical cancer in the United States and other areas with organized screening programs. In low- and middle-income countries, however, access to, availability of, and performance with these modalities is not optimal. Innovative strategies and new technologies are being evaluated to overcome these limitations.

Advances in radiation and surgical technology have enabled us to vastly improve cervical cancer treatment. Women with early-stage cervical cancer are candidates for surgical management, which frequently includes a radical hysterectomy and lymph node dissection. While these surgeries traditionally have been performed via an exploratory laparotomy, minimally invasive techniques (laparoscopic and robot-assisted surgical techniques) have decreased the morbidity with these surgeries. Notable new studies have shed light on the comparative effectiveness of minimally invasive technologies and have shown us that new is not always better.

The US Preventive Services Task Force (USPSTF) recently released its updated cervical cancer screening guidelines. The suggested approach to screening differs from previous recommendations. HPV testing as a primary

IN THIS ARTICLE

test (that is, HPV testing alone or followed by cytology) takes the spotlight now, according to the analysis by the Task Force.

In this Update, we highlight important studies published in the past year that address these issues.

New tech's potential to identify high-grade cervical dysplasia may be a boon to low-resource settings

Hu L, Bell D, Antani S, et al. An observational study of deep learning and automated evaluation of cervical images for cancer screening. J Natl Cancer Inst. 2019;doi:10.1093/jnci/djy225.

When cervical screening tests like cytology and HPV testing show abnormal results, colposcopy often is recommended. The goal of colposcopy is to identify the areas that might harbor a high-grade precancerous lesion or worse. The gold standard in this case, however, is histology, not colposcopic impression, as many studies have shown that colposcopy without biopsies is limited and that performance is improved with more biopsies.[3,4]

Visual inspection with acetic acid (VIA) is an approach used often in low-resource settings where visual impression is the gold standard. However, as with colposcopy, a visual evaluation without histology does not perform well, and often women are overtreated. Many attempts have been made with new technologies to overcome the limitations of time, cost, and workforce required for cytology and histology services. New disruptive technologies may be able to surmount human limitations and improve on not only VIA but also the need for histology.

ON THE **WEB**

at mdedge.com/obgyn

Don't miss the Figure showing AVE's performance versus other methods in identifying CIN 2+.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Colposcopy remains the gold standard for evaluating abnormal cervical cancer screening tests in the United States. But can we do better for our patients using new technologies like AVE? If validated in large-scale trials, AVE has the potential to revolutionize cervical cancer screening in low-resource settings where follow-up and adequate histology services are limited or nonexistent. Future large studies are necessary to evaluate the role of AVE alone versus in combination with other diagnostic testing (such as HPV testing) to detect cervical lesions globally.

Novel technology uses images to develop algorithm with predictive ability

In a recent observational study, Hu and colleagues used images that were collected during a large population study in Guanacaste, Costa Rica.[5] More than 9,000 women were followed for up to 7 years, and cervical photographs (cervigrams) were obtained. Well-annotated histopathology results were obtained for women with abnormal screening, and 279 women had a high-grade dysplastic lesion or cancer.

Cervigrams from women with high-grade lesions and matched controls were collected, and a deep learning-based algorithm using artificial intelligence technology was developed using 70% of the images. The remaining 30% of images were used as a validation set to test the algorithm's ability to "predict" high-grade dysplasia without knowing the final result.

Findings. Termed automated visual evaluation (AVE), this new technology demonstrated a very accurate ability to identify high-grade dysplasia or worse, with an area under the curve (AUC) of 0.91 from merely a cervicogram. This outperformed conventional Pap smears (AUC, 0.71), liquid-based cytology (AUC, 0.79) and, surprisingly, highly sensitive HPV testing (AUC, 0.82) in women in the prime of their screening ages (>25 years of age).

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Data offer persuasive evidence to abandon minimally invasive surgery in management of early-stage cervical cancer

Melamed A, Margul DJ, Chen L, et al. Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. N Engl J Med. 2018;379:1905-1914.

Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med. 2018;379:1895-1904.

Over the past decade, gynecologic cancer surgery has shifted from what routinely were open procedures to the adoption of minimally invasive techniques. Recently, a large, well-designed prospective study and a large retrospective study both demonstrated worse outcomes with minimally invasive radical hysterectomy (MIRH) as compared with traditional open radical abdominal hysterectomy (RAH). These 2 landmark studies, initially presented at the Society of Gynecologic Oncology's 2018 annual meeting and later published in the *New England Journal of Medicine,* have really affected the gynecologic oncology community.

Shorter overall survival in women who had MIRH

Melamed and colleagues conducted a large, retrospective US–based study to evaluate all-cause mortality in women with cervical cancer who underwent MIRH compared with those who had RAH.[6] The authors also sought to evaluate national trends in 4-year relative survival rates after minimally invasive surgery was adopted.

The study included 2,461 women who met the inclusion criteria; 49.8% (1,225) underwent MIRH procedures and, of those, 79.8% (978) had robot-assisted laparoscopy. Most women had stage IB1 tumors (88%), and most carcinomas were squamous cell (61%); 40.6% of tumors were less than 2 cm in size. There were no differences between the 2 groups with respect to rates of positive parametria, surgical margins, and lymph node involvement. Administration of adjuvant therapy, in those who qualified, was also similar between groups.

Results. At a median follow-up of 45 months, 94 deaths occurred in the minimally invasive group and 70 in the open surgery group. The risk of death at 4 years was 9.1% in the minimally invasive group versus 5.3% in the open surgery group, with a 65% higher risk of death from any cause, which was highly statistically significant.

Prospective trial showed MIRH was associated with lower survival rates

From 2008 to 2017, Ramirez and colleagues conducted a phase 3, multicenter, randomized controlled trial to prospectively establish the noninferiority of MIRH compared with RAH.[7] The study included 631 women from 33 centers. The prespecified expected disease-free survival rate was 90% at 4.5 years.

To be included as a site, centers were required to submit details from 10 minimally invasive cases as well as 2 unedited videos for review by the trial management committee. In contrast to Melamed and colleagues' retrospective study, of the 319 procedures that were classified as minimally invasive, only 15.6% were robotically assisted. Similarly, most women had stage IB1 tumors (91.9%), and most were squamous cell carcinomas (67%). There were also no differences in the postoperative pathology findings or the need for adjuvant therapy administered between

FAST TRACK

Two large landmark studies have both shown worse outcomes with minimally invasive radical hysterectomy compared with traditional open radical abdominal hysterectomy

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The evidence is compelling and demonstrates potentially worse disease-related outcomes using MIRH when compared to traditional RAH with respect to cervical cancer recurrence, rates of death, and disease-free and overall survival. Several hypotheses have been proposed, and future research is needed to elucidate the differences in variables responsible for the outcomes demonstrated in these studies. Although there has been no ban on robot-assisted surgical devices or traditional minimally invasive techniques, the National Comprehensive Cancer Network has updated its recommendations to include careful counseling of patients who require a surgical approach for the management of early-stage cervical cancer.

groups. The median follow-up was 2.5 years.

Results. At that time there were 27 recurrences in the MIRH group and 7 in the RAH group; there were also 19 deaths after MIRH and 3 after RAH. Disease-free survival at 4.5 years was 86% with MIRH versus 96.5% with RAH. Reported 3-year disease-free survival and overall survival were also significantly lower in the minimally invasive subgroup (91.2% vs 97.1%, 93.8% vs 99.0%, respectively).

Study limitations. Criticisms of this trial are that noninferiority could not be declared; in addition, the investigators were unable to complete enrollment secondary to early enrollment termination after the data and safety monitoring board raised survival concerns.

Many argue that subgroup analyses suggest a lower risk of poor outcomes in patients with smaller tumors (<2 cm); however, it is critical to note that this study was not powered to detect these differences.

FAST TRACK

Large trials of cotesting in 25- to 65-year-olds consistently showed that primary hrHPV screening led to a statistically significant increased detection of CIN 3+ in the initial screening round

USPSTF updated guidance on cervical cancer screening

Melnikow J, Henderson JT, Burda BU, et al. Screening for cervical cancer with high-risk human papillomavirus testing: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2018;320:687-705.

US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;320:674-686.

Past guidelines for cervical cancer screening have included testing for high-risk HPV (hrHPV) as a cotest with cytology or for triage of atypical squamous cells of undetermined significance (ASCUS) in women aged 30 to 65 years.[8] The American Society for Colposcopy and Cervical Pathology and the Society of Gynecologic Oncology, with other stakeholder organizations, issued interim guidance for primary HPV testing—that is, HPV test first and, in the case of non-16/18 hrHPV types, cytology as a triage. The most recent evidence report and systematic review by Melnikow and colleagues for the USPSTF offers an in-depth analysis of risks, benefits, harms, and value of cotesting and other management strategies.[9]

Focus on screening effectiveness

Large trials of cotesting were conducted in women aged 25 to 65.[10-13] These studies all consistently showed that primary hrHPV screening led to a statistically significant increased detection of cervical intraepithelial neoplasia (CIN) 3+ in the initial round of screening, with a relative risk of detecting CIN 3+ ranging from 1.61 to 7.46 compared with cytology alone.

Four additional studies compared cotesting with conventional cytology for the

TABLE USPSTF recommendations for cervical cancer screening[14]

Population age	Screening recommendation
21–29 years	Every 3 years with cytology alone
30–65 years	Every 3 years with cytology alone Every 5 years with hrHPV testing alone, or Every 5 years with cotesting
<21 years, >65 years with adequate prior screening, and women who have had a hysterectomy	Do not screen

Clinical summary

Risk assessment	Screening tests	Treatments and interventions
All women 21–65 years are at risk for cervical cancer because of potential exposure to high-risk HPV types (hrHPV) through sexual intercourse and should be screened Certain risk factors increase risk for cervical cancer: HIV infection, compromised immune system, in utero exposure to diethylstilbestrol, previous treatment of a high-grade precancerous lesion Women with the above risk factors should receive individualized follow-up	Screening with cervical cytology alone, primary testing for hrHPV alone, or both at the same time (cotesting) can detect high-grade precancerous cervical lesions and cervical cancer Clinicians should focus on ensuring that women receive adequate screening, appropriate evaluation of abnormal results, and indicated treatment, regardless of the screening strategy used	High-grade cervical lesions may be treated with excisional and ablative therapies Early-stage cervical cancer may be treated with surgery (hysterectomy) or chemotherapy

detection of CIN 3+. None of these trials demonstrated a significantly higher detection rate of CIN 3+ with cotesting compared with conventional cytology testing alone. Notably, the studies reviewed were performed in European countries that had organized screening programs in place and a nationalized health care system. Thus, these data may not be as applicable to women in the United States, particularly to women who have limited health care access.

Risks of screening

In the same studies reviewed for screening effectiveness, the investigators found that overall, screening with hrHPV primary or cotesting was associated with more false-positive results and higher colposcopy rates. Women screened with hrHPV alone had a 7.9% referral rate to colposcopy, while those screened with cytology had a 2.8% referral rate to colposcopy. Similarly, the rate of biopsy was higher in the hrHPV-only group (3.2% vs 1.3%).

Overall, while cotesting might have some improvement in performance compared with hrHPV as a single modality, there might be risks of overreferral to colposcopy and overtreatment with additional cytology over hrHPV testing alone.

This evidence review also included an analysis of more potential harms. Very limited evidence suggests that positive hrHPV test results may be associated with greater psychological harm, including decreased sexual satisfaction, increased anxiety and distress, and worse feelings about sexual partners, than abnormal cytology results. These were assessed, however, 1 to 2 weeks after the test results were provided to the patients, and long-term assessment was not done.

New recommendations from the USPSTF

Based on these data, the USPSTF issued new recommendations regarding screening (**TABLE**).[14] For women aged 21 to 29, cytology alone should be used for screening every

CONTINUED ON PAGE 24

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

FIRST OF ITS KIND: INTRODUCING THE ONLY FDA-APPROVED BIO-IDENTICAL COMBINATION HORMONE THERAPY[1,2]

TWO BIO-IDENTICAL* HORMONES PRECISELY COMBINED[1-3]

*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.

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

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.

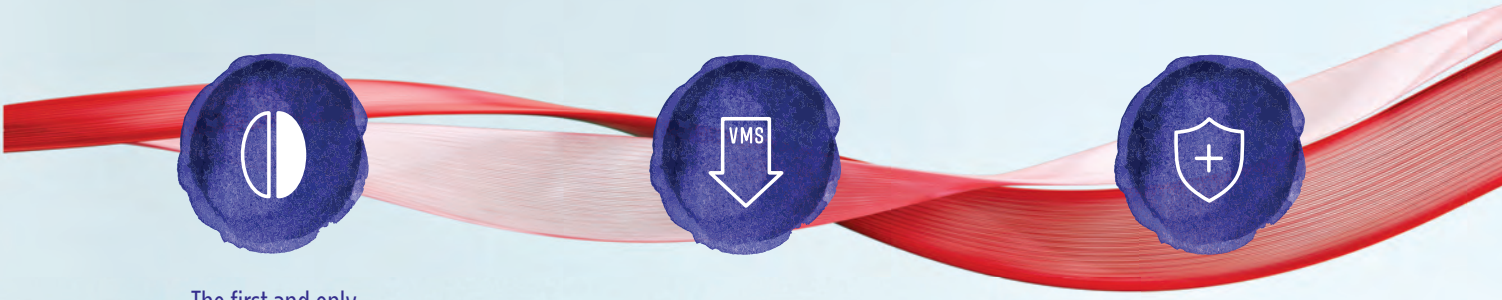
Estrogen Plus Progestin Therapy

- **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**

OFFER HER VMS RELIEF WITH THE CONVENIENCE OF BIJUVA[1,3]



The first and only FDA-approved combination of bio-identical estradiol and bio-identical progesterone in a single, once-daily oral capsule[1,2]

Reduction in moderate to severe VMS (hot flashes) with improvements in Menopause-specific Quality of Life and sleep measures[1,2,4]

A steady state of estradiol that reduces moderate to severe VMS with progesterone to reduce the risk to the endometrium[1,3]

TO LEARN MORE ABOUT BIJUVA OR REQUEST SAMPLES, VISIT BIJUVAHCP.COM OR CALL 1-877-533-8096

IMPORTANT SAFETY INFORMATION (CONT'D)

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 the BOXED WARNING, on the following pages.

References: 1. BIJUVA [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2018. **2.** Kagan R, Constantine G, Kaunitz AM, Bernick B, Mirkin S. Improvement in sleep outcomes with a 17β-estradiol-progesterone oral capsule (TX-001HR) for postmenopausal women. *Menopause.* 2018;25(6). doi:10.1097/GME.0000000000001278 **3.** Lobo RA, Archer DF, Kagan R, et al. A 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women. *Menopause.* 2018;132(1):161-170. **4.** Simon JA, Kaunitz AM, Kroll R, Graham S, Bernick B, Mirkin S. Oral 17β-estradiol/progesterone (TX-001HR) and quality of life in postmenopausal women with vasomotor symptoms. *Menopause.* 2019;26(5). doi:10.1097/GME.0000000000001271

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. See package insert for Full Prescribing Information.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST 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 of older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), 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)]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

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[2] [see Clinical Studies (14.4)]. Subgroup analysis of women 50 to 59 years of age suggests a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In 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[4] [see Clinical Studies (14.4)]. 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][6] [see Clinical Studies (14.4)]. 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 1684 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.

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

(continued on next page)

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[8] [see Use in Specific Populations (8.5), and Clinical Studies (14.5)]. 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 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).

Abnormal Vaginal Bleeding

Inform postmenopausal women of the importance of reporting abnormal vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.2) in full prescribing information]*.

Possible Serious Adverse Reactions with Estrogen Plus Progesterone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen plus progesterone therapy including cardiovascular disorders, malignant neoplasms, and probable dementia *[see Warnings and Precautions (5.1, 5.2, 5.3) in full prescribing information]*.

Possible Less Serious but Common Adverse Reactions with Estrogen Plus Progesterone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen plus progesterone therapy such as breast tenderness, headache, vaginal discharge, and pelvic pain *[see Adverse Reactions (6.1) in full prescribing information]*.

Missed Evening Dose of BIJUVA

Advise the patient that if she misses her evening dose, she should take the dose with food as soon as she can, unless it is within two hours of the next evening dose.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Primary screening with hrHPV is more effective in diagnosing a CIN 3+ than cytology alone. Cotesting with cytology and hrHPV testing appears to have limited performance improvement, with potential harm, compared with hrHPV testing alone in diagnosing CIN 3+. The Task Force recommendation is hrHPV testing alone or cotesting every 5 years.

3 years. Women aged 30 to 65 can be screened with cytology alone every 3 years, with hrHPV testing alone every 5 years, or with cotesting every 5 years. ●

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Coming soon...

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Chetna Arora, MD; Patricia J. Mattingly, MD; Arnold P. Advincula, MD; and Jin Hee Kim, MD

» **What's the verdict: The mesh mess, enmeshed in controversy**
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» **What to do when a patient presents with breast pain**
Laila Samiian, MD

» **3 cases of postmenopausal AUB managed by hysteroscopy**
Amy Garcia, MD

The ARRIVE trial: Women's desideratum versus logistical concerns

Do findings from the ARRIVE study and subsequent outcomes and cost analyses require a full reconsideration of long-held obstetric practices?

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Of the 1.5 million nulliparous women who deliver annually in the United States, more than 50% are low-risk pregnancies. Among clinicians, there is a hesitancy to offer elective induction of labor to low-risk nulliparous women, mainly due to early observational studies that noted an association between elective induction of labor and higher rates of cesarean delivery (CD) and other adverse maternal and perinatal outcomes.[1-3] This reluctance over time has permeated throughout the ObGyn specialty and is culturally embedded in contemporary practice. The early observational studies lacked proper comparison groups because outcomes of women undergoing induction (elective and medically indicated) were compared to those in spontaneous labor. Since women who are being induced do not have the option to be in spontaneous labor, the appropriate comparator group for women undergoing elective induction is women who are being managed expectantly.

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ARRIVE addresses appropriate comparator groups

Challenging this pervaded practice, in August 2018, Grobman and colleagues published the findings of the ARRIVE trial (A Randomized Trial of Induction Versus Expectant Management).[4] This trial, conducted by Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, recruited participants from 41 geographically dispersed centers in the United States. Nulliparous women with low-risk pregnancies between 34 0/7 and 38 6/7 weeks were randomly assigned to either induction of labor at 39 0/7 to 39 4/7 weeks or to expectant management, which was defined as delaying induction until 40 5/7 to 42 2/7 weeks. The objective of the ARRIVE trial was to determine if, among low-risk nulliparous women, elective induction of labor at 39 weeks, compared with expectant management, would reduce the rate of adverse outcomes.

The primary outcome was a composite: perinatal death or severe neonatal complications (need for respiratory support within 72 hours of birth, Apgar score of ≤ 3 at 5 minutes, hypoxic-ischemic encephalopathy, seizures, infection [confirmed sepsis or pneumonia], meconium aspiration syndrome, birth trauma [bone fracture, neurologic injury, or retinal damage], intracranial or subgaleal hemorrhage, or hypotension requiring vasopressor support). The secondary outcomes included CD, hypertensive disorders of pregnancy, number of hours in the labor and delivery (L&D) unit, length of postpartum hospital stay, and assessment of satisfaction with labor process.

Mothers induced at 39 weeks fared better, while neonatal outcomes were similar. Of 22,533 eligible women, 6,106 (27%) were randomized: 3,062 were assigned to the induction group, and, 3,044 to the expectant management group. The primary composite outcome—perinatal death or severe neonatal complications—was similar in both groups (4.3% in the induction group vs 5.4% in the expectant management group).

However, women who were induced had significantly lower rates of:

- CD (18.6% with induction vs 22.2%

for expectant management; relative risk [RR], 0.84; 95% confidence interval [CI], 0.76–0.93)
- hypertensive disorders of pregnancy (9.1% vs 14.1%; RR, 0.64; 95% CI, 0.56–0.74)
- neonatal respiratory support (3.0% vs. 4.2%; RR, 0.71; 95% CI, 0.55–0.93).

In addition, although women in the induction group had a longer stay in the L&D unit (an expected outcome), the overall postpartum length of stay was shorter. Finally, women in the induction group had higher patient satisfaction scores, with less pain and more control reported during labor.

What about uncommon adverse outcomes compared at 39 vs 41 weeks?

Due to the study's sample size, ARRIVE investigators could not ascertain if uncommon adverse outcomes (maternal admission to intensive care unit or neonatal seizure) are significantly more common at 40 and 41 weeks than at 39 weeks.

To address the issue of uncommon adverse outcomes, Chen and colleagues analyzed the US Vital Statistics datasets to compare composite maternal and neonatal morbidity among low-risk nulliparous women with nonanomalous singleton gestations who labored at 39 to 41 weeks.[5] The primary outcome was composite neonatal morbidity that included Apgar score < 5 at 5 minutes, assisted ventilation longer than 6 hours, seizure, or neonatal mortality. The secondary outcome was composite maternal morbidity that included intensive care unit admission, blood transfusion, uterine rupture, or unplanned hysterectomy.

The investigators found that from 2011–2015, among 19.8 million live births in the United States, there were 3.3 million live births among low-risk nulliparous women. Among these women, 43% delivered at 39 weeks' gestation, 41% at 40 weeks, and 15% at 41 weeks. The overall rate of composite neonatal morbidity was 8.8 per 1,000 live births; compared with those who delivered at 39 weeks, composite neonatal morbidity was significantly higher for those delivered at 40 (adjusted RR [aRR], 1.22; 95% CI, 1.19–1.25) and 41 weeks (aRR, 1.53; 95% CI, 1.49–1.58).

The secondary outcome, the overall rate of composite maternal morbidity, was 2.8 per 1,000 live births. As with composite neonatal morbidity, the risk of composite maternal morbidity was also significantly higher for those delivered at 40 (aRR, 1.19; 95% CI, 1.14–1.25) and 41 weeks' gestation (aRR, 1.56; 95% CI, 1.47–1.65) than at 39 weeks.

Thus, among low-risk nulliparous pregnancies, there is an incremental increase in the rates of composite neonatal and maternal morbidity from 39 to 41 weeks.

Is induction of labor at 39 weeks feasible?

As the evidence demonstrating multiple benefits of 39-week inductions increases, concerns regarding the feasibility and cost of implementation in the current US health care system mount. A planned secondary analysis of the ARRIVE trial evaluated medical resource utilization among low-risk nulliparous women randomly assigned to elective induction at 39 weeks or expectant management.[6] Resource utilization was compared between the 2 groups during the antepartum period, delivery admission, and from discharge to 8 weeks postpartum.

For the antepartum period, women in the induction group were significantly less likely than women undergoing expectant management to have at least 1: office visit for routine prenatal care (32.4% vs 68.4%), unanticipated office visit (0.5% vs 2.6%), urgent care/emergency department/triage visit (16.2% vs 44.3%), or hospital admission (0.8% vs 2.2%). When admitted for delivery, as expected, women in the induction group spent significantly more time on the L&D unit (14 hours vs 20 hours) and were more likely to receive interventions for induction (cervical ripening, oxytocin, intrauterine pressure catheter placement). However, they required magnesium sulfate and antibiotics significantly less frequently. For the postpartum group comparison, women in the induction group and their neonates had a significantly shorter duration of hospital stay.

In summary, the investigators found that, compared to women undergoing expectant management, women undergoing elective induction spent longer duration in L&D units and utilized more resources, but they required significantly fewer antepartum clinic and hospital visits, treatments for hypertensive disorders or chorioamnionitis, and had shorter duration of postpartum length of stay.

Is induction of labor at 39 weeks cost-effective?

Hersh and colleagues performed a cost-effectiveness analysis for induction of labor at 39 weeks versus expectant management for low-risk nulliparous women.[7] Based on 2016 National Vital Statistics Data, there were 3.5 million term births in the United States. Following the exclusion of high-risk pregnancies and term parous low-risk pregnancies, a theoretical cohort of 1.6 million low-risk nulliparous women was included in the analysis. A decision-tree

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analytic model was created, in which the initial node stratified low-risk nulliparous women into 2 categories: elective induction at 39 weeks and expectant management. Probabilities of maternal and neonatal outcomes were derived from the literature.

Maternal outcomes included hypertensive disorders of pregnancy and delivery mode. Neonatal outcomes included macrosomia, shoulder dystocia, brachial plexus injury, stillbirth, and neonatal death. Costs of clinic and triage visits, induction of labor, modes of delivery, and maternal and neonatal outcomes were derived from previous studies and adjusted for inflation to 2018 dollars. Finally, quality-adjusted life years (QALYs) were calculated for mothers and neonates and were then used to estimate the incremental cost-effectiveness ratio (ICER) of elective induction of labor at 39 weeks. Following accepted standards, the threshold for cost-effectiveness was set at $100,000/QALYs or less.

Induction at 39 weeks comes in lower cost-wise than the standard threshold for QALY. In their analysis, the investigators found that if all 1.6 million women in their theoretical cohort underwent an elective induction of labor at 39 weeks (rather than expectant management), there would be approximately 54,498 fewer CDs, 79,152 fewer cases of hypertensive disorders, 795 fewer cases of stillbirth, and 11 fewer neonatal deaths. Due to the decreased CD rates, the investigators did project an estimated 86 additional cases of neonatal brachial plexus injury. Using these estimates, costs, and utilities, the authors demonstrated that, compared with expectant management, elective induction of labor at 39 weeks was marginally cost-effective with an ICER of $87,692 per QALY, which was lower than the cost-effectiveness threshold of $100,000 per QALY.

Based on additional sensitivity analyses, the authors concluded that cost-effectiveness of elective induction of labor varied based on variations in model inputs. Specifically, the authors demonstrated that cost-effectiveness of induction of labor varied based on labor induction techniques, modes of delivery, and fluctuations in the rates of CD in induction versus expectant management groups.

Despite these theoretically imputed findings, the authors acknowledged the limitations of their study. Their cost-effectiveness model did not account for costs associated with long-term health impact of CD and hypertensive disease of pregnancy. Additionally, their model did not account for an increase in cost and resource utilization associated with increased time on L&D units to accommodate women undergoing induction. Furthermore, the analysis did not take into account the bundled payments for vaginal versus CDs, which are increasing in prevalence. Lastly, the analysis did not consider the incremental increase in severe neonatal and maternal morbidity from 39 to 41 weeks that Chen et al found in their study.[5]

Will ARRIVE finally arrive?

Cognizant of the medical and economic benefits of 39-week inductions, the Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists published a joint practice advisory recommending "shared decision-making" when counseling low-risk women about induction.[8] While more research is needed to validate the aforementioned findings, particularly in regard to resource utilization, the ARRIVE trial and its associated analyses suggest that a reconsideration to deliver term low-risk nulliparous women at 39 weeks is warranted.

In summary, the overwhelming evidence suggests that, among low-risk nulliparous women there are maternal and neonatal benefits with delivery at 39 weeks, as compared with expectant management. Logistical concerns should not interfere with women's desideratum for optimal outcomes. ●

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OBG MANAGEMENT

SPECIAL SECTION

THE 2019 SCIENTIFIC MEETING OF THE SOCIETY OF GYNECOLOGIC SURGEONS

HIGHLIGHTS ISSUE, PART 2

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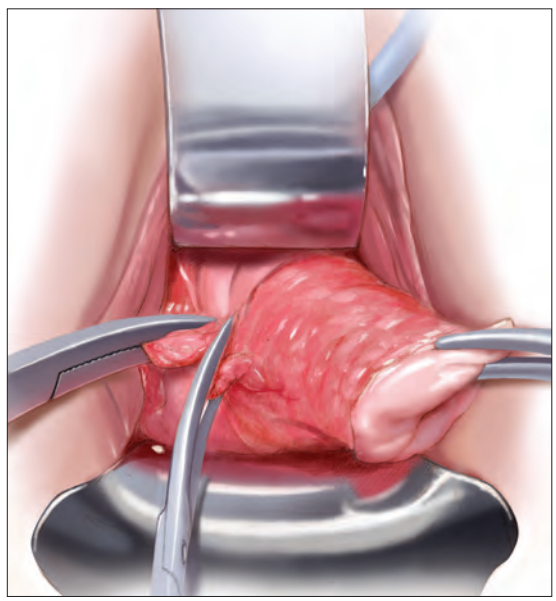
ILLUSTRATION: SCIENCE SOURCE IMAGES

Assessing and treating sexual function after vaginal surgery

Keys to treatment include knowing the patient's preoperative history of any dysfunction; understanding her concerns, needs, and expectations; and starting conservatively

Cassandra L. Carberry, MD; Danielle Antosh, MD; Rebecca G. Rogers, MD



Studies of sexual function post–vaginal surgery are lacking. When a problem is reported, surgical management is required to address sexual function in some cases, but many patients respond to nonsurgical management.

Sexual dysfunction is challenging for patients and clinicians. Just as sexual function is multidimensional—with physical and psychosocial elements—sexual dysfunction can likewise have multiple contributing factors, and is often divided into dysfunction of desire, arousal, orgasm, and sex-related pain. Addressing each of these dimensions of sexual dysfunction in relationship to pelvic reconstructive surgery is beyond the scope of this article. Here, we focus on aspects of sexual dysfunction most likely to be reported by patients after surgery for pelvic organ prolapse (POP) or urinary incontinence, or for both. We discuss what is known about why sexual dysfunction develops after these procedures; how to assess symptoms when sexual dysfunction occurs; and how best to treat these difficult problems.

The authors report no financial relationships relevant to this article.

CASE Postoperative sexual concerns

Your 62-year-old patient presents 2 weeks after vaginal hysterectomy, uterosacral vault suspension, anterior and posterior colporrhaphy, and retropubic midurethral polypropylene sling placement. She reports feeling tired but otherwise doing well.

The patient returns 8 weeks postoperatively, having just resumed her customary exercise routine, and reports that she is feeling well. Upon questioning, she says that she has not yet attempted to have sexual intercourse with her 70-year-old husband.

The patient returns 6 months later and reports that, although she is doing well overall, she is unable to have sexual intercourse.

How can you help this patient? What next steps in evaluation are indicated? Then, with an understanding of her problem in hand, what treatment options can you offer to her?

Surgery for pelvic-floor disorders and sexual function

The impact of surgery on sexual function is important to discuss with patients preoperatively and postoperatively. Because patients with POP and urinary incontinence have a higher rate of sexual dysfunction at baseline, it is important to know

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

how surgery to correct these conditions can affect sexual function.[1] Regrettably, many studies of surgical procedures for POP and urinary incontinence either do not include sexual function outcomes or are not powered to detect differences in these outcomes.

Native-tissue repair. A 2015 systematic review looked at studies of women undergoing native-tissue repair for POP without mesh placement of any kind, including a midurethral sling.[2] Based on 9 studies that reported validated sexual function questionnaire scores, investigators determined that sexual function scores generally improved following surgery. Collectively, for studies included in this review that specifically reported the rate of dyspareunia before and after surgery, 47% of women reported improvement in dyspareunia; 39% reported no change; 18% reported deterioration in dyspareunia; and only 4% had de novo dyspareunia.

Colporrhaphy. Posterior colporrhaphy, commonly performed to correct posterior vaginal prolapse, can narrow vaginal caliber and the introitus, potentially causing dyspareunia. Early description of posterior colporrhaphy technique included plication of the levator ani muscles, which was associated with significant risk of dyspareunia postoperatively.[3] However, posterior colporrhaphy that involves standard plication of the rectovaginal muscularis or site-specific repair has been reported to have a dyspareunia rate from 7% to 20%.[4,5] It is generally recommended, therefore, that levator muscle plication during colporrhaphy be avoided in sexually active women.

Vaginal mesh. Mesh has been used in various surgical procedures to correct pelvic floor disorders. Numerous randomized trials have comparatively evaluated the use of transvaginal polypropylene mesh and native tissue for POP repair, and many of these studies have assessed postoperative sexual function. In a 2013 systematic review on sexual function after POP repair, the authors found no significant difference in postoperative sexual function scores or the dyspareunia rate after vaginal mesh repair (14%) and after native-tissue repair (12%).[6]

Studies of postsurgical sexual function are lacking

Important aspects of sexual function—orgasm, arousal, desire, lubrication, sexual satisfaction, effects on the partner—lack studies. A study of 71 sexually active couples assessed sexual function with questionnaires before and after vaginal native-tissue repair and found that, except for orgasm, all domains improved in female questionnaires. In male partners, interest, sexual drive, and overall satisfaction improved, whereas erection, ejaculation, and orgasm remained unchanged.[7]

Urinary incontinence during sexual intercourse affects approximately 30% of women with overactive bladder or stress incontinence.[8] Several reviews have analyzed data on overall sexual function following urinary incontinence surgery:

- After stress incontinence surgery, the rate of coital incontinence was found to be significantly lower (odds ratio, 0.11).[9] In this review, 18 studies, comprising more than 1,500 women, were analyzed, with most participants having undergone insertion of a midurethral mesh sling. Most women (55%) reported no change in overall sexual function, based on validated sexual questionnaire scores; 32% reported improvement; and 13% had deterioration in sexual function.
- As for type of midurethral sling, 2 reviews concluded that there is no difference in sexual function outcomes between retropubic and transobturator sling routes.[9,10]

Although most studies that have looked at POP and incontinence surgeries show either improve-

Key touchpoints in managing sexual dysfunction after pelvic reconstructive surgery

- ✓ Ask; then ask again
  - Talk about sexual function before and after surgery
- ✓ Remember the basics
  - A thorough history and physical exam are paramount
- ✓ Ask in a different way
  - Any of several validated questionnaires can be a valuable adjunct to the history and physical exam
- ✓ Individualize treatment
  - Many patients respond to nonsurgical treatment, but surgical management is necessary in some cases

ment or no change in sexual function, we stress that sexual function is a secondary outcome in most of those studies, which might not be appropriately powered to detect differences in outcomes. Furthermore, although studies describe dyspareunia and overall sexual function in validated questionnaire scores, most do not evaluate other specific domains of sexual function. It remains unclear, therefore, how POP and incontinence surgeries affect orgasm, desire, arousal, satisfaction, and partner sexual domains; more studies are needed to focus on these areas of female sexual function.

How do we assess these patients?

We do know that sexual function is important to women undergoing gynecologic surgery: In a recent qualitative study of women undergoing pelvic reconstruction, patients rated lack of improvement in sexual function following surgery a "very severe" adverse event.[11] Unfortunately, however, sexual activity and function is not always measured before gynecologic surgery. Although specific reporting guidelines do not exist for routine gynecologic surgery, a terminology report from the International Urogynecologic Association/International Continence Society (IUGA/ICS) recommends that sexual activity and partner status be evaluated prior to and following surgical treatment as essential outcomes.[12] In addition, the report recommends that sexual pain be assessed prior to and following surgical procedures.[12]

Ascertain sexual health. First, asking your patients simple questions about sexual function, pain, and bother before and after surgery opens the door to dialogue that allows them, and their partner, to express concerns to you in a safe environment. It also allows you to better understand the significant impact of your surgical interventions on their sexual health.

Questionnaires. Objective measures of vaginal blood flow and engorgement exist, but assessment of sexual activity in the clinical setting is largely limited to self-assessment with questionnaires. Incorporating simple questions, such as "Are you sexually active?," "Do you have any problems with sexual activity?," and "Do you have pain with activity?" are likely to be as effective as a more detailed interview and can identify women with sexual concerns.[13] Many clinicians are put at a disadvantage, however, because they are faced with the difficult situation of addressing postoperative sexual problems without knowing whether the patient had such reports prior to surgery.

Aside from simple screening tools, a number of sexual function questionnaires have been developed. Some are generic, and others are condition-specific:

- **Generic questionnaires** are typically designed to address the function of a range of women. For example, the Female Sexual Function Index comprises 19 questions. Domains include orgasm, desire, arousal, lubrication, pain and satisfaction.[14]
- **Condition-specific questionnaires** of sexual function each have been validated in their target population so that they measure nuances in sexual health relevant to that population. The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire—IUGA-Revised includes questions about the domains listed for the generic Index (above) plus questions about the impact of coital incontinence or bulge symptoms on sexual function.[12]

History-taking. If a woman identifies a problem with sexual function, a thorough history helps elicit whether the condition is lifelong or acquired, situational or general, and, most important, whether or not it is bothersome to her.[14,15] It is important not to make assumptions when pursuing this part of the history, and to encourage patients to be candid about how they have sex and with whom.

Physical examination. The patient should undergo a complete physical exam, including 1) a detailed pelvic exam assessing the vulva, vagina, and pelvic-floor musculature, and 2) estrogenization of the tissue.

Partner concerns. For women who have a partner, addressing the concerns of that partner following gynecologic surgery can be useful to the couple: The partner might be concerned about inflicting pain or doing damage during sex after gynecologic surgery.

CASE Informative discussion

While ascertaining her sexual symptoms, your patient reveals to you that she has attempted sexual intercourse on 3 occasions; each time, penetration was too painful to continue. She tells you she did not have this problem before surgery.

CONTINUED ON PAGE SS6

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CONTINUED FROM PAGE SS4

The patient says that she has tried water-based lubricants and is using vaginal estrogen 3 times per week, but "nothing helps." She reports that she is arousable and has been able to achieve orgasm with clitoral stimulation, but would like to have vaginal intercourse. Her husband does have erectile dysfunction, which, she tells you, can make penetration difficult.

On physical examination, you detect mild atrophy. Vaginal length is 9 cm; no narrowing or scarring of the vaginal introitus or canal is seen. No mesh is visible or palpable. The paths of the midurethral sling arms are nontender. However, levator muscles are tender and tense bilaterally.

Given these findings on examination, what steps can you take to relieve your patient's pain?

What can we offer these patients?

Treating sexual dysfunction after pelvic reconstructive surgery must, as emphasized earlier, be guided by a careful history and physical exam. Doing so is critical to determining the underlying cause. Whenever feasible, offer the least invasive treatment.

The IUGA/ICS terminology report describes several symptoms of postoperative sexual dysfunction[12]:

- de novo sexual dysfunction
- de novo dyspareunia
- shortened vagina
- tight vagina (introital or vaginal narrowing, or both)
- scarred vagina (including mesh-related problems)
- hispareunia (pain experienced by a male partner after intercourse).

Of course, any one or combination of these symptoms can be present in a given patient. Furthermore, de novo sexual dysfunction, de novo dyspareunia, and hispareunia can have various underlying causes—again, underscoring the importance of the history and exam in determining treatment.

Nonsurgical treatment

Nonhormonal vaginal lubricants and moisturizers; vaginal estrogen therapy. Although, in older women, vaginal atrophy is often not a new diagnosis postsurgically, the condition might have been untreated preoperatively and might therefore come into play in sexual dysfunction postoperatively. If a patient reports vaginal dryness or pain upon penetration, assess for vaginal atrophy and, if present, treat accordingly.

Vaginal dilation and physical therapy. A shortened, tight, or scarred vagina might be amenable to therapy with vaginal dilators and physical therapy, but might ultimately require surgery.

Pelvic-floor myalgia or spasm can develop after surgery or, as with atrophy, might have existed preoperatively but was left untreated. Pelvic-floor myalgia should be suspected if the patient describes difficult penetration or a feeling of tightness, even though scarring or constriction of the vagina is not seen on examination. Physical therapy with a specialist in pelvic floor treatment is a first-line treatment for pelvic-floor myalgia,[16] and is likely to be a helpful adjunct in many situations, including mesh-related sexual problems.[17]

Oral or vaginal medications to relax pelvic-floor muscle spasm are an option, although efficacy data are limited. If pain is of longstanding duration and is thought to have a neuropathic component, successful use of tricyclic antidepressants, neuroleptics, and serotonin–norepinephrine reuptake inhibitors has been reported.[18]

Surgery

Data are sparse regarding surgical treatment of female sexual dysfunction after pelvic reconstructive surgery. Again, it is clear, however, that the key is carefully assessing each patient and then individualizing treatment. Patients can have any type of dysfunction that a patient who hasn't had surgery can—but is also at risk of conditions directly related to surgery.

In any patient who has had mesh placed as part of surgery, thorough examination is necessary to determine whether or not the implant is involved in sexual dysfunction. If the dysfunction is an apparent result of surgery performed by another surgeon, make every effort to review the operative report to determine which material was implanted and how it was placed.

Trigger-point injection can be attempted in a patient who has site-specific tenderness that is not clearly associated with tissue obstruction of the vagina or mesh erosion.[12,19] Even in areas of apparent banding or scarring related to mesh, trigger-point

injection can be attempted to alleviate pain. How often trigger-point injections should be performed is understudied.

If, on examination, tenderness that replicates the dyspareunia is elicited when palpating the levator or obturator internus muscle, pelvic-floor muscle trigger-point injection can be offered (although physical therapy is first-line treatment). Trigger-point injection also can be a useful adjunct in women who have another identified cause of pain but also have developed pelvic-floor muscle spasm.

Not addressing concomitant pelvic-floor myalgia could prevent successful treatment of pain. Inclusion of a pudendal block also might help to alleviate pain.

Surgical resection. If a skin bridge is clearly observed at the introitus, or if the introitus has been overly narrowed by perineorrhaphy but the remainder of the vagina has adequate length and caliber, surgical resection of the skin bridge might relieve symptoms of difficult penetration. In the case of obstructive perineorrhaphy, an attempt at reversal can be made by incising the perineum vertically but then reapproximating the edges transversely—sometimes referred to as reverse perineorrhaphy.

If scar tissue found elsewhere in the vagina might obstruct penetration, this condition might also be amenable to resection. When scarring is annular, relaxing incisions can be made bilaterally to relieve tension on that tissue; alternatively, it might be necessary to perform a Z-plasty. Nearly always, severe scarring is accompanied by levator myalgia, and a combined approach of surgery and physical therapy is necessary.

Neovagina. It is possible to find vaginal stenosis or shortening, to a varying degree, after surgical prolapse repair, with or without mesh or graft. As discussed, vaginal dilation should be offered but, if this is ineffective, the patient might be a candidate for surgical creation of a neovagina. Numerous techniques have been described for patients with congenital vaginal agenesis, with a few reports of similar techniques used to treat iatrogenic vaginal stenosis or obliteration.

The general principle of all neovagina procedures is to create a space between bladder and rectum of adequate caliber and length for desired sexual function. Reported techniques include a thigh or buttock skin graft, use of bowel or peritoneum, and, recently, a buccal mucosa graft.[20,21]

Resection or excision of mesh. In patients who develop sexual dysfunction after mesh placement, the problem can be caused by exposure of the mesh in the vagina or erosion into another organ, but can also arise in the absence of exposure or erosion. Patients might have tenderness to palpation at points where the mesh is palpable through the mucosa but not exposed.

Again, complete investigation is necessary to look for mesh involvement in the vagina and, depending on the type of implant, other adjacent organs. Assessing partner symptoms, such as pain and scratches, also can be telling.

If there is palpable tenderness on vaginal examination of the mesh, resection of the vaginal portion might be an option.[17] Complete excision of mesh implants can be morbid, however, and might not provide a better outcome than partial excision. The risk of morbidity from complete mesh excision must be weighed against the likelihood that partial excision will not resolve pain and that the patient will require further excision subsequently.[17,22] Excising fragmented mesh can be difficult; making every attempt to understand the contribution of mesh to sexual dysfunction is therefore critical to determining how, and how much of, the mesh comes out at the first attempt.

Last, for any woman who opts for surgical intervention to treat pain, you should engage in a discussion to emphasize the multidimensional nature of sexual function and the fact that *any* surgical intervention might not completely resolve her dysfunction.

CASE Discussing options, choosing an intervention

You discuss the examination findings (no shortening or narrowing of the vagina) with the patient. She is relieved but puzzled as to why she cannot have intercourse. You discuss the tension and tenderness of her pelvic floor and that this is likely the cause. You offer her physical therapy (PT). You also discuss muscle relaxing medications and trigger-point injections if physical therapy alone is unsuccessful or if she cannot do PT (as there are barriers, including insurance coverage and scheduling issues, to accessing PT for many patients). You encourage her to continue use of vaginal estrogen and lubricant during intercourse. She agrees to try PT.

At 3-month follow-up, she reports great improvement. She is able to have intercourse, although she says she still has discomfort sometimes. She continues to work with the pelvic floor physical therapist and feels optimistic. You plan to see her in 6 months but counsel her to call if symptoms are not improving or are worsening.

Sexual function must be part of the conversation

It is difficult to counsel patients about sexual function after pelvic reconstructive surgery because data that could guide identification of problems (and how to treat them) are incomplete. Assessing sexual function preoperatively and having an open conversation about risks and benefits of surgery, with specific mention of its impact on sexual health, are critical (see "Key touchpoints in managing sexual dysfunction after pelvic reconstructive surgery," page SS3).

It is also crucial to assess sexual function postoperatively as a matter of routine. Validated questionnaires can be a useful adjunct to a thorough history and physical exam, and can help guide your discussions.

Treatment of postop sexual dysfunction must, first, account for the complex nature of sexual function and, second, be individualized, starting with the least invasive options, when feasible. ■

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Energy-based therapies in female genital cosmetic surgery: Hype, hope, and a way forward

Laser and radiofrequency devices are "out there" as therapeutic options for gyn cosmetic conditions, and some studies show efficacy. Robust evidence on long-term effectiveness and safety is needed before clinicians widely adopt these technologies for their patients.

Sarah Ward, MD, and Cheryl B. Iglesia, MD

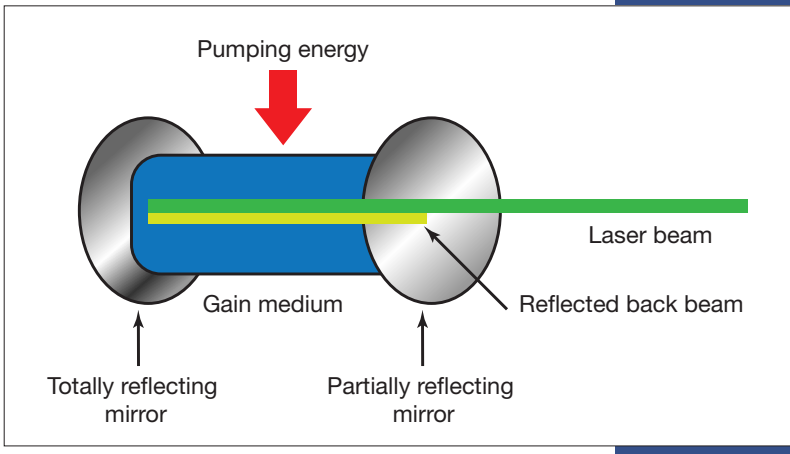
Energy-based therapy use in gynecology dates back to the early 1970s, when ablative carbon dioxide (C02) lasers were employed to treat cervical erosions.[1] Soon after, reports were published on laser treatment for diethylstilbestrol-associated vaginal adenosis, laser laparoscopy for adhesiolysis, laser hysteroscopy, and laser genital wart ablation.[2] Starting around 2011, the first articles were published on the use of fractional C02 laser treatment for vulvovaginal atrophy.[3,4] Use of laser and light-based therapies to treat "vaginal rejuvenation" is now increasing at an annual rate of 26%. In a few years, North America is expected to be the largest market for vaginal laser rejuvenation. In 2016, more than 500,000 feminine rejuvenation procedures were performed in the United States, and it is estimated that more than 27,000 energy-based devices will be in operation by 2021.[5]

Clearly, there is considerable public interest and intrigue in office-based female genital cosmetic procedures. In 2018, the US Food and Drug Administration contacted 7 manufacturers of energy-based devices to request revision and clarification for marketing of these devices, since these technologies are neither cleared nor approved for cosmetic vulvovaginal conditions.[6] The companies responded within 30 days.

In this article, we appraise the existing literature regarding the mechanism of action of energy-based therapies used in gynecology and review outcomes of their use in female genital cosmetic surgery.

The authors report no financial relationships relevant to this article.

FIGURE 1 Components of a laser



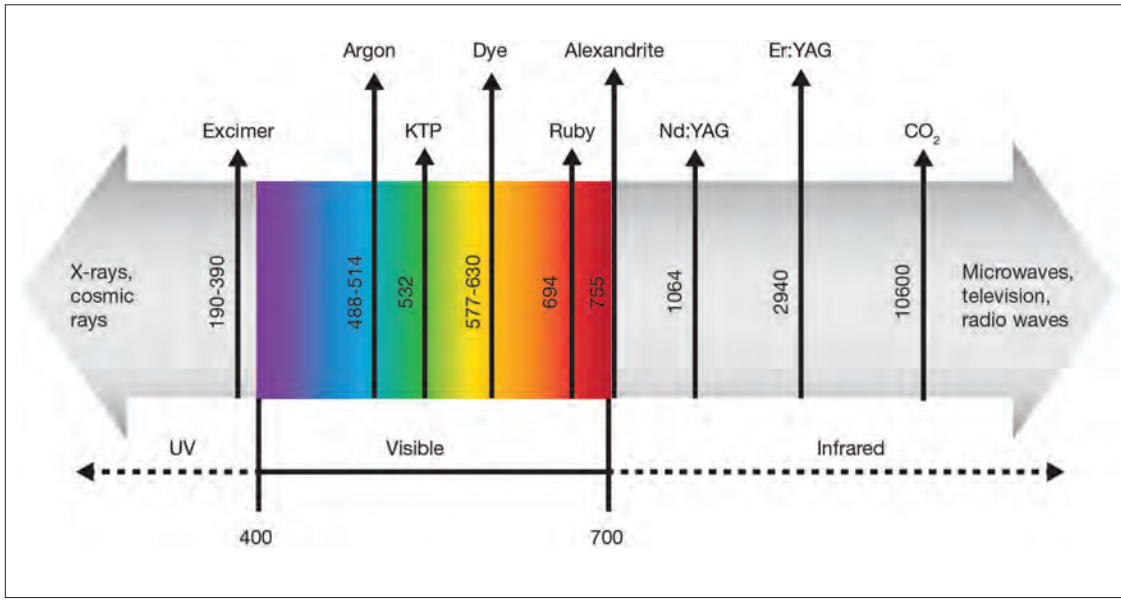
Laser technology devices and how they work

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation. Laser devices are composed of 1) an excitable medium (gas, liquid, solid) needed to emit light, 2) an energy source to excite the medium, 3) mirrors to bounce the light back and forth, and 4) a delivery and cooling system (**FIGURE 1**).

The electromagnetic spectrum is the range of all the wavelengths of light, including visible light, radio waves, infrared light, ultraviolet light, x-rays, and gamma rays (**FIGURE 2**). Most lasers used for the treatment of vulvovaginal disorders, typically C02 and erbium:yttrium aluminum garnet (Er:YAG) lasers, involve the infrared wavelengths.

The basic principle of laser treatment is to match the wavelength of the laser with the

FIGURE 2 Electromagnetic spectrum



absorption spectrum of the desired target—a chromophore such as hemoglobin, melanin, or water (**FIGURE 3**). In essence, light is absorbed by the chromophore (which in vulvar and vaginal tissues is mostly water) and transformed into heat, leading to target destruction. In a fractionated (or fractional) laser beam, the laser is broken up into many smaller beams that treat only portions of the treatment area, with areas of intact epithelium in between the treated areas. At appropriately low thermal denaturation temperatures (45° to 50°C), tissue regeneration can occur through activation of heat shock proteins and tissue growth factors, creating neocollagenesis and neovascularization.

The concept of ablative resurfacing versus fractional resurfacing is borrowed from dermatology (**FIGURE 4**), understanding that tissue ablation and thermal denaturation occur at temperatures greater than 100°C, as occurs with carbonization of vulvar condylomata.

In dermatology, fractionated lasers have been used in the treatment of hair removal, vascular and pigmented lesions, scars, wound healing, tattoo removal, warts, and actinic keratoses. For these conditions, the targeted chromophores are water, hemoglobin, melanosomes, and tattoo ink. The laser pulses must be shorter than the target tissue thermal relaxation times in order to avoid excess heating and collateral tissue damage. Choosing appropriate settings is critical to achieve selective heating, or destruction, of the target tissue. These settings include appropriate wavelengths, pulse durations, and fluence, which is energy delivered per unit area (typically, joules per square centimeter).

For gynecologic conditions, the lasers used are most often CO2, Er:YAG, and hybrid (which include ablative and nonablative wavelengths) devices. In the epithelium of the vagina and vulva, these lasers generally have a very shallow depth of optical penetration, on the order of 10 to 200 µm.

Radiofrequency-based devices emit focused electromagnetic waves

Radiofrequency systems use a wand to deliver radiofrequency energy to create heat within the subepithelial layers of vulvar and vaginal tissues, while the surface remains cool. These devices can use monopolar or bipolar energy (current) to create a reverse thermal gradient designed to heat the deeper tissues transepithelially at a higher temperature while a coolant protects the surface epithelium. Some wand technologies require multiple treatments, while others require only a single treatment.

The **TABLE** on page SS13 lists currently available energy-based technologies.

Therapeutic uses for energy-based devices

Investigators have studied laser devices for treating various gynecologic conditions, including vulvovaginal atrophy, stress urinary incontinence (UI), vaginal laxity, lichen sclerosus, and vulvodynia.

Vulvovaginal atrophy

Genitourinary syndrome of menopause (GSM) includes symptoms of vulvovaginal irritation, burning, itching, discharge, dyspareunia, lower urinary tract symptoms such as frequency and urinary tract infections, and vaginal dryness or vulvovaginal atrophy.[7] First-line treatment for vulvovaginal atrophy includes the use of nonhormonal lubricants for intercourse and vaginal moisturizers, which temporarily moisten the vaginal epithelium. Low-dose vaginal estrogen is a second-line therapy for symptomatic vulvovaginal atrophy; newer pharmacologic options include dehydroepiandrosterone (DHEA) suppositories (prasterone), solubilized estradiol capsules, and the selective estrogen receptor modulator (SERM) ospemifene.

Fractionated CO2, Erb:YAG, and hybrid lasers also have been used to treat women with symptomatic vulvovaginal atrophy and GSM through similar mechanisms described in dermatologic conditions with low-temperature laser activation of tissue proteins and growth factors creating new connective tissue and angiogenesis. A number of landmark studies have been published detailing patient outcomes with energy-based treatments for these symptoms.

Three-arm trial. Cruz and colleagues conducted a double-blind randomized trial to evaluate the efficacy of fractional CO2 laser vaginal treatment compared with local estriol therapy and the combination of laser plus estriol.[8] The investigators randomly assigned 45 postmenopausal women to treatment with fractional CO2 laser with placebo vaginal cream, estriol with sham laser, or laser plus estriol. Treatment consisted of 2 sessions 4 weeks apart, with 20 consecutive weeks of estriol or placebo 3 times per week.

At weeks 8 and 20, the Vaginal Health Index (VHI) average score was significantly higher in all study arms. At week 20, the laser plus estriol group also showed incremental improvement in the VHI score ($P = .01$). The laser and the laser plus estriol groups had significant improvement in dyspareunia, burning, and dryness, while the estriol group improved only in dryness ($P<.001$). The laser plus estriol group had significant improvement in the total Female Sexual Function Index (FSFI) score ($P = .02$) and in the individual domains of pain, desire, and lubrication. Although the laser-alone group had significant worsening in the FSFI pain domain ($P = .04$), all treatment arms had comparable FSFI total scores at week 20. No adverse events were recorded during the study period.

Retrospective study. To assess the efficacy of 3, 4, or 5 treatments with microablative fractional CO2 laser therapy for symptoms of GSM, Athanasiou and colleagues studied outcomes in 94 postmenopausal women.[9] The intensity or bothersomeness of GSM symptoms as well as sexual function significantly improved in this cohort. The

FIGURE 3 Laser mechanism of action: Match the wavelength of light with the absorption spectrum of the target chromophore (water)

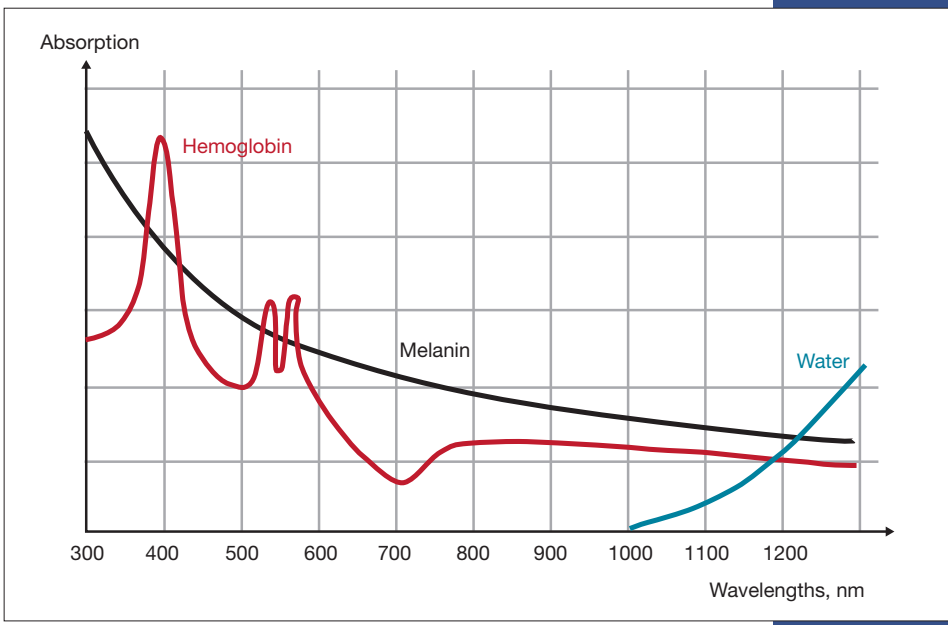
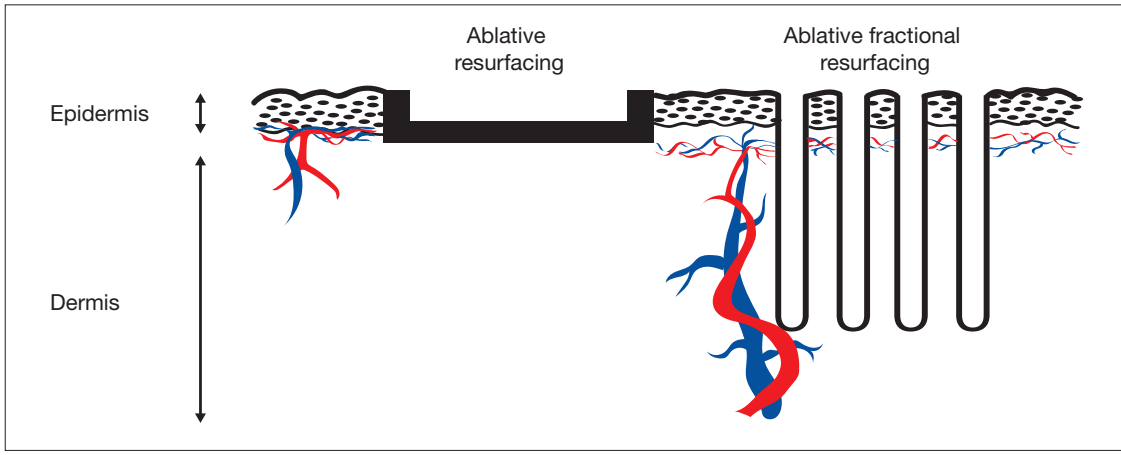


FIGURE 4 Ablative resurfacing and ablative fractional resurfacing of epidermal tissue



intensity of dyspareunia and dryness decreased from a median of 9 (minimum–maximum, 5–10) and 8 (0–10), respectively, at baseline to 0 (0–6) and 0 (0–8) at 1 month after the last laser therapy (P<.001 for all). The FSFI score and the frequency of sexual intercourse rose from 10.8 (2–26.9) and 1 (0–8) at baseline to 27.8 (15.2–35.4) and 4 (2–8) at 1 month after the last laser therapy (P<.001 for all).

The positive effects of laser therapy were unchanged throughout the 12 months of follow-up, and the pattern was the same for symptom-free rates. No adverse events were recorded during the study period.

The investigators noted that, based on short- and long-term follow-up, 4 or 5 laser treatments may be superior to 3 treatments for lowering the intensity of GSM symptoms. They found no differences in outcomes between 4 and 5 laser treatments.

Prospective comparative cohort study. Gaspar and colleagues recruited 50 postmenopausal women with GSM and assigned 25 participants to 2 weeks of pretreatment with estriol ovules 3 times per week (for epithelial hydration) followed by 3 sessions of Er:YAG nonablative laser treatments; 25 women in the active control group received treatment with estriol ovules over 8 weeks.[10] Pre- and posttreatment biopsies, maturation index, maturation value, pH, and VAS symptom analysis were recorded up to 18 months after treatment.

Up to the 6-month follow-up, both treatment groups had a statistically significant reduction of all GSM symptoms. At all follow-ups, however, symptom relief was more prominent in the laser-treated group. In addition, the effects of the laser therapy remained statistically significant at the 12- and 18-month follow-ups, while the treatment effects of estriol were diminished at 12 months and, at 18 months, this group had some symptoms that were significantly worse than before treatment.

Overall, adverse effects were minimal and transient in both groups, affecting 4% of participants in the laser group, and 12% in the estriol group.

Long-term effectiveness evaluation. To assess the long-term efficacy and acceptability of vaginal laser treatment for the management of GSM, Gambacciani and colleagues treated 205 postmenopausal women with an Er:YAG laser for 3 applications every 30 days, with evaluations performed after 1, 3, 6, 12, 18, and 24 months from the last laser treatment.[11] An active control group (n = 49) received 3 months of local treatment with either hormonal (estriol gel twice weekly) or nonhormonal (hyaluronic acid-based preparations or moisturizers and lubricants) agents.

Treatment with the ER:YAG laser induced a significant decrease (P<.01) in scores of the Visual Analog Scale (VAS) for vulvovaginal atrophy symptoms for vaginal dryness and dyspareunia and an increase in the VHI score (P<.01) up to 12 months after the last treatment. After 18 and 24 months, values returned to levels similar to those at baseline.

Women who also had stress UI (n = 114)

received additional laser treatment of the anterior vaginal wall specifically designed for UI, with assessment based on the International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form (ICIQ-UI SF). Laser treatment induced a significant decrease ($P<.05$) in ICIQ-UI SF scores compared with baseline values, and scores remained lower than baseline values after 1, 2, 3, 6, and 12 months after the last laser treatment. Values measured after 18 and 24 months, however, did not differ significantly from baseline.

In the control group, the VAS score showed a similar decrease and comparable pattern during the treatment period. However, after the end of the treatment period, the control group's VAS scores for vaginal dryness and dyspareunia showed a progressive increase, and after 6 months, the values were significantly different from corresponding values measured in the laser therapy group. The follow-up period in the control group ended after 6 months, because almost all patients started a new local or systemic treatment for their GSM symptoms. No adverse events related to treatment were recorded throughout the study period.

In an earlier pilot study by the same authors, 19 women with GSM who also had mild to moderate stress UI were treated with a vaginal Er:YAG laser.[12] Compared with vaginal estriol treatment in the active control group, laser treatment was associated with a significant improvement ($P<.01$) in ICIQ-SF scores, with rapid and long-lasting effects that persisted up to week 24 of the observation period.

Urinary incontinence

The cause of UI is considered to be multifactorial, including disruption in connective tissue supports of the urethrovesical junction leading to urethral hypermobility, pelvic floor muscle weakness, nerve damage to the urethral rhabdosphincter related to pudendal neuropathy or pelvic plexopathy, and atrophic changes of the urethra mucosa and submucosa. Purported mechanisms of action for energy-based therapies designed for treatment of UI relate to direct effects on connective tissue, blood vessels, and possibly nerves.

In 3 clinical trials designed specifically to treat UI with an Er:YAG laser, women showed subjective symptomatic improvement.

Ogrinc and colleagues followed 175 pre- and postmenopausal women with stress UI or mixed UI in a prospective nonrandomized study.[13] They treated women with an Er:YAG laser for an average of 2.5 (0.5) procedures separated by a 2-month period and performed follow-up assessments at 2, 6, and 12 months after treatment.

After treatment, 77% of women with stress UI had significant improvement in symptoms based on the ICIQ SF and the Incontinence Severity Index (ISI), while only 34% of those with mixed UI had no symptoms at 1-year follow-up. No major adverse effects were noted in either group.

Okui compared the effects of Er:YAG laser treatment with those of tension-free vaginal tape (TVT) or transobturator tape (TOT) sling procedures (n = 50 in each group) in women with stress UI or mixed UI.[14] At 12 months after treatment, all 3 treatments demonstrated comparable improvements in the women with stress UI. Some patients with mixed UI in the TVT and TOT groups showed

TABLE Energy-based technologies available for female genital cosmetic surgery

Radiofrequency devices

- ThermiVa (ThermiGen)
- Viveve system cryogen-cooled monopolar radiofrequency device (Viveve)
- Ultrafemme (BTL Industries)
- Votiva FormaV (InMode)
- Venus Fiore (Venus Concept)

Er:YAG devices

- IntimaLase (Fotona)
- Petit Lady (Lutronic)
- Juliet (Cutera)
- EVA (Novavision)

Fractionated CO2 devices

- MonaLisa Touch (DEKA Laser; Hologic/Cynosure)
- GyneLase (INTERmedic)
- FemiLift (Alma)
- SeleneTouch (Hyperion Medical)
- CO2RE Intima (Syneron-Candela)
- FemTouch (Lumenis)

Hybrid fractional device

- diVa (Sciton)

exacerbation, while all women in the laser-treated group tended to have symptom improvement.

In another recent study, Blaganje and colleagues randomly assigned 114 premenopausal parous women with stress UI to an Er:YAG laser procedure or sham treatment.[15] Three months after treatment, ICIQ-UI SF scores were significantly more improved ($P<.001$) in the laser-treated group than in the sham group. In addition, 21% of laser-treated patients were dry at follow-up compared with 4% of the sham-treated group.

Key takeaway. While these studies showed promising short-term results for laser treatment of UI, they need to be replicated in appropriately powered clinical trials that include critical subjective and objective outcomes as well as longer-term follow-up for both effectiveness and safety.

Vaginal laxity/pre-prolapse

Vaginal laxity is defined as the symptom of excessive vaginal looseness.[16] Also referred to as "pre-prolapse," this subjective symptom generally refers to a widened vaginal opening (genital hiatus) but with pelvic organ prolapse that is within the vagina or hymen.[17] Notably, the definition is ambiguous, and rigorous clinical data based on validated outcomes and prolapse grading are lacking.

Krychman and colleagues conducted the first randomized controlled study comparing monopolar radiofrequency at the vaginal introitus with sham therapy for vaginal laxity in 174 premenopausal women, known as the VIVEVE I trial.[18] The primary outcome, the proportion of women reporting no vaginal laxity at 6 months after treatment, was assessed using a vaginal laxity questionnaire, a 7-point rating scale for laxity or tightness ranging from very loose to very tight. With a single radiofrequency treatment, 43.5% of the active group and 19.6% ($P = .002$) of the sham group obtained the primary outcome.

There were also statistically significant improvements in overall sexual function and decreased sexual distress. The adjusted odds ratio (OR, 3.39; 95% confidence interval, 1.54–7.45) showed that the likelihood of no vaginal laxity at 6 months was more than 3 times greater for women who received the active treatment compared with those who received sham treatment. Adverse events were mild, resolved spontaneously, and were similar in the 2 groups.

Outlook for energy-based therapies: Cautiously optimistic

Preliminary outcome data on the use of energy-based therapies for female genital cosmetic surgery is largely positive for the treatment of vulvovaginal atrophy, but some case series suggest the potential for scarring, burning, and inefficacy. This prompted the FDA to send "It has come to our attention" letters to a number of device manufacturers in 2018.[6]

Supportive evidence is weak. Early data are encouraging regarding fractionated laser therapy for the treatment of vulvovaginal atrophy and stress UI and radiofrequency wand therapy for vaginal laxity and stress UI. Unfortunately, the level of evidence to support wide use of these technologies for all pelvic floor disorders is weak. A recent committee opinion from the International Urogynecology Association noted that only 8 studies (1 randomized trial and 7 observational studies) on these conditions fulfilled the criteria of good quality.[19] The International Continence Society and the International Society for the Study of Vulvovaginal Disorders recently published a best practice consensus document declaring laser and energy-based treatments in gynecology and urology to be largely experimental.[20]

Questions persist. Knowledge gaps exist, and recommendations related to subspecialty training—who should perform these procedures (gynecologists, plastic surgeons, urologists, dermatologists, family practitioners) and the level of training needed to safely perform them—are lacking. Patient selection and physician knowledge and experience related to female genital anatomy, female sexual function and dysfunction, multidisciplinary treatment options for various pelvic support problems and UI, as well as psychologic screening for body dysmorphic disorders, need to be considered in terms of treating both the functional and aesthetic aspects related to cosmetic and reconstructive gynecologic surgery.

Special considerations. The use of energy-based therapies in special populations, such as survivors of breast cancer or other gynecologic cancers, as well as women undergoing chemotherapy, radiation therapy, and hormonal manipulation (particularly with antiestrogenic SERMs and aromatase inhibitors) has not been adequately evaluated. A

discussion of the risks, benefits, alternatives, and limited long-term outcome data for energy-based therapies in cancer survivors, as for all patients, must be included for adequate informed consent prior to undertaking these treatments.

Guidelines for appropriate tissue priming, laser settings, and concomitant energy-based technology with local hormone treatment (also known as laser-augmented drug delivery) need to be developed. Comparative long-term studies are needed to determine the safety and effectiveness of these technologies.

Caution advised. Given the lack of long-term safety and effectiveness data on energy-based therapies for the vague indications of vaginal laxity, and even for the well-defined conditions of stress UI and vulvovaginal atrophy, clinicians should exercise caution before promoting treatment, which can be expensive and is not without potential complications, such as vaginal pain, adhesive agglutination, and persistent dryness and dyspareunia.[21]

Fortunately, many randomized trials on various energy-based devices for gynecologic indications (GSM, stress UI, vaginal laxity, lichen sclerosus) are underway, and results from these studies will help inform future clinical practice and guideline development. ■

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Treating the pregnant patient with opioid addiction

Women are increasingly the face of the opioid epidemic, says this addiction expert, and not receiving the care they need. Here, how to help close the gap on treatment.

Q&A with Mishka Terplan, MD

OBG MANAGEMENT: How has the opioid crisis affected women in general?

Mishka Terplan, MD: Everyone is aware that we are experiencing a massive opioid crisis in the United States, and from a historical perspective, this is at least the third or fourth significant opioid epidemic in our nation's history.[1] It is similar in some ways to the very first one, which also featured a large proportion of women and also was driven initially by physician prescribing practices. However, the magnitude of this crisis is unparalleled compared with prior opioid epidemics.

There are lots of reasons why women are overrepresented in this crisis. There are gender-based differences in pain—chronic pain syndromes are more common in women. In addition, we have a gender bias in prescribing opioids and prescribe more opioids to women (especially older women) than to men. Cultural differences also contribute. As providers, we tend not to think of women as people who use drugs or people who develop addictions the same way as we think of these risks and behaviors for men. Therefore, compared with men, we are less likely to screen, assess, or refer women for substance use, misuse, and addiction. All of this adds up to creating a crisis in which women are increasingly the face of the epidemic.

Dr. Terplan is Professor of Obstetrics and Gynecology and Psychiatry and Associate Director of Addiction Medicine at Virginia Commonwealth University, Richmond, Virginia.

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

OBG MANAGEMENT: What are the concerns about opioid addiction and pregnant women specifically?

Dr. Terplan: Addiction is a chronic condition, just like diabetes or depression, and the same principles that we think of in terms of optimizing maternal and newborn health apply to addiction. Ideally, we want, for women with chronic diseases to have stable disease at the time of conception and through pregnancy. We know this maximizes birth outcomes.

Unfortunately, there is a massive treatment gap in the United States. Most people with addiction receive no treatment. Only 11% of people with a substance use disorder report receipt of treatment. By contrast, more than 70% of people with depression, hypertension, or diabetes receive care. This treatment gap is also present in pregnancy. Among use disorders, treatment receipt is highest for opioid use disorder; however, nationally, at best, 25% of pregnant women with opioid addiction receive any care.

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Keypoints

- Only up to one-quarter of pregnant women with opioid addiction receive treatment for that addiction.
- Untreated addiction is a serious medical condition associated with preterm delivery and low-birth weight infants; treated addiction is associated with term delivery and normal-weight infants.
- Medically supervised withdrawal is not recommended during pregnancy. In addition to appropriate prenatal care, the standard treatment of opioid use disorder in pregnancy is pharmacotherapy with either methadone *or* buprenorphine plus behavioral counseling.
- As with many other medications, fetal dependence may occur with methadone or buprenorphine, resulting in neonatal abstinence syndrome (NAS) at birth. NAS is treatable, time-limited, and not associated with long-term harms.
- ObGyns should express empathy for pregnant women with addiction, in order to counter the discrimination these women experience from society and other health care providers.

FAST TRACK

"I encourage every provider to get a waiver to prescribe buprenorphine."

In other words, when we encounter addiction clinically, it is often untreated addiction. Therefore, many times providers will have women presenting to care who are both pregnant and have untreated addiction. From both a public health and a clinical practice perspective, the salient distinction is not between people with addiction and those without but between people with treated disease and people with untreated disease.

Untreated addiction is a serious medical condition. It is associated with preterm delivery and low birth weight infants. It is associated with acquisition and transmission of HIV and hepatitis C. It is associated with overdose and overdose death. By contrast, treated addiction is associated with term delivery and normal weight infants. Pharmacotherapies for opioid use disorder stabilize the intrauterine environment and allow for normal fetal growth. Pharmacotherapies for opioid use disorder help to structure and stabilize the mom's social circumstance, providing a platform to deliver prenatal care and essential social services. And pharmacotherapies for opioid use disorder protect women and their fetuses from overdose and from overdose deaths. The goal of management of addiction in pregnancy is treatment of the underlying condition, treating the addiction.

OBG MANAGEMENT: What should the ObGyn do when faced with a patient who might have an addiction?

Dr. Terplan: The good news is that there are lots of recently published guidance documents from the World Health Organization,[2] the American College of Obstetricians and Gynecologists (ACOG),[3] and the Substance Abuse and Mental Health Services Administration (SAMHSA),[4] and there have been a whole series of trainings throughout the United States organized by both ACOG and SAMHSA.

There is also a collaboration between ACOG and the American Society of Addiction Medicine (ASAM) to provide buprenorphine waiver trainings specifically designed for ObGyns. Check both the ACOG and ASAM pages for details. I encourage every provider to get a waiver to prescribe buprenorphine. There are about 30 ObGyns who are also board certified in addiction medicine in the United States, and all of us are more than happy to help our colleagues in the clinical care of this population, a population that all of us really enjoy taking care of.

Although care in pregnancy is important, we must not forget about the postpartum period. Generally speaking, women do quite well during pregnancy in terms of treatment. Postpartum, however, is a vulnerable period, where relapse happens, where gaps in care happen, where child welfare involvement and sometimes child removal happens, which can be very stressful for anyone much less somebody with a substance use disorder. Recent data demonstrate that one of the leading causes of maternal mortality in the US is from overdose, and most of these deaths occur in the postpartum period.[5] Regardless of what happens during pregnancy, it is essential that we be able to link and continue care

for women with opioid use disorder throughout the postpartum period.

OBG MANAGEMENT: How do you treat opioid use disorder in pregnancy?

Dr. Terplan: The standard of care for treatment of opioid use disorder in pregnancy is pharmacotherapy with either methadone or buprenorphine (**TABLE**) plus behavioral counseling—ideally, co-located with prenatal care. The evidence base for pharmacotherapy for opioid use disorder in pregnancy is supported by every single professional society that has ever issued guidance on this, from the World Health Organization to ACOG, to ASAM, to the Royal College in the UK as well as Canadian and Australian obstetrics and gynecology societies; literally every single professional society supports medication.

The core principle of maternal fetal medicine rests upon the fact that chronic conditions need to be treated and that treated illness improves birth outcomes. For both maternal and fetal health, treated addiction is way better than untreated addiction. One concern people have regarding methadone and buprenorphine is the development of dependence. Dependence is a physiologic effect of medication and occurs with opioids, as well as with many other medications, such as antidepressants and most hypertensive agents. For the fetus, dependence means that at the time of delivery, the infant may go into withdrawal, which is also called neonatal abstinence syndrome. Neonatal abstinence syndrome is an expected outcome of in-utero opioid exposure. It is a time-limited and treatable condition. Prospective data do not demonstrate any long-term harms among infants whose mothers received pharmacotherapy for opioid use disorder during pregnancy.[6]

The treatment for neonatal abstinence syndrome is costly, especially when in a neonatal intensive care unit. It can be quite concerning to a new mother to have an infant that has to spend extra time in the hospital and sometimes be medicated for management of withdrawal. There has been a renewed interest amongst ObGyns in investigating medically-supervised withdrawal during pregnancy. Although there are remaining questions, overall, the literature does not support withdrawal during pregnancy—mostly because withdrawal is associated with relapse, and relapse is associated with cessation of care (both prenatal care and addiction treatment), acquisition and transmission of HIV and hepatitis C, and overdose and overdose death. The pertinent clinical and public health goal is the treatment of the chronic condition of addiction during pregnancy. The standard of care remains pharmacotherapy plus behavioral counseling for the treatment of opioid use disorder in pregnancy.

Clinical care, however, is both evidence-based and person-centered. All of us who have worked in this field, long before there was attention to the opioid crisis, all of us have provided medically-supervised withdrawal of a pregnant person, and that is because we understand the principles of care. When evidence-based care conflicts with person-centered care, the ethical course is the provision of person-centered care. Patients have the right of refusal. If someone wants to discontinue medication, I have tapered the medication during pregnancy, but continued to provide (and often increase) behavioral counseling and prenatal care.

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TABLE My preferred pharmacologic regimen for managing opioid addiction during pregnancy

Day 1	• Assess withdrawal using clinical opiate withdrawal scale (COWS) • Begin medication when COWS score ≥8 —COWS score 8–10: Give buprenorphine 2 mg[a] —COWS score >10: Give buprenorphine 4 mg • Repeat COWS every 1–2 hours and give additional buprenorphine when COWS score ≥8 • Typical Day 1 total dosage = 6–8 mg
Day 2	• Assess withdrawal using COWS • Give total Day 1 dosage of buprenorphine • Assess withdrawal using COWS 1 hr later and give additional buprenorphine dosage based on COWS score • Typical Day 2 dose = 12–16 mg • If patient is stable, write up to a 7-day prescription for buprenorphine

[a]Buprenorphine regulation varies by state.

FAST TRACK

"Prospective data do not demonstrate any long-term harms among infants whose mothers received pharmacotherapy for opioid use disorder during pregnancy."

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Treated addiction is better for the fetus than untreated addiction. Untreated opioid addiction is associated with preterm birth and low birth weight. These obstetric risks are not because of the opioid per se, but because of the repeated cycles of withdrawal that an individual with untreated addiction experiences. People with untreated addiction are not getting "high" when they use, they are just becoming a little bit less sick. It is this repeated cycle of withdrawal that stresses the fetus, which leads to preterm delivery and low birth weight.

Medications for opioid use disorder are long-acting and dosed daily. In contrast to the repeated cycles of fetal withdrawal in untreated addiction, pharmacotherapy stabilizes the intrauterine environment. There is no cyclic, repeated, stressful withdrawal, and consequentially, the fetus grows normally and delivers at term. Obstetric risk is from repeated cyclic withdrawal more than from opioid exposure itself.

FAST TRACK

"...because we prescribed so many opioids to so many people for so long, the absolute number of people with opioid use disorder from physician opioid prescribing is large..."

OBG MANAGEMENT: Research reports that women are not using all of the opioids that are prescribed to them after a cesarean delivery. What are the risks for addiction in this setting?

Dr. Terplan: I mark a distinction between use (ie, using something as prescribed) and misuse, which means using a prescribed medication not in the manner in which it was prescribed, or using somebody else's medications, or using an illicit substance. And I differentiate use and misuse from addiction, which is a behavioral condition, a disease. There has been a lot of attention paid to opioid prescribing in general and in particular postdelivery and post–cesarean delivery, which is one of the most common operative procedures in the United States.

It seems clear from the literature that we have overprescribed opioids postdelivery, and a small number of women, about 1 in 300 will continue an opioid script.[7] This means that 1 in 300 women who received an opioid prescription following delivery present for care and get another opioid prescription filled. Now, that is a small number at the level of the individual, but because we do so many cesarean deliveries, this is a large number of women at the level of the population. This does not mean, however, that 1 in 300 women who received opioids after cesarean delivery are going to become addicted to them. It just means that 1 in 300 will continue the prescription. Prescription continuation is a risk factor for opioid misuse, and opioid misuse is on the pathway toward addiction.

Most people who use substances do not develop an addiction to that substance. We know from the opioid literature that at most only 10% of people who receive chronic opioid therapy will meet criteria for opioid use disorder.[8] Now 10% is not 100%, nor is it 0%, but because we prescribed so many opioids to so many people for so long, the absolute number of people with opioid use disorder from physician opioid prescribing is large, even though the risk at the level of the individual is not as large as people think.

OBG MANAGEMENT: From your experience in treating addiction during pregnancy, are there clinical pearls you would like to share with ObGyns?

Dr. Terplan: There are a couple of takeaways. One is that all women are motivated to maximize their health and that of their baby to be, and every pregnant woman engages in behavioral change; in fact most women quit or cutback substance use during pregnancy. But some can't. Those that can't likely have a substance use disorder. We think of addiction as a chronic condition, centered in the brain, but the primary symptoms of addiction are behaviors. The salient feature of addiction is continued use despite adverse consequences; using something that you know is harming yourself and others but you can't stop using it. In other words, continuing substance use during pregnancy. When we see clinically a pregnant woman who is using a substance, 99% of the time we are seeing a pregnant woman who has the condition of addiction, and what she needs is treatment. She does not need to be told that injecting heroin is unsafe for her and her fetus, she knows that. What she needs is treatment.

The second point is that pregnant women who use drugs and pregnant women with addiction experience a real specific and strong form of discrimination by providers, by other people with addiction, by the legal system, and by their friends and families. Caring for people who have substance use disorder is grounded in human rights, which means treating people with dignity and respect. It is important for providers to have empathy, especially for pregnant people who use drugs, to counter the discrimination these women experience from society and from other health care providers.

OBG MANAGEMENT: Are there specific ways in which ObGyns can show empathy when speaking with a pregnant woman who likely has addiction?

Dr. Terplan: In general when we talk to people about drug use, it is important to ask their permission to talk about it. For example, "Is it okay if I ask you some questions about smoking, drinking, and other drugs?" If someone says, "No, I don't want you to ask those questions," we have to respect that. Assessment of substance use should be a universal part of all medical care, as substance use, misuse, and addiction are essential domains of wellness, but I think we should ask permission before screening.

One of the really good things about prenatal care is that people come back; we have multiple visits across the gestational period. The behavioral work of addiction treatment rests upon a strong therapeutic alliance. If you do not respect your patient, then there is no way you can achieve a therapeutic alliance. Asking permission, and then respecting somebody's answers, I think, goes a really long way to establishing a strong therapeutic alliance, which is the basis of any medical care. ●

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

All reasonable efforts to decrease the CD rate in the United States should be encouraged, with particular attention paid to avoiding the first CD. However, this should not be done at the expense of patient safety. Large-scale quality improvement initiatives, similar to CMQCC efforts in California in 2016, appear to be one such strategy. Other successful strategies may include, for example, routine induction of labor for all low-risk nulliparous women at 39 weeks' gestation.[7] The current report suggests that implementing a large-scale quality improvement initiative to reduce the primary CD rate can likely be done safely, without a significant increase in maternal or neonatal morbidity.

FAST TRACK

The NTSV CD rate decreased from 29.3% to 25% without significantly increasing 6 patient safety measures

toolkit, increased nursing labor support, and monthly meetings to share best practices across all collaborating sites. The NTSV CD rate in these hospitals did decrease from 29.3% in 2015 to 25.0% in 2017 (adjusted odds ratio, 0.76; 95% confidence interval, 0.73–0.78).

Whether or not implementation of the bundle resulted in an inappropriate delay in indicated CDs and, as such, in an increase in maternal or neonatal morbidity is not known. To address this issue, Main and colleagues collected cross-sectional data from more than 50 hospitals with more than 119,000 deliveries throughout California and measured rates of chorioamnionitis, blood transfusions, third- or fourth-degree perineal lacerations, operative vaginal delivery, severe unexpected newborn complications, and 5-minute Apgar scores of less than 5. None of the 6 safety measures showed any difference when comparing 2017 (after implementation of the CMQCC bundle) to 2015 (before implementation), suggesting that patient safety was not compromised significantly.

Study strengths and weaknesses

Strengths of this study include its large sample size and multicenter design with inclusion of a variety of collaborating hospitals. Earlier studies examining the effect of standardized protocols to reduce CD rates have been largely underpowered and conducted at single institutions.[2-6] Moreover, results have been mixed, with some studies reporting an increase in maternal/neonatal adverse events,[2-4] while others suggesting an improvement in select newborn quality outcome metrics.[5] The current study provides reassurance to providers and institutions employing strategies to reduce NTSV CD rates that such efforts are safe.

This study has several limitations. Data collection relied on birth certificate and discharge diagnoses without a robust quality audit. As such, ascertainment bias, random error, and undercounting cannot be excluded. Although the population was heterogeneous, most women had more than a high school education and private insurance, and only 1 in 5 were obese. Whether these findings are generalizable to other areas within the United States is not known. ●

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Andrew M. Kaunitz, MD, NCMP

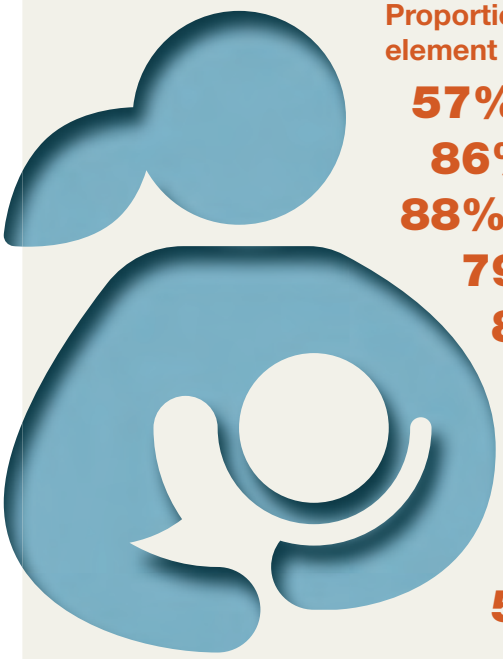
INDEX OF ADVERTISERS

How are US hospitals faring when it comes to implementing breastfeeding-friendly policies?

WHO and other organizations support "10 Steps to Successful Breastfeeding," guidelines that positively impact breastfeeding outcomes. Step 1 requires "a written breastfeeding policy that is routinely communicated to all health care staff."[a] How many US hospitals that provide maternity care (with birth centers excluded) have adopted such model policies, and their individual elements, that support breastfeeding mothers and infants?

33%

of hospitals have a model breastfeeding policy that includes all 10 individual policy elements



Proportion of hospitals that incorporated an individual policy element in their breastfeeding policies

- **57%** Offer prenatal breastfeeding education
- **86%** Ask about mother's feeding plans
- **88%** Initiate early breastfeeding
- **79%** Teach breastfeeding techniques
- **87%** Teach feeding cues
- **76%** Limit non–breast milk feeding of breastfed infants
- **68%** Limit use of pacifiers
- **74%** Have rooming-in
- **76%** Provide postdischarge support
- **58%** Assess staff competency

PLUS

29%

of hospitals do not receive free infant formula[b]

[a]Researchers analyzed 2009–2015 data from the Maternity Practices in Infant Nutrition and Care Survey (a CDC census tool administered every 2 years from 2007 to 2015) to assess trends. Prevalence estimates and percentage point change were calculated for 1) having a model breastfeeding policy, 2) individual breastfeeding policy elements, 3) policy dissemination methods, and 4) not receiving free infant formula. The survey response rate was ≥82% for all (2-year) cycles.

[b]Hospitals seeking designation as a Baby-Friendly center are required to purchase infant formula at fair market value.

Source: Nelson JM, Grossniklaus DA. Trends in hospital breastfeeding policies in the United States from 2009–2015: results from the Maternity Practices in Infant Nutrition and Care Survey. *Breastfeed Med*. 2019. doi:10.1089/bfm.2018.0224.

Abbreviations: CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

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~80% Patients
receive a negative result

~20% Patients
receive a positive result

Benefits of a Negative Result

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High NPV:

NPV for delivery within:

7 days = 99.5%
14 days = 99.2%

Benefits of a Positive Result

A positive result can help clinicians identify patients that may benefit from interventions, such as steroids or maternal transfer.

Useful PPV:

PPV for delivery within:

7 days = 12.7%
14 days = 16.7%

Reference: 1. Rapid fFN for the TIi$_{IQ}$ System [package insert]. AW-04196-001, Rev. 004, Sunnyvale, CA: Hologic, Inc.; 2017

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