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OBG MANAGEMENT

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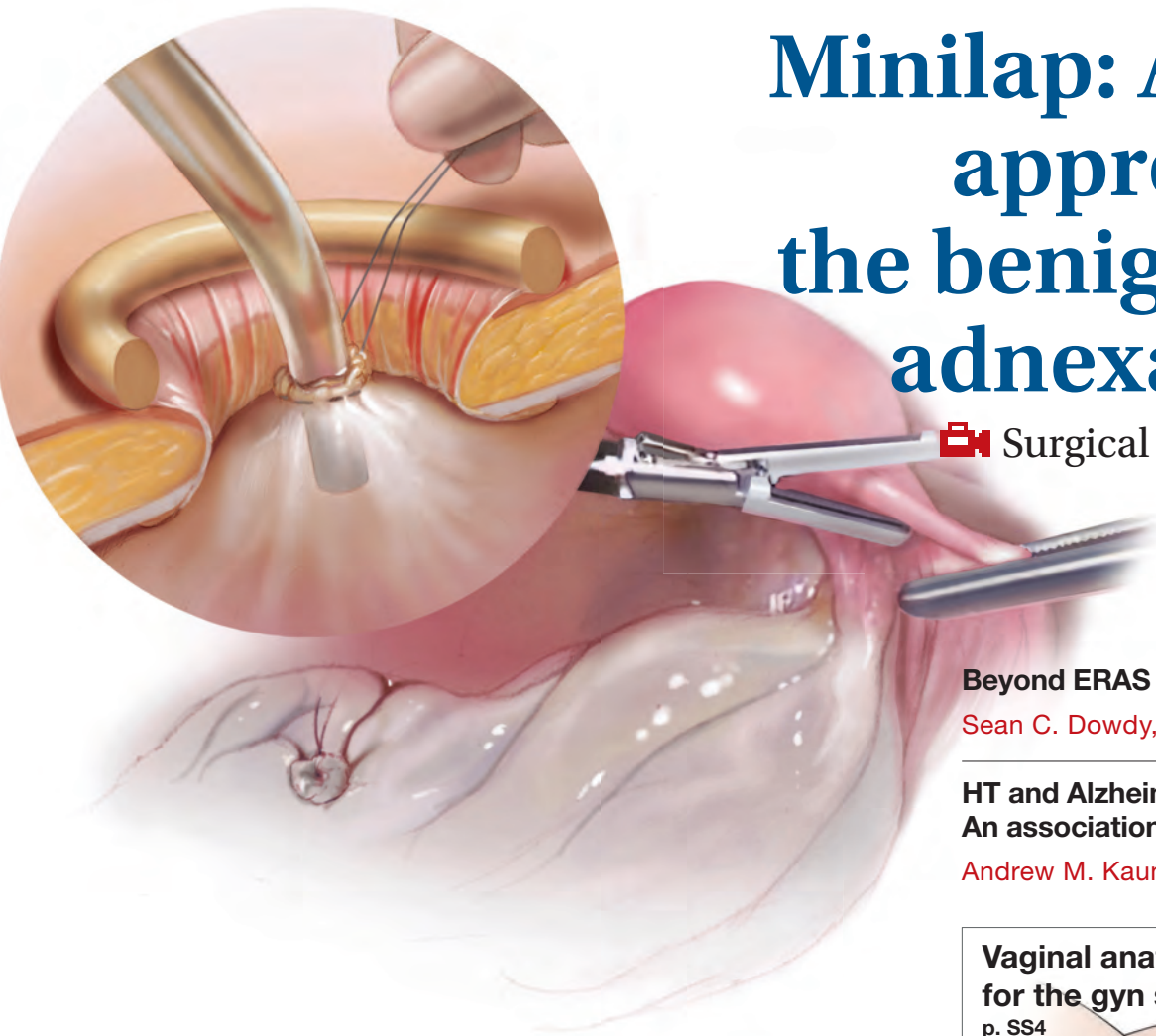
Society of Gynecologic Surgeons Annual Meeting Highlights Issue

Peripartum depression: New counseling guidelines
Robert L. Barbieri, MD

Update on prenatal exome sequencing
Anne H. Mardy, MD; Mary E. Norton, MD



Minilap: A MIGS approach to the benign large adnexal mass

Surgical technique video

Beyond ERAS
Sean C. Dowdy, MD

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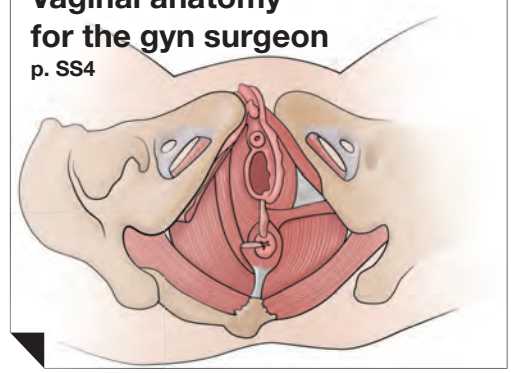


TAKE A NEXT STEP IN MODERATE TO SEVERE ENDOMETRIOSIS PAIN[1]

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]

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

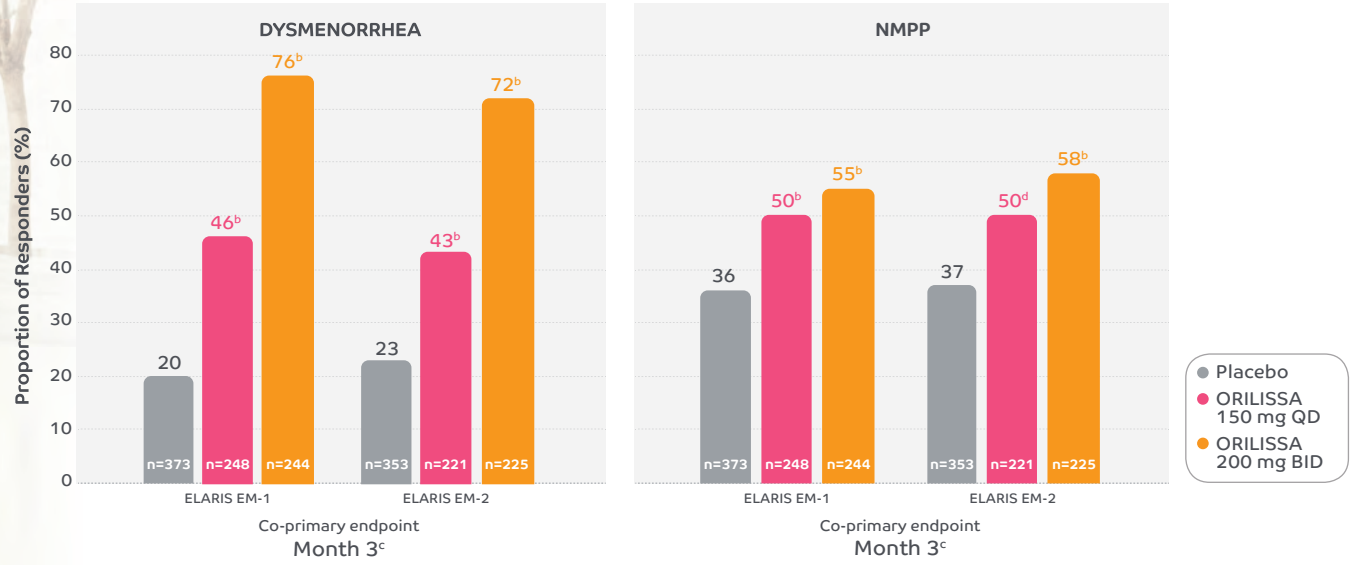
- Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials.
- ORILISSA users had a higher incidence of depression and mood changes compared to placebo and ORILISSA users with a history of suicidality or depression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

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

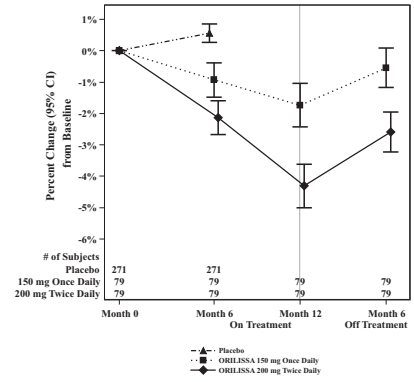
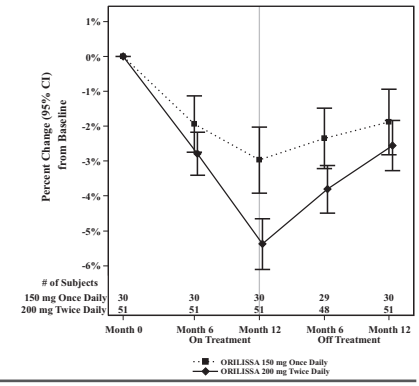


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



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

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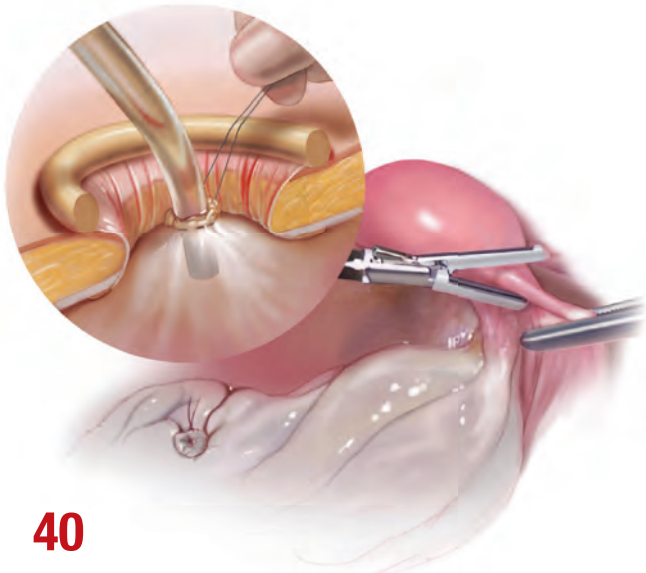
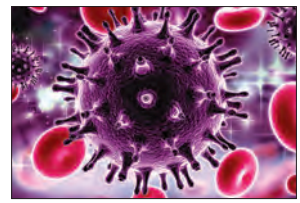
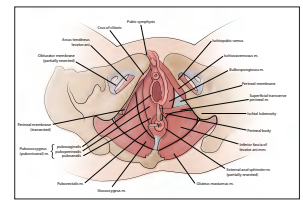




PrEP for HIV **33**



Vaginal anatomy **SS4**

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Prasterone VAGINAL INSERTS 6.5 mg

Indication

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

Important Safety Information

INTRAROSA is contraindicated in women with undiagnosed abnormal genital bleeding.

Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not been studied in women with a history of breast cancer.

In four 12-week randomized, placebo-controlled clinical trials, the most common adverse reaction with an incidence ≥2 percent was vaginal discharge. In one 52-week open-label clinical trial, the most common adverse reactions with an incidence ≥2 percent were vaginal discharge and abnormal Pap smear.

Please see the following page for a Brief Summary of full Prescribing Information.

References: 1. Intrarosa [package insert]. Waltham, MA: AMAG Pharmaceuticals, Inc.; 2018. **2.** *FDA approves Intrarosa for postmenopausal women experiencing pain during sex.*; 2016. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm529641.htm. Accessed February 14, 2019. **3.** Labrie F, Archer DF, Koltun W, et al. *Menopause*. 2016;23(3):243-256.

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Intrarosa®
Prasterone VAGINAL INSERTS 6.5 mg

INTRAROSA® (prasterone) vaginal inserts

Brief Summary: Consult full Prescribing Information for complete product information.

INDICATION
INTRAROSA is a steroid indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

CONTRAINDICATIONS
Undiagnosed abnormal genital bleeding: Any postmenopausal woman with undiagnosed, persistent or recurring genital bleeding should be evaluated to determine the cause of the bleeding before consideration of treatment with INTRAROSA.

WARNINGS AND PRECAUTIONS Current or Past History of Breast Cancer
Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not been studied in women with a history of breast cancer.

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

In four (4) placebo-controlled, 12-week clinical trials [91% - White Caucasian non-Hispanic women, 7% - Black or African American women, and 2% - "Other" women, average age 58.8 years of age (range 40 to 80 years of age)], vaginal discharge is the most frequently reported treatment-emergent adverse reaction in the INTRAROSA treatment group with an incidence of ≥ 2 percent and greater than reported in the placebo treatment group. There were 38 cases in 665 participating postmenopausal women (5.71 percent) in the INTRAROSA treatment group compared to 17 cases in 464 participating postmenopausal women (3.66 percent) in the placebo treatment group.

In a 52-week non-comparative clinical trial [92% - White Caucasian non-Hispanic women, 6% - Black or African American women, and 2% - "Other" women, average age 57.9 years of age (range 43 to 75 years of age)], vaginal discharge and abnormal Pap smear at 52 weeks were the most frequently reported treatment-emergent adverse reaction in women receiving INTRAROSA with an incidence of ≥ 2 percent. There were 74 cases of vaginal discharge (14.2 percent) and 11 cases of abnormal Pap smear (2.1 percent) in 521 participating postmenopausal women. The eleven (11) cases of abnormal Pap smear at 52 weeks include one (1) case of low-grade squamous intraepithelial lesion (LSIL), and ten (10) cases of atypical squamous cells of undetermined significance (ASCUS).

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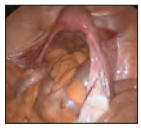

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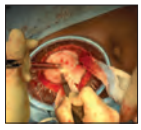

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EDITORIAL

Screening and counseling interventions to prevent peripartum depression: A practical approach

After successful implementation of screening for perinatal depression, the USPSTF is recommending a new approach: screen for women at high risk for peripartum depression and recommend that screen-positive women receive preventive counseling

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Perinatal depression is an episode of major or minor depression that occurs during pregnancy or in the 12 months after birth; it affects about 10% of new mothers.[1] Perinatal depression adversely impacts mothers, children, and their families. Pregnant women with depression are at increased risk for preterm birth and low birth weight.[2] Infants of mothers with postpartum depression have reduced bonding, lower rates of breastfeeding, delayed cognitive and social development, and an increased risk of future mental health issues.[3] Timely treatment of perinatal depression can improve health outcomes for the woman, her children, and their family.

Clinicians follow current screening recommendations

The American College of Obstetricians and Gynecologists (ACOG) currently recommends that ObGyns screen all pregnant women for depression and anxiety symptoms at least once during the perinatal period.[1] Many practices use the Edinburgh Postnatal Depression Scale (EPDS) during pregnancy and postpartum. Women who screen positive are referred to mental health clinicians or have treatment initiated by their primary obstetrician.

Clinicians have been **phenomenally successful** in screening for perinatal depression. In a recent study from Kaiser Permanente Northern California, 98% of pregnant women were screened for perinatal depression, and a diagnosis of depression was made in 12%.[4] Of note, only 47% of women who screened positive for depression initiated treatment, although 82% of women with the most severe symptoms initiated treatment. These data demonstrate that ObGyns consistently screen pregnant women for depression but, due to patient and system issues, treatment of all screen-positive women remains a yet unattained goal.[5,6]

New USPSTF guideline: Identify women at risk for perinatal depression and refer for counseling

In 2016 the United States Preventive Services Task Force (USPSTF) recommended that pregnant and postpartum women be screened for depression with adequate systems in place to ensure diagnosis, effective treatment, and follow-up.[7] The 2016 USPSTF recommendation was consistent with prior guidelines from both the American Academy of Pediatrics in 2010[8] and ACOG in 2015.[9]

Now, the USPSTF is making a bold new recommendation, jumping ahead of professional societies: screen pregnant women to identify those at risk for perinatal depression and refer them for counseling (B recommendation; net benefit is moderate).[10,11] The USPSTF recommendation is based on growing literature that shows counseling women at risk for perinatal depression reduces the risk of having an episode of major depression by 40%.[11] Both

interpersonal psychotherapy and cognitive behavioral therapy have been reported to be effective for preventing perinatal depression.[12,13]

As an example of the relevant literature, in one trial performed in Rhode Island, women who were 20 to 35 weeks pregnant with a high score (≥27) on the Cooper Survey Questionnaire and on public assistance were randomized to counseling or usual care. The counseling intervention involved 4 small group (2 to 5 women) sessions of 90 minutes and one individual session of 50 minutes.[14] The treatment focused on managing the transition to motherhood, developing a support system, improving communication skills to manage conflict, goal setting, and identifying psychosocial supports for new mothers. At 6 months after birth, a depressive episode had occurred in 31% of the control women and 16% of the women who had experienced the intervention (P = .041). At 12 months after birth, a depressive episode had occurred in 40% of control women and 26% of women in the intervention group (P = .052).

Of note, most cases of postpartum depression were diagnosed more than 3 months after birth, a time when new mothers generally no longer are receiving regular postpartum care by an obstetrician. The timing of the diagnosis of perinatal depression indicates that an effective handoff between the obstetrician and primary care and/or mental health clinicians is of great importance. The investigators concluded that pregnant women at very high risk for perinatal depression who receive interpersonal therapy have a lower rate of a postpartum depressive episode than women receiving usual care.[14]

Pregnancy, delivery, and the first year following birth are stressful for many women and their families. Women who are young, poor, and with minimal social supports are at especially high risk for developing perinatal depression. However, it will be challenging for obstetric practices to rapidly implement the new USPSTF recommendations because there is no professional consensus on how to screen women to identify those at high risk for perinatal depression, and mental health resources to care for the screen-positive women are not sufficient.

PHOTO: SHUTTERSTOCK

Challenges to implementing new USPSTF guideline

CHALLENGE 1: There is no widely accepted approach for identifying women at risk for perinatal depression. The USPSTF acknowledges "there is no accurate screening tool for identifying who is at risk of perinatal depression and who might benefit from preventive interventions."[10]

Obstetricians have had great success in screening for perinatal depression because validated screening tools are available. Professional societies need to reach a consensus on recommending a specific screening tool for perinatal depression risk that can be used in all obstetric practices.

CHALLENGE 2: The USPSTF guideline identifies many risk factors for perinatal depression. The USPSTF concluded that pregnant women with one (or more) of the following risk factors are at high risk for perinatal depression and recommended that they be offered a counseling intervention:

- personal history of depression
- current depressive symptoms that do not reach a diagnostic threshold
- low income
- all adolescents
- all single mothers
- recent exposure to intimate partner violence
- elevated anxiety symptoms
- a history of significant negative life events.

For many obstetricians, most of their pregnant patients meet the USPSTF criteria for being at high risk for perinatal depression and, per the guideline, these women should have a counseling intervention.

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CHALLENGE 3: The counseling intervention recommended by the USPSTF may not be available to all women at risk for perinatal depression. The USPSTF literature review, including a meta-analysis of 49 randomized clinical trials, concluded that for women at risk for perinatal depression, a counseling intervention reduces the risk of depression. In the published literature, many counseling interventions to reduce the risk of perinatal depression involve 6 to 12 hours of contact time over 4 to 8 episodes.

For many health systems, the resources available to provide mental health services are very limited. If most pregnant women need a counseling intervention, the health system must evolve to meet this need. In addition, risk factors for perinatal depression are also risk factors for having difficulty in participating in mental health interventions due to limitations, such as lack of transportation, social support, and money.[4]

Fortunately, clinicians from many backgrounds, including psychologists, social workers, nurse practitioners, and public health workers have the experience and/or training to provide the counseling interventions that have been shown to reduce the risk of perinatal depression. Health systems will need to tap all these resources to accommodate the large numbers of pregnant women who will be referred for counseling interventions. Pilot projects using electronic interventions, including telephone counseling, smartphone apps, and internet programs show promise.[15,16] Electronic interventions have the potential to reach many pregnant women without over-taxing limited mental health resources.

A practical approach

Identify women at the greatest risk for perinatal depression and focus counseling interventions on this group. In my opinion, implementation of the USPSTF recommendation will take time. A practical approach would be to implement them in a staged sequence, focusing first on the women at highest risk, later extending the program to women at lesser risk. The two factors that confer the greatest risk of perinatal depression are a personal history of depression and high depression symptoms that do not meet criteria for depression.[17] Many women with depression who take antidepressants discontinue their medications during pregnancy. These women are at very high risk for perinatal depression and deserve extra attention.[18]

To identify women with a prior personal history of depression, it may be helpful to ask open-ended questions about a past diagnosis of depression or a mood disorder or use of antidepressant medications. To identify women with the greatest depression symptoms, utilize a lower cut-off for screening positive in the Edinburgh questionnaire. Practices that use an EPDS screen-positive score of 13 or greater could reduce the cut-off to 10 or 11, which would increase the number of

CONTINUED ON PAGE 37

What is the association of menopausal HT use and risk of Alzheimer disease?

Women with Alzheimer disease (AD) were **more likely to have used postmenopausal systemic hormone therapy** (HT) than controls **(18.6% vs 17.0%, *P*<.001)**, according to results of an observational study that used national records to match 84,739 women with a diagnosis of AD with an equal number of controls. Use of vaginal estrogen was not associated with an increased risk of AD (odds ratio, 0.99). **Small elevations in AD risk with systemic HT use, however, do not imply causation—and they should not impact clinical practice.**

EXPERT COMMENTARY
Andrew M. Kaunitz, MD, is University of Florida Term Professor and Associate Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville; Medical Director and Director of Menopause and Gynecologic Ultrasound Services, UF Women's Health Specialists at Emerson, Jacksonville. Dr. Kaunitz serves on the OBG MANAGEMENT Board of Editors.

Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, et al. Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. BMJ. 2019;364:1665.

Alzheimer disease represents the most common cause of dementia. Although sex hormones may play a role in the etiology of AD in women, studies addressing the impact of menopausal HT on risk of AD have conflicting findings.

Finnish researchers Savolainen-Peltonen and colleagues aimed to compare postmenopausal HT use in women with and without AD. They used national drug and population registries to identify patients with AD, control women without a diagnosis of AD, and data on postmenopausal HT use.

The author reports receiving grant or research support from Allergan and Mithra and that he is a consultant to AMAG, Merck, and Pfizer.

Details of the study

In Finland, reimbursement for treatment related to AD requires cognitive testing, brain imaging, and a statement from a specialist physician. Using national records, the study investigators identified 84,739 women with a diagnosis of AD during the years 1999–2013 and the same number of control women (without AD) during the same period. A national drug reimbursement registry was used to identify HT use from the year 1994.

Findings. Women diagnosed with AD were more likely to have been current or former users of systemic HT than controls (18.6% vs 17.0%, *P*<.001). The odds ratios (ORs) for AD were 1.09 for the estradiol-only group and 1.17 for the estrogen-progestin group (*P*<.05 for both comparisons).

FAST TRACK

According to an observational study, 84,739 women with AD were more likely to have used systemic HT than an equal number of controls without a diagnosis of AD

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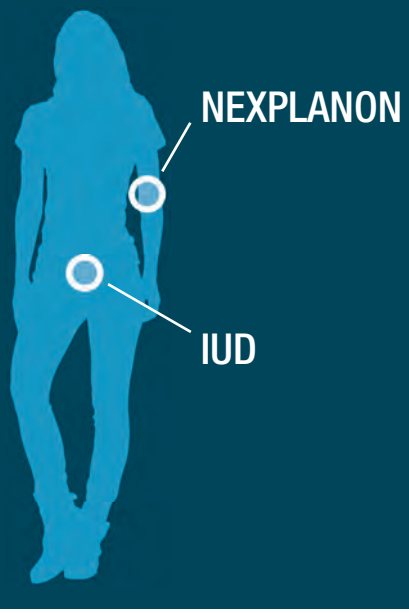

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IUD, intrauterine device; LARC, long-acting reversible contraceptive.

NEXPLANON is indicated for use by women to prevent pregnancy.

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Who is not appropriate for NEXPLANON

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

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

US-XPL-00236 03/19

NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

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

>99% effective†

Reversible if her plans change

Placed subdermally just under the skin in the inner upper arm

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

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

(Actual implant shown; actual implant is 4 cm)

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

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

MERCK

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

Complications of Insertion and Removal

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

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

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

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

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

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

Changes in Menstrual Bleeding Patterns

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

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

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

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

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

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

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

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

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

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

Ectopic Pregnancies

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

Thrombotic and Other Vascular Events

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

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

Ovarian Cysts

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

Carcinoma of the Breast and Reproductive Organs

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

Liver Disease

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

Weight Gain

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

Elevated Blood Pressure

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

Gallbladder Disease

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

Carbohydrate and Lipid Metabolic Effects

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

Depressed Mood

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

Return to Ovulation

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

Nexplanon®
(etonogestrel implant) 68mg

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

For more detailed information, please read the Prescribing Information.
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CONTINUED FROM PAGE 13

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Alzheimer disease is more prevalent in women, and women are more likely to be caregivers for individuals with AD than men, making AD an issue of particular concern to midlife and older women. Current guidance from The North American Menopause Society and other organizations does not recommend use of systemic HT to prevent AD.[1] As Savolainen-Peltonen and colleagues note in their observational study, the small risk increases for AD with use of HT are subject to bias. Editorialists agree with this concern and point out that a conclusive large randomized trial assessing HT's impact on AD is unlikely to be performed.[2] I agree with the editorialists that the findings of this Finnish study should not change current practice. For recently menopausal women who have bothersome vasomotor symptoms and no contraindications, I will continue to counsel that initiating systemic HT is appropriate.

ANDREW M. KAUNITZ, MD

FAST TRACK

The study authors noted that the small risk increases for AD with use of HT are subject to bias—and editorialists agree with this concern

Initiation of HT prior to age 60 was less common among AD cases than controls ($P = .006$). As a continuous variable, age was not a determinant for disease risk in estradiol-only users (OR, 1.0), estrogen-progestin users (OR, 1.0), or any HT use (OR, 1.0).

The exclusive use of vaginal estrogen therapy was not associated with an elevated risk of AD (OR, 0.99).

Study strengths and limitations

This study on the association between HT and AD included a very large number of participants from a national population registry, and the use of HT was objectively determined from a controlled registry (not self-reported). In addition, AD was accurately diagnosed and differentiated from other forms of dementia.

Limitations of the study include the lack of baseline demographic data for AD risk factors for both HT users and controls. Further, an increased risk of AD may have been a cause for HT use and not a consequence, given that initial cognitive impairments may occur 7 to 8 years prior to AD diagnosis and the possibility exists that such women may have sought help for cognitive symptoms from HT. In addition, the lack of brain imaging or neurologic examination to exclude AD might also account for undiagnosed disease in controls. The authors noted that they were unable to compare the use of oral and transdermal HT preparations or the use of cyclic and continuous estrogen-progestin therapy. ●

References

1. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24:728-753.
2. Maki PM, Girard LM, Manson JE. Menopausal hormone therapy and cognition. *BMJ*. 2019;364:1877.

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UPDATE Prenatal exome sequencing

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Dr. Norton reports that she has received grant or research support from Natera and that she is a consultant to Invitae. Dr. Mardy reports no financial relationships relevant to this article.

Prenatal genetic testing is boldly going to the next frontier: exome sequencing. Here, experts consider studies that explore the technology's potential utility and offer practical society guidance on use.

IN THIS ARTICLE

Prenatal diagnosis of genetic anomalies is important for diagnosing lethal genetic conditions before birth. It can provide information for parents regarding pregnancy options and allow for recurrence risk counseling and the potential use of preimplantation genetic testing in the next pregnancy. For decades, a karyotype was used to analyze amniocentesis and chorionic villus sampling specimens; in recent years, chromosomal microarray analysis provides more information about significant chromosomal abnormalities, including microdeletions and microduplications. However, microarrays also have limitations, as they do not identify base pair changes associated with single-gene disorders.

The advent of next-generation sequencing has substantially reduced the cost of DNA sequencing. Whole genome sequencing (WGS) can sequence the entire genome—both the coding (exonic) and noncoding (intronic) regions—while exome sequencing analyzes only the protein-coding exons, which make up 1% to 2% of the genome and about 85% of the protein-coding genes associated with known human disease. Exome sequencing increasingly is used in cases of suspected genetic disorders when other tests have been unrevealing.

In this Update, we review recent reports of prenatal exome sequencing, including studies exploring the yield in fetuses with structural anomalies; the importance of prenatal phenotyping; the perspectives of parents and health care professionals who were involved in prenatal exome sequencing studies; and a summary of a joint position statement from 3 societies regarding prenatal sequencing.

Prenatal whole exome sequencing has potential utility, with some limitations

Petrovski S, Aggarwal V, Giordano JL, et al. Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study. Lancet. 2019;393:758-767.

Lord J, McMullan DJ, Eberhardt RY, et al; for the Prenatal Assessment of Genomes and Exomes Consortium. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. Lancet. 2019;393:747-757.

Exome sequencing has been shown to identify an underlying genetic cause in 25% to 30% of children with an undiagnosed suspected genetic disorder. Two studies recently published in the *Lancet* sought to determine the incremental diagnostic yield of prenatal whole exome sequencing (WES) in the setting of fetal structural anomalies when karyotype and microarray results were normal.

Details of the studies

In a prospective cohort study by Petrovski and colleagues, DNA samples from 234 fetuses with a structural anomaly (identified on ultrasonography) and both parents (parent-fetus "trios") were used for analysis. WES identified diagnostic genetic variants in 24 trios (10%). An additional 46 (20%) had variants that indicated pathogenicity but without sufficient evidence to be considered diagnostic.

The anomalies with the highest frequency of a genetic diagnosis were lymphatic, 24%; skeletal, 24%; central nervous system, 22%; and renal, 16%; while cardiac anomalies had the lowest yield at 5%.

In another prospective cohort study, known as the Prenatal Assessment of Genomes and Exomes (PAGE), Lord and colleagues sequenced DNA samples from 610 parent-fetus trios, but they restricted sequencing to a predefined list of 1,628 genes. Diagnostic genetic variants were identified in 52 fetuses (8.5%), while 24 (3.9%) had a variant of uncertain significance that was thought to be of potential clinical usefulness.

Fetuses with multiple anomalies had the highest genetic yield (15.4%), followed by skeletal (15.4%) and cardiac anomalies (11.1%), with the lowest yield in fetuses with isolated increased nuchal translucency (3.2%).

Diagnostic yield is high, but prenatal utility is limited

Both studies showed a clinically significant diagnostic yield of 8% to 10% for prenatal exome sequencing in cases of fetal structural anomalies with normal karyotype and microarray testing. While this yield demonstrates the utility of prenatal exome sequencing, it is significantly lower than what has been reported in postnatal studies. One of the reasons for this is the inherent limitation of prenatal phenotyping (discussed below).

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The cohort studies by both Petrovski and Lord and their colleagues show the feasibility and potential diagnostic utility of exome sequencing in cases of fetal structural anomalies where karyotype and microarray are not diagnostic. However, the lower yield found in these studies compared with those in postnatal studies highlights in part the limitations of prenatal phenotyping.

The importance of prenatal phenotyping

Aarabi M, Sniezek O, Jiang H, et al. Importance of complete phenotyping in prenatal whole exome sequencing. Hum Genet. 2018;137:175-181.

In postnatal exome sequencing, the physical exam, imaging findings, and laboratory results are components of the phenotype that are used to interpret the sequencing data. Prenatal phenotyping, however, is limited to the use of fetal ultrasonography and, occasionally, the addition of magnetic resonance imaging. Prenatal phenotyping is without the benefit of an exam to detect more subtle anomalies or functional status, such as developmental delay, seizures, or failure to thrive.

CONTINUED ON PAGE 26

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.

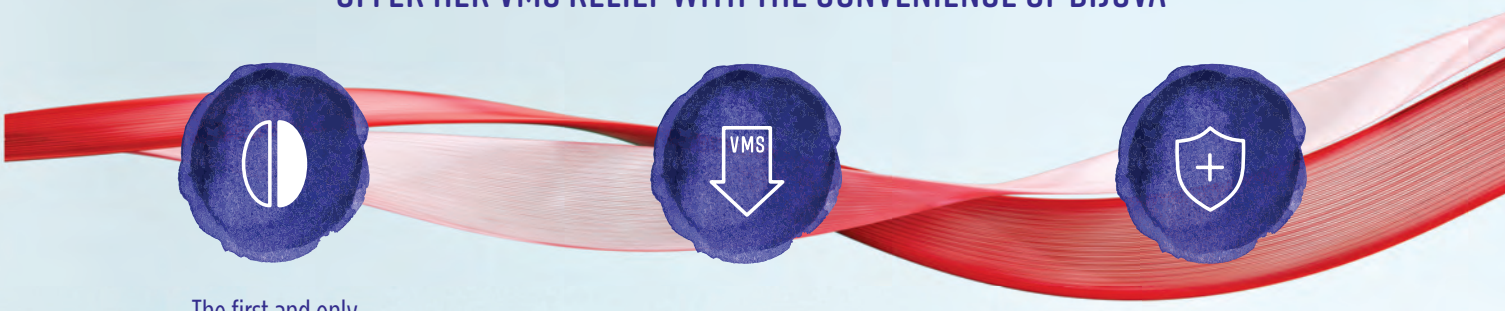
Estrogen Plus Progestin Therapy

- **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][5] [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.

Manufactured for: TherapeuticsMD, Inc. Boca Raton, FL 33487

TherapeuticsMD®

CONTINUED FROM PAGE 21

When a structural anomaly is identified on prenatal ultrasonography, it is especially important that detailed imaging be undertaken to detect other anomalies, including more subtle facial features and dysmorphology.

Value of reanalyzing exome sequencing data

Aarabi and colleagues conducted a retrospective study of 20 fetuses with structural anomalies and normal karyotype and microarray. They performed trio exome sequencing first using information available only prenatally and then conducted a reanalysis using information available after delivery.

With prenatal phenotyping only, the investigators identified no pathogenic, or likely pathogenic, variants. On reanalysis of combined prenatal and postnatal findings, however, they identified pathogenic variants in 20% of cases.

Significance of the findings

This study highlights both the importance of a careful, detailed fetal ultrasonography study and the possible additional benefit of a postnatal examination (such as an autopsy) in order to yield improved results. In addition, the authors noted that the development of a prenatal phenotype-genotype database would significantly help exome sequencing interpretation in the prenatal setting.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Careful prenatal ultrasonography is crucial to help in the interpretation of prenatal exome sequencing. Patients who have undergone prenatal clinical exome sequencing may benefit from reanalysis of the genetic data based on detailed postnatal findings.

FAST TRACK

Most parents reported that they would like to be told about uncertain results of prenatal WES, but that desire decreased as the certainty of results decreased

Social impact of WES: Parent and provider perspectives

Wou K, Weitz T, McCormack C, et al. Parental perceptions of prenatal whole exome sequencing (PPPWES) study. Prenat Diagn. 2018;38:801-811.

Horn R, Parker M. Health professionals' and researchers' perspectives on prenatal whole genome and exome sequencing: 'We can't shut the door now, the genie's out, we need to refine it.' PLoS One. 2018;13:e0204158.

As health care providers enter a new era of prenatal genetic testing with exome sequencing, it is crucial to the path forward that we obtain perspectives from the parents and providers who participated in these studies. Notably, in both of the previously discussed *Lancet* reports, the authors interviewed the participants to discuss the challenges involved and identify strategies for improving future testing.

What parents want

To ascertain the perceptions of couples who underwent prenatal WES, Wou and colleagues conducted semi-structured interviews with participants from the Fetal Sequencing Study regarding their experience. They interviewed 29 parents from 17 pregnancies, including a mix of those who had pathogenic prenatal results, terminated prior to receiving the results, and had normal results.

Expressed feelings and desires. Parents recalled feelings of anxiety and stress around the time of diagnosis and the need for help with coping while awaiting results. The majority of parents reported that they would like to be told about uncertain results, but that desire decreased as the certainty of results decreased.

Parents were overall satisfied with the

CONTINUED ON PAGE 28

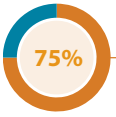
Enhancing patient outcomes, managing costs, and optimizing quality of life.

The value of care:

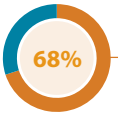
UNIVERSAL SCREENING
for Chlamydia and Gonorrhea

About **ONE** in **TWO** sexually active people will acquire an STI by **AGE 25.**

Infections with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) are commonly asymptomatic.



~75% of women infected with **chlamydia** are asymptomatic[1]



~68% of women infected with **gonorrhea** are asymptomatic[1]

Chlamydia and gonorrhea are two of the most common reportable sexually transmitted infections (STIs) and rates of infection are on the rise.

A universal screening CT/NG strategy would focus on women within the high-risk age group covered by guidelines from USPSTF and CDC guidelines (women 15-24 years old) without regard to the sexual activity they report.

Universal screening may help to:[2]

- Decrease STI prevalence
- Decrease infertility due to undiagnosed infections
- Reduce health care cost

Value beyond testing. LabCorp's full-service offerings, specialty test options, genetic counseling programs, cost estimator, and coast-to-coast patient service centers set our value apart and put your patients at the heart of our efforts to improve health and improve lives.

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References
1. Farley TA, Cohen DA, Elkins W. Asymptomatic sexually transmitted diseases: the case for screening. *Prev Med.* 2003;36(4)502-509.
2. Owusu-Edusei K, Hoover KW, Gift TL. Cost-effectiveness of opt-out chlamydia testing for high-risk young women in the U.S. *Am J Prev Med.* 2016;51(2):216-24. doi: 10.1016/j.amepre.2016.01.007.

CONTINUED FROM PAGE 26

prenatal genetic testing experience, but they added that they would have liked to receive written materials beforehand and a written report of the test results (including negative cases). They also would like to have connected with other families with similar experiences, to have received results sooner, and to have an in-person meeting after telephone disclosure of the results.

Health professionals articulate complexity of prenatal genomics

In a qualitative interview study to explore critical issues involved in the clinical practice use of prenatal genomics, Horn and Parker conducted interviews with 20 health care professionals who were involved in the previously described PAGE trial. Patient recruiters, midwives, genetic counselors, research assistants, and laboratory staff were included.

Interviewees cited numerous challenges involved in their day-to-day work with prenatal whole genome and exome sequencing, including:

- the complexity of achieving valid parental consent at a time of vulnerability
- management of parent expectations
- transmitting and comprehending complex information
- the usefulness of information
- the difficulty of a long turnaround time for study results.

All the interviewees agreed that prenatal exome sequencing studies contribute to knowledge generation and the advancement of technology.

The authors concluded that an appropriate next step would be the development of appropriate guidelines for good ethical practice that address the concerns encountered in genomics clinical practice.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The prenatal experience can be overwhelming for parents. Pretest and posttest counseling on genetic testing and results are of the utmost importance, as is finding ways to help support parents through this anxious time.

FAST TRACK

Professional societies recommend extensive parental pretest education, counseling, and informed consent, as well as posttest counseling

Societies offer guidance on using genome and exome sequencing

International Society for Prenatal Diagnosis, Society for Maternal and Fetal Medicine, Perinatal Quality Foundation. Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis. Prenat Diagn. 2018;38:6-9.

In response to the rapid integration of exome sequencing for genetic diagnosis, several professional societies—the International Society for Prenatal Diagnosis, Society for Maternal Fetal Medicine, and Perinatal Quality Foundation—issued a joint statement addressing the clinical use of prenatal diagnostic genome wide sequencing, including exome sequencing.

Guidance at a glance

The societies' recommendations are summarized as follows:

- Exome sequencing is best done as a trio analysis, with fetal and both parental samples sequenced and analyzed together.
- Extensive pretest education, counseling, and informed consent, as well as posttest counseling, are essential. This should include:

CONTINUED ON PAGE 30

A New Era in MIGS with CO_2 Laser

The Lumenis UltraPulse DUO CO_2 Laser and its comprehensive set of surgical tools are perceived as a superior solution when it comes to use and protection of delicate anatomy, aiming for minimal thermal damage and fertility preservation.

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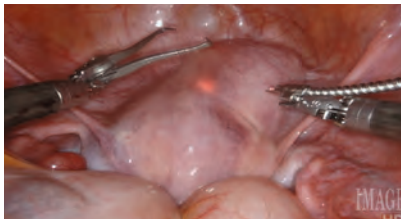
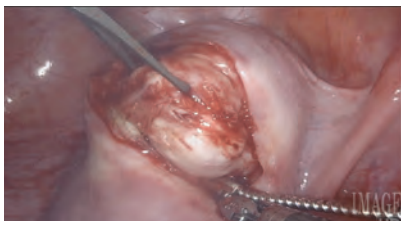
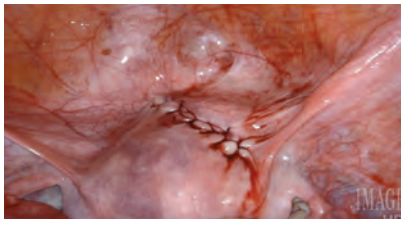
With the freedom to select the surgical tool of your choice, the UltraPulse DUO platform represents a new era in delicate and precise CO_2 Laser MIGS.

The DUO platforms utilize the traditional FreeBeam laparoscopy and the flexible approach with the FiberLase CO_2 fiber which is used through a 2mm trocar for mini-lap, a suction/irrigator, or 5mm trocar with or without the robot.

The FiberLase offers a fast learning curve and can be easily adopted in the surgical sphere.







"An added advantage to using the CO_2 laser for myomectomy is that it can be very effectively used in the chance of concurrent endometriosis findings. In my practice, a good number of patients with fibroids also have endometriosis. The flexible CO_2 laser allows us to treat endometriosis of all degrees and types, with minimal negative impact on the patient's fertility."

Antonio Gargiulo, M.D., REI and Reproductive Surgeon at the Center for Infertility and Reproductive Surgery and the Boston Center for Endometriosis at Brigham and Women's Hospital in Boston, Medical Director of Robotic Surgery for Brigham Health, and an Associate Professor of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical School

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*a complete list of indications can be found in the system user manual

References: **1.** Candiani M, Ottolina J, Posadzka E…et al. Assessment of ovarian reserve after cystectomy versus 'one-step' laser vaporization in the treatment of ovarian endometrioma: a small randomized clinical trial. Hum Reprod. 2018 1;33(12):2205-2211 **2.** Ottolina J, Castellano LM, Ferrari S…et al. The impact on ovarian reserve of CO2 laser fiber vaporization in the treatment of ovarian endometrioma: a prospective clinical trial. J Endometr Pelvic Pain Disord 2017;9:206–210. **3.** Vanni VS, Ottolina J, Candotti G…et al. Flexible CO2 laser fiber: first look at the learning curve required in gynecological laparoscopy training. Minerva Ginecol. 2018;70(1):53-57 **4.** Gargiulo AR, Bailey AP, Nimble laser devices for minimally invasive gynecologic surgery. Contemporary OBGYN, October 2015. Available in: http:// contemporaryobgyn.modernmedicine.com/contemporary-obgyn/news/nimble-laser-devices-minimally-invasive-gynecologic-surgery

Risk information: CO_2 lasers (10.6 µm wavelength) are intended solely for use by trained physicians. Incorrect treatment settings or misuse of the technology can present risk of serious injury to patient and operating personnel. The use of Lumenis CO_2 laser is contraindicated where a clinical procedure is limited by anesthesia requirements, site access, or other general operative considerations. The use of Lumenis CO_2 laser is contraindicated for patients who are not candidates for general surgery, or when local or spinal epidural anesthesia is inappropriate, laparoscopic applications where laparoscopy is contraindicated. Risks may include excessive thermal injury and infection. Read and understand the CO_2 systems and accessories operator manuals for a complete list of intended use, contraindications and risks. PB-2012195 Rev A

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CONTINUED FROM PAGE 28

FAST TRACK

A multidisciplinary team-based approach should be used to interpret prenatal exome sequencing results

  - —the types of results to be conveyed (variants that are pathogenic, likely pathogenic, of uncertain significance, likely benign, and benign)
  - —the possibility that results will not be obtained or may not be available before the birth of the fetus
  - —realistic expectations regarding the likelihood that a significant result will be obtained
  - —the timeframe to results
  - —the option to include or exclude in the results incidental or secondary findings (such as an unexpected childhood disorder, cancer susceptibility genes, adult-onset disorders)
  - —the possibility of uncovering nonpaternity or consanguinity
  - —the potential reanalysis of results over time
  - —how data are stored, who has access, and for what purpose.
- Fetal sequencing may be beneficial in the following scenarios:
  - —multiple fetal anomalies or a single major anomaly suggestive of a genetic disorder, when the microarray is negative
  - —no microarray result is available, but the fetus exhibits a pattern of anomalies strongly suggestive of a single-gene disorder
  - —a prior undiagnosed fetus (or child) with anomalies suggestive of a genetic etiology, and with similar anomalies in the current pregnancy, with normal karyotype or microarray. Providers also can consider sequencing samples from both parents prior to preimplantation genetic testing to check for shared carrier status for autosomal recessive mutations, although obtaining exome sequencing from the prior affected fetus (or child) is ideal.
  - —history of recurrent stillbirths of unknown etiology, with a recurrent pattern of anomalies in the current pregnancy, with normal karyotype or microarray.
- Interpretation of results should be done using a multidisciplinary team-based approach, including clinical scientists, geneticists, genetic counselors, and experts in prenatal diagnosis.
- Where possible and after informed consent, reanalysis of results should be undertaken if a future pregnancy is planned or ongoing, and a significant amount of time has elapsed since the time the result was last reported.
- Parents should be given a written report of test results.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Three professional societies have convened to issue consensus opinion that includes current indications for prenatal exome sequencing and important factors to include in the consent process. We follow these guidelines in our own practice.

Summary

Exome sequencing is increasingly becoming mainstream in postnatal genetic testing, and it is emerging as the newest diagnostic frontier in prenatal genetic testing. However, there are limitations to prenatal exome sequencing, including issues with consent at a vulnerable time for parents, limited information available regarding the phenotype, and results that may not be available before the birth of a fetus. Providers should be familiar with the indications for testing, the possible results, the limitations of prenatal phenotyping, and the implications for future pregnancies. ●

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The Paragard Promise:

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

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

Indication

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

Important Safety Information

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

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

Over 6 million Paragard units distributed[3]

Paragard® T380A
intrauterine copper contraceptive

simple, honest pregnancy prevention™

CooperSurgical

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

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

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

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

WARNINGS

1. Intrauterine Pregnancy

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

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

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

2. Ectopic Pregnancy

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

3. Pelvic Infection

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

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

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

4. Immunocompromise

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

5. Embedment

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

6. Perforation

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

7. Expulsion

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

8. Wilson's Disease

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

PRECAUTIONS

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

1. Information for patients

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

2. Insertion precautions, continuing care, and removal.

3. Vaginal bleeding

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

4. Vasovagal reactions, including fainting

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

5. Expulsion following placement after a birth or abortion

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

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

6. Magnetic resonance imaging (MRI)

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

7. Medical diathermy

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

8. Pregnancy

ParaGard® is contraindicated during pregnancy.

9. Nursing mothers

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

10. Pediatric use

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

ADVERSE REACTIONS

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

Intrauterine pregnancy	Pelvic infection
Septic abortion	Perforation
Ectopic pregnancy	Embedment

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

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

CooperSurgical

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

PAR-41287 01/18

Pre-exposure prophylaxis for the prevention of HIV infection: Ready for prime time

For prophylaxis to be effective, we must screen asymptomatic individuals during routine health encounters

Patrick Duff, MD

Dr. Duff is Professor of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville.

The first cases of HIV infection in the United States were reported in 1981. Since that time, more than 700,000 individuals in our country have died of AIDS. Slightly more than 1 million persons in the United States are currently living with HIV infection; approximately 15% of them are unaware of their infection. Men who have sex with men (MSM) and African American and Hispanic/Latino men and women are disproportionately affected by HIV infection.[1] Among men, MSM is the most common method of infection transmission, accounting for 83% of infections. Heterosexual contact accounts for 9.4% of new infections and injection drug use for 4.0%. Among women in the United States, heterosexual contact is the most common mechanism of transmission, accounting for about 87% of cases; injection drug use accounts for about 12%.[1] Perinatal transmission rates are extremely low—less than 1%—when women receive effective treatment during pregnancy and their infants are treated in the neonatal period.[1,2]

The author reports no financial relationships relevant to this article.

The prognosis for HIV-infected patients has improved dramatically in recent years with the availability of many new and exceptionally effective highly-active antiretroviral treatment regimens. Nevertheless, the disease is not yet completely curable. Therefore, preventive measures are of great importance in reducing the enormous toll imposed by this condition.[2]

Evaluating effectiveness of PrEP

At the request of the US Preventive Services Task Force, Chou and colleagues recently conducted a systematic review to determine the effectiveness of pre-exposure prophylaxis (PrEP) in preventing the horizontal transmission of HIV infection.[1] The authors' secondary objectives included assessing the relationship between degree of adherence to the prophylactic regimen and degree of effectiveness and evaluating the accuracy of various screening systems for identifying patients at high risk for acquiring HIV infection.

The authors reviewed prospective, randomized controlled trials (treatment versus no treatment or treatment versus placebo) published through 2018. Pregnant women were excluded from the studies, as were women who became pregnant after enrollment.

Two different prophylactic regimens were used in the reviewed studies: 1) the combination of tenofovir disoproxil fumarate 300 mg or 245 mg plus emtricitabine 200 mg and 2) tenofovir 300 mg alone. Most trials used the combination regimen. With the exception of one trial, the medications were given daily to uninfected patients at high risk of acquiring HIV infection. In one investigation, the administration of prophylaxis was event driven (administered after a specific high-risk exposure).

Key study findings

PrEP decreased HIV transmission in high-risk patients. Chou and colleagues found that high-risk

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patients included primarily MSM who did not use condoms consistently or who had a high number of sex partners, individuals in an HIV-serodiscordant relationship, and intravenous drug users who shared injection equipment.

In these high-risk patients, PrEP was associated with a significantly decreased risk of HIV transmission. Observations from 11 trials demonstrated a relative risk (RR) of 0.46 (95% confidence interval [CI], 0.33–0.66). The absolute risk reduction was -2.0% (95% CI, -2.8% to -1.2%). The duration of follow up ranged from 4 months to 4 years.

Better medication adherence = greater prophylaxis effectiveness. When adherence was ≥70%, the RR was 0.27 (95% CI, 0.19–0.39). When adherence was 40% to 70%, the RR was 0.51 (95% CI, 0.38–0.70). When adherence was ≤40%, the relative risk was 0.93 (95% CI, 0.72–1.20). Adherence was better with daily administration, as opposed to event-driven administration.

Although the combination prophylactic regimen (tenofovir plus emtricitabine) was most frequently used in the clinical trials, tenofovir alone was comparable in effectiveness.

PrEP resulted in more mild adverse effects. Patients who received PrEP were more likely to develop gastrointestinal adverse effects and renal function abnormalities when compared with patients in the control arms of the studies. These adverse effects were virtually always mild and did not necessitate discontinuation of treatment.

No increase in promiscuous sexual behavior with PrEP. Specifically, investigators did not document an increased incidence of new sexually transmitted infections (STIs) in treated patients.

PrEP did not increase adverse pregnancy outcomes. In women who became pregnant while on PrEP, and who then discontinued treatment, there was no increase in the frequency of spontaneous abortion, congenital anomalies, or other adverse pregnancy outcomes.

In addition, PrEP posed a low risk for causing drug resistance in patients who became infected despite prophylaxis. Finally, the authors found that screening instruments for identifying patients at highest risk for acquiring HIV infection had low to modest sensitivity.

My recommendations for practice

Based on the study by Chou and colleagues, and on a recent commentary by Marcus et al, I believe that the following actions are justified[1–3]:

- For prophylaxis to be effective, we must identify all infected patients. Therefore, screening of asymptomatic individuals during routine health encounters is essential.
- All patients should have access to easy-to-understand information related to risk factors for HIV infection.
- Every effort should be made to promote safe sex practices, such as use of latex condoms, avoidance of sex during menses and in the presence of ulcerative genital lesions, and avoidance of use of contaminated drug-injection needles.
- All high-risk patients, as defined above, should be offered PrEP.
- To the greatest extent possible, financial barriers to PrEP should be eliminated.
- Patients receiving PrEP should be monitored for evidence of renal dysfunction. Should they become infected despite prophylaxis, they should be evaluated carefully to detect drug-resistant viral strains.
- Although PrEP is definitely effective in reducing the risk of transmission of HIV infection, it does not prevent the transmission of other STIs, such as syphilis, gonorrhea, and chlamydia.

In my practice, I administer prophyaxis on a daily basis rather than just before, or after, a high-risk exposure. This approach enhances patient adherence and, hopefully, will lead to maximum effectiveness over time. I also use the combination of tenofovir disoproxil fumarate plus emtricitabine rather than tenofovir alone because there is more published information regarding the effectiveness of the combination regimen. ●

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OBG MANAGEMENT

SPECIAL SECTION

THE 2019 SCIENTIFIC MEETING OF THE SOCIETY OF GYNECOLOGIC SURGEONS

HIGHLIGHTS ISSUE, PART 1

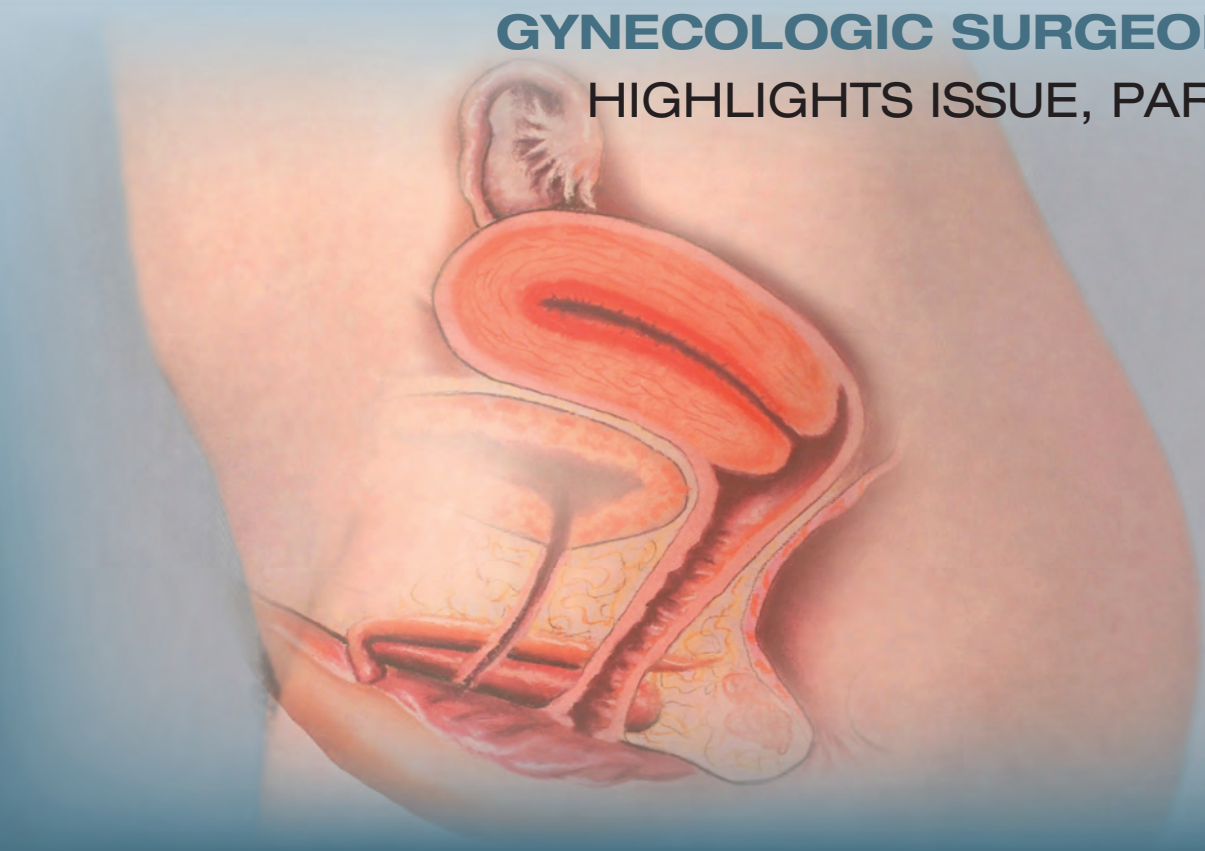

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PHOTO: SCIENCE SOURCE IMAGES

Rising to the challenges in gynecologic surgical care

Derived from presentations at this year's Society of Gynecologic Surgeons (SGS) meeting, this special section kicks off with features on enhanced recovery after surgery protocols and efforts to standardize pelvic anatomy terminology

B. Star Hampton, MD

As the face of health care changes and physicians are presented with new challenges, we need to keep focused on our priorities: maintain outstanding patient care, continue to grow ourselves as physicians, and train the next generation of women's health care providers. The theme of the SGS 2019 annual scientific meeting in Tucson, Arizona, "Looking Forward: Achieving Excellence in Gynecologic Surgery for Ourselves, Our Learners, and Our Patients," focused on these very concepts. This 2-part special section of OBG MANAGEMENT highlights some of the meeting's outstanding presentations.

The excellent postgraduate workshops included courses on simulation of laparoscopic suturing, surgical strategies for fibroid management, and a quality improvement boot camp. In addition, Rebecca Rogers, MD, Cassandra Carberry, MD, and Danielle Antosh, MD, along with physical therapist Uchenna Ossai, PT, DPT, WCS, ran a course on pelvic surgery and its impact on sexual function, tackling an important, often difficult topic for gynecologic surgeons. In part 2 of this special section, these authors highlight current knowledge on sexual function related to surgery and offer an initial evaluation and treatment approach for women with sexual dysfunction after surgery.

Peter Jeppson, MD, Audra Jolyn Hill, MD, and Sunil Balgobin, MD, have been integral leaders of the SGS Pelvic Anatomy Group, which has a mission to educate physicians about pelvic anatomy. Early discussions made it clear that standardized terms needed to be established and used for pelvic structures. On page SS4, these authors illustrate the importance of standard terminology to optimize patient care, and they review pertinent vaginal compartment structures for the gynecologist.

Along with outstanding plenary talks focusing on surgical education research by Gary Dunnington, MD, and health disparities in gynecologic surgery by Marcela del Carmen, MD, MPH, 2 special focus speakers were featured. Sean Dowdy, MD, highlighted advances in the perioperative care of gynecologic surgery patients. On page SS8, he reviews best practices for enhanced recovery after surgery (ERAS) and describes his experience with implementing a successful ERAS program.

Cheryl Iglesia, MD, covered energy-based therapies in female genital cosmetic surgery. In part 2 of this special section, she highlights, with Sarah Ward, MD, the salient points from her presentation, including the mechanism of action of laser therapy on tissue remodeling as well as some therapeutic uses for and outcomes of laser therapy in gynecologic care.

I hope you enjoy the content of this special section (part 2 will follow in the May issue) and find that it helps you achieve excellence in gynecologic surgery for yourself, your learners, and your patients! ■

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Anterior, apical, posterior: Vaginal anatomy for the gynecologic surgeon

The SGS Pelvic Anatomy Group is working to establish standard pelvic anatomic terminology for surgeons, with the ultimate goal of improving clinician communication and enhancing patient care

Peter C. Jeppson, MD; Audra Jolyn Hill, MD; and Sunil Balgobin, MD

CASE 1 **Defining anatomic structures to assure surgical precision**

A 44-year-old woman is scheduled for a vaginal hysterectomy and bilateral salpingectomy for abnormal uterine bleeding. In your academic practice, a resident routinely operates with you and is accompanied by a medical student. As this is your first case with each learner, you review the steps of the procedure along with pertinent anatomy. During this discussion, numerous anatomic terms are used to describe anterior cul-de-sac entry, including pubocervical fascia, vesicouterine fold, and vesicovaginal space. Which of these terms, if any, are correct? Is there a preferred term that should be used to teach future learners so we can all "speak" the same language?

What's in a name?

ObGyns must thoroughly understand pelvic anatomy, since much of our patient care relates to structures in that region. We also must understand the terminology that most appropriately describes each pelvic structure so that we can communicate effectively with colleagues and other providers. The case described above lists several terms that are commonly found in gynecologic textbooks and surgical atlases to describe dissection for vaginal hysterectomy. Lack of a standardized vocabulary, however, often confuses teachers and learners alike, and it highlights the importance of having a universal language to ensure the safe, effective performance of surgical procedures.[1]

At first glance, it may seem that anatomic terms are inherently descriptive of the structure they represent; for example, the terms uterus and vagina seem rather obvious. However, many anatomic terms convey ambiguity. Which muscles, for example, constitute the levator ani: pubococcygeus, pubovisceral, pubovisceralis, puboperinealis, puboanalis, pubovaginalis, puborectalis, puborectal, iliococcygeus, ischiococcygeus? Do any of these terms redundantly describe the same structure, or does each term refer to an independent structure?

Standard terminology is essential

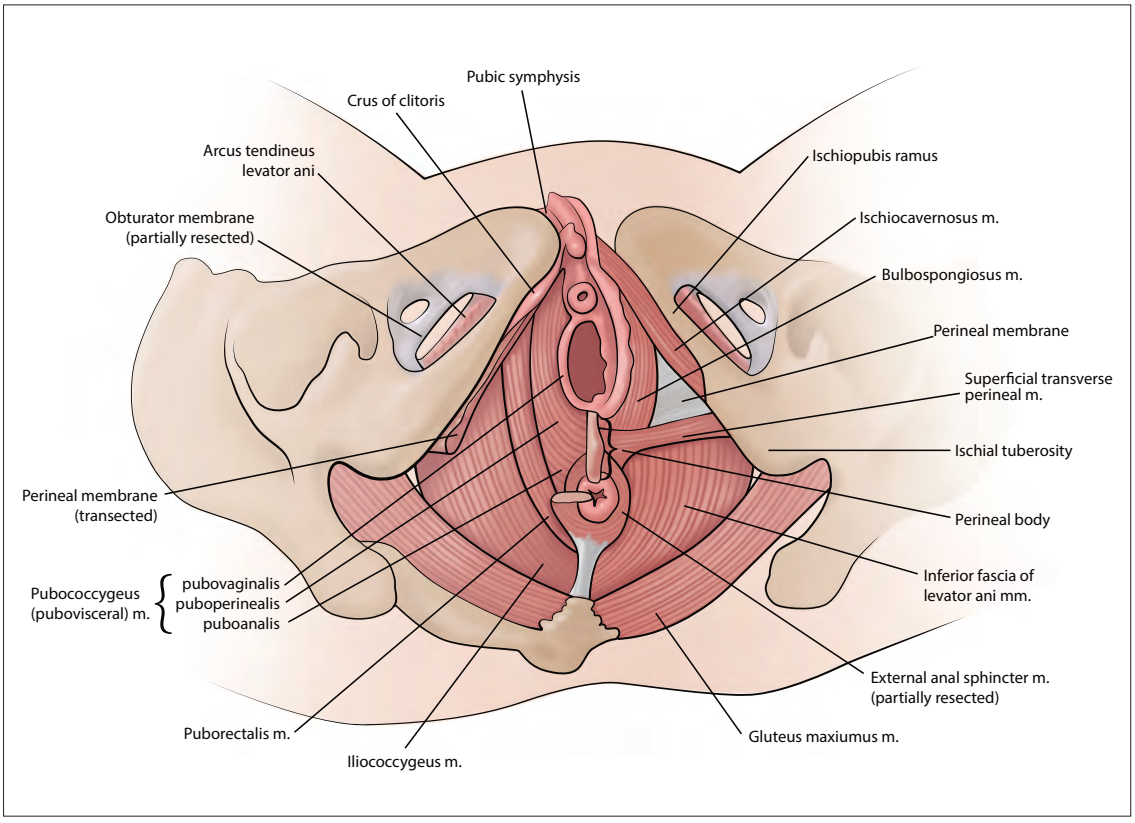
Anatomists long have recognized the need for standardized terminology to facilitate clear communication. To provide historical background, the term anatomy is derived from the Greek word for "dissection" or "to cut open."[2] Records on the scientific study of human anatomy date back thousands of years.

A brief review of current standardized terminology can be traced back to 1895, with the publication of *Basle Terminologia Anatomica*.[3] That work was intended to provide a consolidated reference with clear direction regarding which anatomic terms should be used. It was updated several times during the ensuing century and was later published as *Nomina Anatomica*.

In 1990, an international committee was formed with representatives from many anatomical organizations, again with the intention of providing standardized anatomic terminology. Those efforts resulted in the publication of *Terminologia Anatomica: International Anatomical Terminology*, commonly referred to as TA, in 1998. TA continues to be the referent standard for

The authors report no financial relationships relevant to this article.

FIGURE 1 Muscle components of the levator ani



human anatomic terminology; it was most recently updated in 2011.[4]

CASE 2 Conveying details of mesh erosion

A 52-year-old woman presents to the general gynecology clinic with a 10-year history of pelvic pain and dyspareunia after undergoing vaginal mesh surgery for prolapse and urinary incontinence. On examination, there is a visible ridge of mesh extending from the left side of the midurethra along the anterior and lateral vagina for a length of 1.5 cm. There also is a palpable tight band on the right vaginal wall near the ischial spine that reproduces her pain and causes spasm of the levator ani. You believe the patient needs a urogynecology referral for complications of vaginal mesh. How do you best describe your findings to your urogynecology colleague?

Pelvic anatomy from the SGS perspective

The Society of Gynecologic Surgeons (SGS) recognized the importance of standardizing terminology specific to the pelvis. The SGS Pelvic Anatomy Group thus was organized in 2016. The Pelvic Anatomy Group's purpose is to help educate physicians about pelvic anatomy, with the overarching goal of compiling instructional materials, primarily from dissections (surgical or cadaveric), and radiologic imaging for all pelvic structures. Throughout the discussions on this initiative, it became clear that standardized terms needed to be established and used for pelvic structures.

While TA is an excellent reference work, it does not include all of the clinically relevant structures for gynecologic surgeons. As physicians, surgeons, and women's health care providers, we read about and discuss pelvic anatomy structures in medical textbooks, medical literature, and clinical settings that are not necessarily included in TA. In addition, advances in information technology have facilitated the creation of clinically oriented computer-based anatomy programs and expanded the number and availability of electronic publications on surgical and clinical anatomy.[5] As a result, there is a need not only to standardize nomenclature but

ILLUSTRATION: JOE GORMAN FOR OBG MANAGEMENT

also to continually revise and update terminology and integrate new terms, both from an anatomic and a clinical perspective.

The Pelvic Anatomy Group developed a novel approach to anatomic terminology. We decided to review the medical literature, identify the terms used, adjudicate the terms with current TA terms, and provide consensus for the terms and structures in the pelvis. Because of the volume of literature available and the existing number of terms, we divided the pelvis into 4 regions—anterior, apical, posterior, and vulvar—to improve the feasibility of reviewing the medical literature for the entire female pelvis.

Our process for tackling terminology

Our literature review started with the anterior compartment. (For complete details, see our prior publication.[3]) Modeled on a systematic review, we searched the MEDLINE database for terms related to the anterior pelvis, screened all associated abstracts, and then extracted terms from appropriate papers. We also identified several book chapters from various disciplines (anatomy, gynecology, urology, and radiology) to ensure wide representation of disciplines. We then extracted all terms pertinent to the anterior pelvis.

We organized the terms, with terms that referred to the same anatomic structure grouped together. Whenever possible, we used TA terms as the preferred terms. In this process, however, we identified several clinically relevant terms that were not included in TA: pelvic sidewall, pelvic bones, anterior compartment, pubourethral ligament, vaginal sulcus, and levator hiatus, among others. The new terms were then proposed and agreed on by members of the SGS Pelvic Anatomy Group and accepted by SGS members. We currently are completing a similar process for the apical pelvis, posterior pelvis, and vulvar regions.

TA code numbers pinpoint the nomenclature

As we move forward, we suggest that physicians use TA or other approved terms for patient and research communication. Such use will help standardize anatomic terms and also will improve communication between providers and education for learners.

TA includes approved options in English and Latin and lists a unique identification number for each term (shown in parentheses in the examples that follow). For instance, to answer the question posed earlier, the levator ani (A04.5.04.002) is comprised of the pubococcygeus (A04.5.04.003), puborectalis (A04.5.04.007), and iliococcygeus (A04.5.04.008) muscles (**FIGURE 1**, page SS5). The terms pubovisceral and pubovisceralis are used synonymously in the literature with pubococcygeus (A04.5.04.003).[3] The additional terms puboperinealis (A04.5.04.004), pubovaginalis (A04.5.04.005), and puboanalis (A04.5.04.006) are subcomponents of the pubococcygeus (A04.5.04.003), and this relationship is indicated in TA by indentation formatting.[4] Finally, the ischiococcygeus (A04.5.04.011) muscle is not considered part of the levator ani (A04.5.04.002).

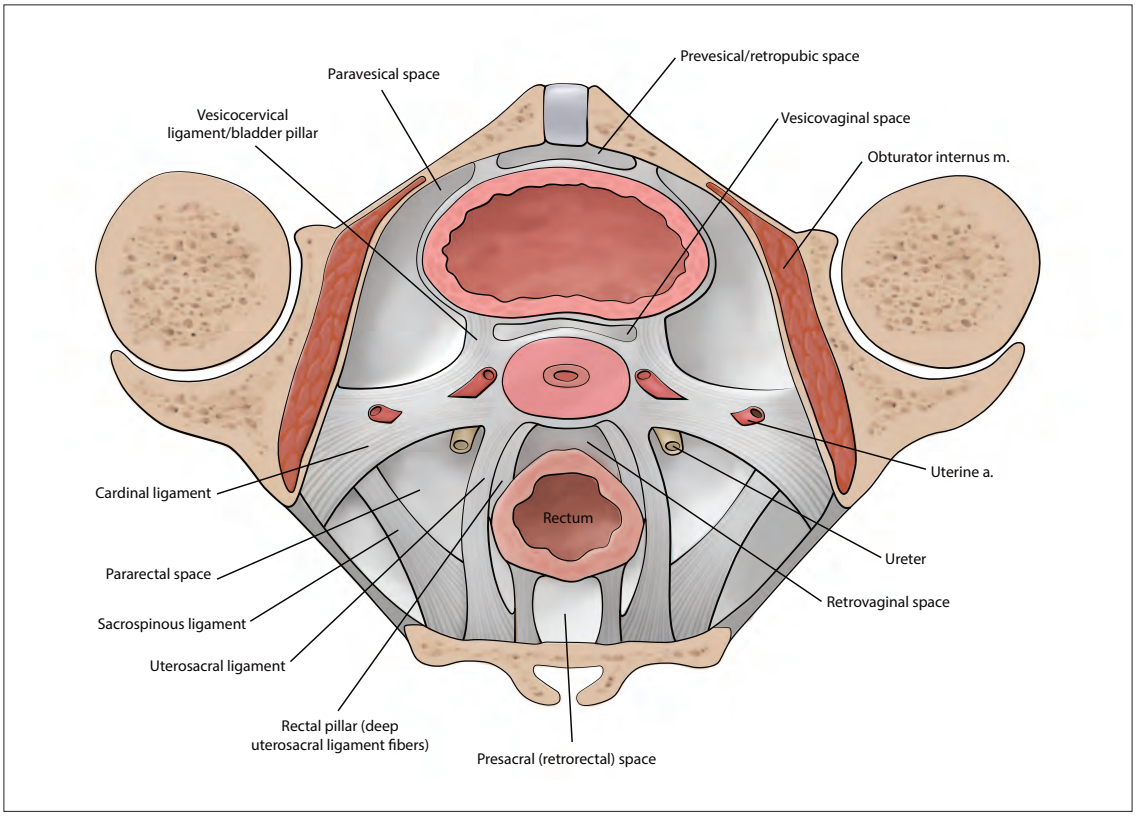
Revisiting the mesh erosion case: Reporting your findings

After reviewing the recommended terminology for the anterior pelvis,[3,4] you might draft a report as follows: "A mesh erosion was visualized in anterior vaginal wall (A09.1.04.006) at the level of the midurethra extending into 'anterior and lateral vaginal sulci' (proposed term). In addition, there is a painful tight band in the 'lateral vaginal wall' (proposed term) near the ischial spine (A02.5.01.205). Palpation of this band reproduces the patient's pain and causes secondary spasm of the levator ani (A04.5.04.002)." Certainly, TA identification numbers would not be expected to be included in medical communication; they are included here for reference.

From your description, your urogynecology colleague has a better understanding of the location of your patient's vaginal mesh and requests her operative report from an outside facility. In the operative report, the surgeon described "placement of mesh into the vagina, dissection through the rectal spaces, and anchoring of the mesh into the levator/pelvic muscles, the cervix, and lastly to the paraurethral ligaments," and "passage of trocars through the cave of Retzius at the level of the midurethra" (**FIGURE 2**).

Based on this description, the urogynecologist ascertains that the mesh is located in the anterior vaginal wall (A09.1.04.006), with passage of anchoring arms through the bilateral sacro-

FIGURE 2 Spaces and ligaments in the anterior pelvis pertinent to determining the location of vaginal mesh



spinous ligaments (A03.6.03.007) and retropubic space (A10.1.01.003). Exposed mesh is visible, extending from the midurethra to the "anterior and lateral vaginal sulci" (proposed term).

This case clearly demonstrates the importance of communication between providers for patient care, since understanding the patient's anatomy and the location of the vaginal mesh is important for planning surgical excision of the exposed mesh.

Additional initiatives

Outlining standardized terminology is just the first step toward improving the anatomic "language" used among providers. Ongoing efforts from the SGS Pelvic Anatomy Group include a special imaging group's review of imaging modalities (ultrasonography, magnetic resonance imaging, computerized tomography) to improve standardization on reporting clinical anatomy. In addition, SGS has developed a group to create educational content related to the structures identified by the terminology group from cadaveric or surgical dissections. Educational materials will be compiled to help physicians and learners expand their anatomic understanding and improve their communication.

Further details of the Pelvic Anatomy Group's efforts can be found on the SGS website at https://www.sgsonline.org. ■

ILLUSTRATION: JOE GORMAN FOR OBG MANAGEMENT

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Beyond enhanced recovery after surgery

An expert explains the key elements required to develop an effective ERAS program and strategies to facilitate change in the face of resistance

Sean C. Dowdy, MD

Our specialty is focusing now more intently on perioperative optimization, commonly referred to as *enhanced recovery after surgery (ERAS)*, a concept championed first and most visibly by colorectal surgeons in the 1990s.[1] Both academic and nonacademic practices are challenging long-held beliefs about perioperative management.

The 3 tenets of ERAS

In multiple surgical specialties, proper implementation of 3 tenets—early feeding, perioperative euvolemia, and multimodal pain control—reduces the length of hospital stay, improves patient satisfaction, reduces complications, lowers health care costs, and most importantly hastens patient recovery.

1 Early feeding

Just as athletes hydrate and carbohydrate load prior to a competition, patients benefit if fluids and calories are not withheld in anticipation of a physiologically stressful surgical procedure. Similarly, modest benefit is associated with carbohydrate loading as a liquid supplement 2 hours before surgery.[2] The American Society of Anesthesiologists guidelines state that while solid foods should not be consumed after midnight before surgery, clear liquids safely may be withheld for only 2 hours prior to anesthesia induction, and systematic reviews have failed to show harm.[3,4] All patients, including those undergoing colonic resections, are allowed to eat a general diet as tolerated the evening before surgery, supplemented with caloric-dense nutritional supplements.

The author reports no financial relationships relevant to this article.

2 Multimodal pain control

Postsurgical pain is a top patient concern. Pain control is critical for rapid recovery; it helps avoid upregulation of the sympathetic axis and permits ambulation and resumption of normal activities. Although opioids relieve pain, they should not be considered a primary pain control approach.

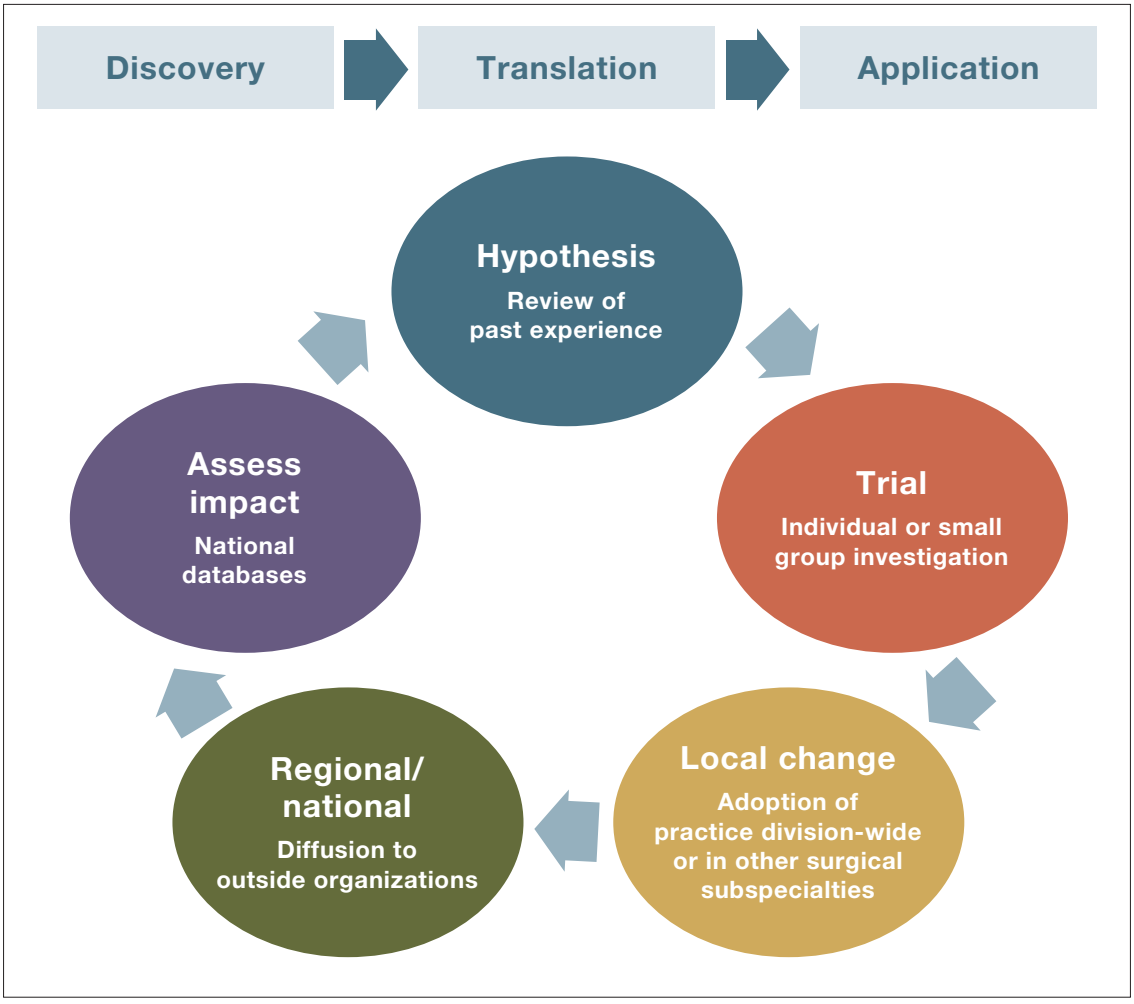
Responding to the opioid epidemic, in 2015 the Centers for Disease Control and Prevention identified opioid overdose prevention as one of the top 5 public health challenges; notably, approximately 6% of patients will experience new, persistent opioid use following surgery.[5] Optimal pain management therefore should provide effective pain relief while minimizing opioid use.

Preemptive oral acetaminophen, gabapentin, and celecoxib should be used routinely prior to incision; nonsteroidal anti-inflammatory drugs should be scheduled postoperatively. Even after a complex cytoreductive laparotomy, pain may be controlled with oral rather than intravenous (IV) medications in most patients, with opioid requirements averaging just 2 to 4 tablets of oxycodone in the first 48 hours after surgery, in our experience. The most critical need for pain medications occurs in the first 48 hours after surgery, which highlights the importance of local or regional analgesia. In one investigation, implementation of multimodal pain management that included incisional injection of liposomal bupivacaine reduced patient-controlled analgesia use to less than 5% after laparotomy.[6] The need for opioids more than a week postoperatively is uncommon even after a laparotomy.

3 Perioperative euvolemia

Maintaining euvolemia is a central and underrecognized tenet of enhanced recovery pathways,

FIGURE 1 ERAS cycle of diffusion and continuous improvement



Tailored solutions are required to overcome obstacles at each transition.
Abbreviation: ERAS, enhanced recovery after surgery.

and it facilitates the other 2 tenets of early feeding and optimal pain control. Overhydrated patients have more pain and prolonged recovery of bowel function. Unfortunately, euvolemia is the most difficult ERAS component to implement, requiring seamless communication between all members of the surgical team.

Fluid therapy should be respected as a pharmacologic agent with both benefits and risks. Recognizing that a single liter of lactated Ringer's solution contains the sodium load of more than 30 bags of potato chips (and normal saline contains far more), one can imagine the impact of 10 L of solution on peripheral and bowel edema and on overall recovery. Importantly, euvolemia must be initiated during surgery. A meta-analysis of nearly 1,000 randomly assigned patients showed that benefits were limited when euvolemia was initiated in the postoperative period.[7]

When it comes to maintaining euvolemia, particular care must be taken to avoid erring toward hyperadherence. No difference in hospital length of stay, complications, or ileus was observed when patients were randomly assigned to goal-directed fluid therapy or standard practice.[8] However, differences in the volume of fluid administered were relatively small, and while there was evidence of underhydration (likely responsible for acute kidney injury), there was no evidence of overhydration. For example, 4 L of fluid

is likely superior to 15 L, but it may not be clinically different from 4.5 L. A threshold of fluid restriction is likely to be reached; that is, additional benefit is not achieved and, instead, detrimental effects may occur.

Rather than a specific directive, a more clinically relevant goal may be to replace insensible fluid losses and to maintain perfusion and blood pressure with the lowest volume possible. Note that estimation of fluid requirements is vastly simplified by omitting mechanical bowel preparation. Postoperatively, permissive oliguria (20 mL/h) is allowed since reduced urine output is a normal response to surgery (as a result of inappropriate secretion of antidiuretic hormone) and does not necessitate administration of a fluid bolus. Above all, anesthesiologists should acknowledge that fluid administration's effects on a patient extend past the postanesthesia care unit, and the entire surgical team should be invested in the patient's long-term recovery.

Our experience with ERAS

In 2011, Mayo Clinic was the first institution to implement enhanced recovery on a large scale in gynecologic surgery. We have subsequently made multiple pathway modifications in the spirit of continuous improvement (**FIGURE 1,** page SS9).

For patients with ovarian cancer requiring extended procedures for cytoreduction via laparotomy (such as colon resection, splenectomy, diaphragm resection), enhanced recovery reduced the median hospital stay by 3 days, patient-controlled IV analgesia use by 88%, and postoperative opioid requirements by 90%.[9,10]

At 48 hours after surgery, 40% of our patients require no opioids or tramadol, and epidurals are not utilized because of their effects on ambulation and the potential for hypotension. These reductions were met with stable to improved pain scores, a 60% decrease in nausea, and a 50% reduction in adynamic ileus.[9,10]

Our initial efforts reduced 30-day costs of care by more than $850,000 in just 6 months, with savings of more than $7,600 for each patient undergoing a complex cytoreduction. Furthermore, these improvements allowed consolidation of our inpatient unit with those of other surgical specialties, serving higher volumes of patients within a smaller inpatient footprint. This contraction of inpatient services has accounted for an additional $1.1 million in savings every year since implementation (**FIGURE 2**).[9,10]

Our group is not alone in realizing these benefits, and interest has intensified as demonstrated by the fact that the ERAS Society guidelines are among the all-time most downloaded articles in *Gynecologic Oncology*.[11,12] Although our research to demonstrate safety has focused on women undergoing complex oncologic operations, ERAS nevertheless hastens recovery, improves patient satisfaction, and adds value for all patients undergoing gynecologic surgery.

Collateral improvements to practice

Clinical optimization using evidence-based practices such as enhanced recovery pathways can result in immediate patient benefit. Affecting such profound clinical improvements is energizing and creates a unique opportunity to transform the culture of the entire health care team. Irrespective of our provider roles (surgeon, anesthesiologist, nurse) or areas of interest (practice, research, education, leadership), we are united by a common purpose: to improve the human condition.[13] Reaffirming this common purpose, through the collective effort involved in establishing a standardized enhanced recovery pathway, has allowed our practice and those of others to move beyond enhanced recovery and improve other areas of practice.

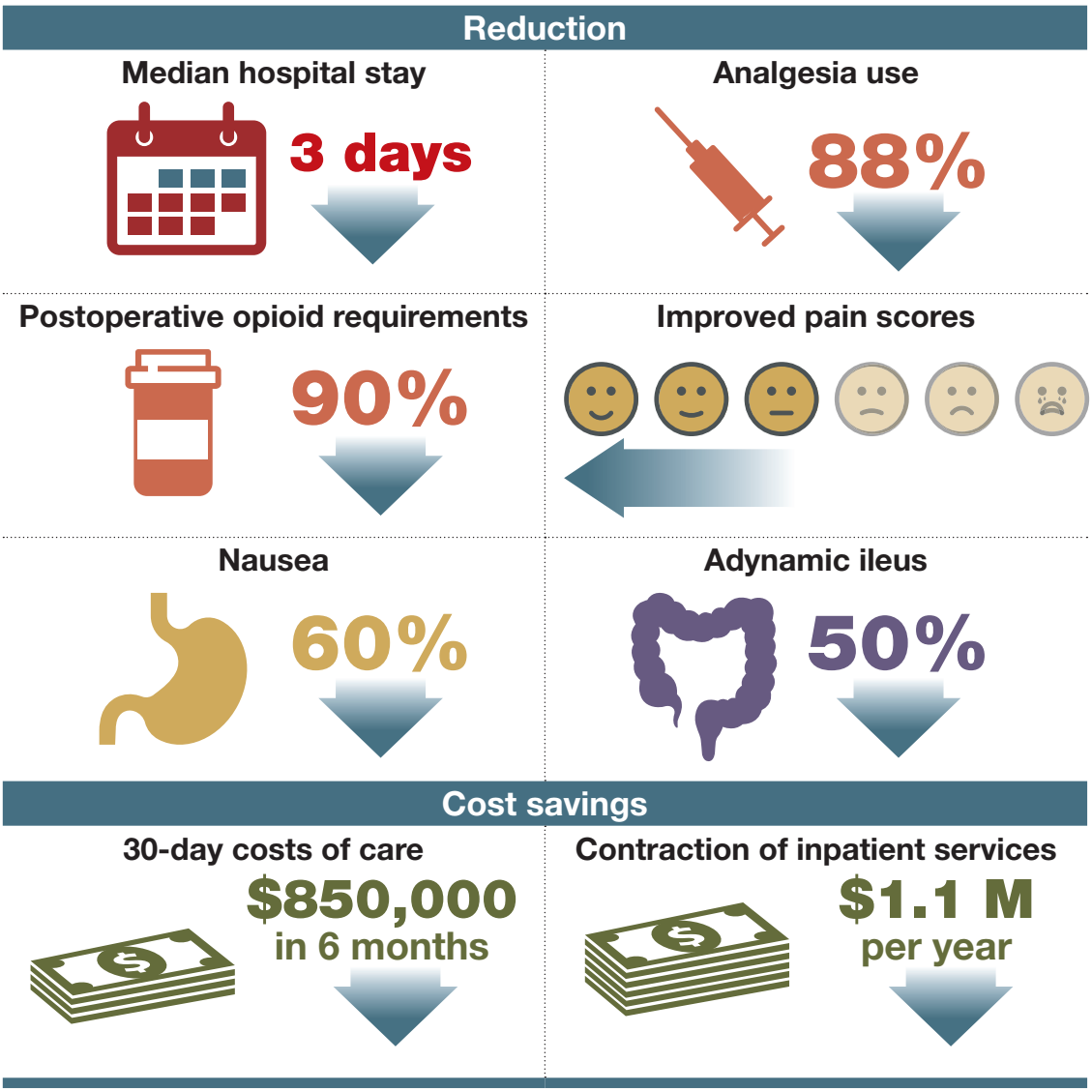
Other positive effects. The long-term collateral impact of this culture change at our institution is arguably more important than enhanced recovery itself. Examples of downstream impact include[14,15]:

- 80% reduction in surgical site infection
- 50% reduction in anastomotic leaks
- 60% reduction in blood utilization for patients undergoing surgery for ovarian cancer.

Team-based pragmatic strategies. Additionally, our willingness to make decisions as a division rather than as individuals facilitated universal implementation of sentinel lymph node biopsy for patients with endometrial cancer and standardized imaging, testing, and surgical decision making for patients with ovarian and endometrial cancer.

The interventions associated with these im-

FIGURE 2 Beyond ERAS: Clinical improvements and cost savings



provements were not tested in a randomized fashion; however, rather than await perfect data, we made informed decisions based on imperfect data together with a commitment to continuous data review. We find this to be an effective strategy if our goal is to ensure that tomorrow's outcomes will be better than yesterday's. In this way, pragmatic trials can be extremely effective in rural settings and tertiary centers.

Barriers to innovation

The widely reported benefits of enhanced recovery beg the question, Why has enhanced recovery not been adopted universally as standard of care? The answer is multifaceted and highlights long-standing shortcomings in our health care system.

Most importantly, our health care system lacks a robust interface to link discovery of new techniques, treatments, and workflows to clinical practice. Perhaps the best example of this is the adoption of minimally invasive surgery (MIS) for endometrial cancer. Ten years have passed since randomized trials showed MIS has equivalent oncologic outcomes and superior recovery compared to laparotomy, yet in the United States less than 50% of women with endometrial cancer benefit.[16,17]

CONTINUED ON PAGE SS13

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ERAS resource: The Improving Surgical Care and Recovery program

The national Improving Surgical Care and Recovery program is available to specifically aid with ERAS implementation. A collaboration between the Agency for Healthcare Research and Quality (AHRQ) and the American College of Surgeons, the program aims to diffuse enhanced recovery to 750 service lines in 4 surgical subspecialties, including gynecologic surgery, over the next 5 years. (Note: The author is the content expert for the gynecology portion of this program.) The program's larger aim is to measurably improve patient outcomes, reduce health care utilization, and improve patient experience through the use of an adaptation to AHRQ's Comprehensive Unit-based Safety Program (CUSP).

The backbone for this program is the recent systematic review to establish best practices for gynecologic surgery.[1] Free to all participants, the program includes resources such as webinars and coaching calls to assist with the inevitable barriers to ERAS implementation. For more information and to enroll, visit https://www.ahrq.gov/professionals/quality-patient-safety/hais/tools/enhanced-recovery/index.html.

An important aspect of the program is a registry for tracking outcomes and identifying areas for improvement. For members who currently participate in the National Surgical Quality Improvement Program, clinical data are automatically uploaded into the database.

Programs such as Improving Surgical Care and Recovery may be the most reliable way to facilitate diffusion of best practices and take collective responsibility for not only "my outcomes" but also for "our outcomes" as a national community of gynecologic surgeons.

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However, even surgeons who are knowledgeable about recent innovations and genuinely wish to promote improvements may face near-insurmountable skepticism. Blind faith in our abilities and outcomes, overprotection of autonomy, close-mindedness, and satisfaction with the status quo are common responses to innovation and are the enemies of change. Resistance often comes from good intentions, but our desire to avoid complications may result in actions that could just as accurately be labeled superstitious as conservative. These observations suggest that developing methods to incorporate evidence-based practice into routine clinical use is the rate-limiting step in improving surgical quality.

Principles essential to change

Various methodologies have been described to manage change and facilitate implementation of new workflows and practices. Irrespective of the method used, including the more formal discipline of implementation science, at least 4 principles must be followed:

1. Teamwork. Mutual trust, mutual respect, and a sense of common purpose are minimum requirements for any successful initiative. Standardization is difficult or impossible without these elements. Thus, establishing a healthy team is the first step in implementing change.

2. Stakeholder analysis. Feedback from surgeons, nurses, residents, fellows, anesthesiologists, pharmacists, nurse anesthetists, and administrators is necessary to obtain diverse perspectives, facilitate engagement, and promote collaborative management. Negativity and resistance are common reactions to change, and it is particularly important to include those who are most skeptical in the stakeholder analysis to mitigate sabotage.

3. Concrete metrics. Success is possible only if defined a priori by specific and achievable goals. Counterbalances also are important to ensure that interventions do not have unintended consequences. Once a goal is met (for example, reduced hospital length of stay or costs), relevant metrics should be monitored after project completion for a minimum of 3 years to avoid regression to the pre-project state.

4. Leadership. The project champion responsible for the initiative must objectively facilitate all of the above and ensure excellent communication between stakeholders to nurture long-term

CONTINUED ON PAGE SS15

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engagement. Despite best efforts, if a minority of the group rejects compromise, this creates an opportunity to compare outcomes between those who do and do not accept the proposed change. Progress realized by early adopters may convince resistors to conform at a later time. Alternatively, the project champion also must have the insight to recognize when a proposed change is impossible at that point in time with that particular group. For example, our own initial attempts to implement enhanced recovery stalled in 2008, but they were successful 3 years later in a different environment.

Although a discussion of leadership styles is beyond the scope of this article, in our experience, the most successful model is one of servant leadership that is team oriented rather than star dominated. Rather than being led by a single surgeon, each of the 4 quality improvement projects reviewed above (ERAS, and reductions in anastomotic leak, surgical site infection, and blood transfusion) that grew from enhanced recovery included trainees and was led by a different champion, encouraging teamwork and promoting career development. Such a model also supports the Accreditation Council for Graduate Medical Education's emphasis on quality improvement education. ■

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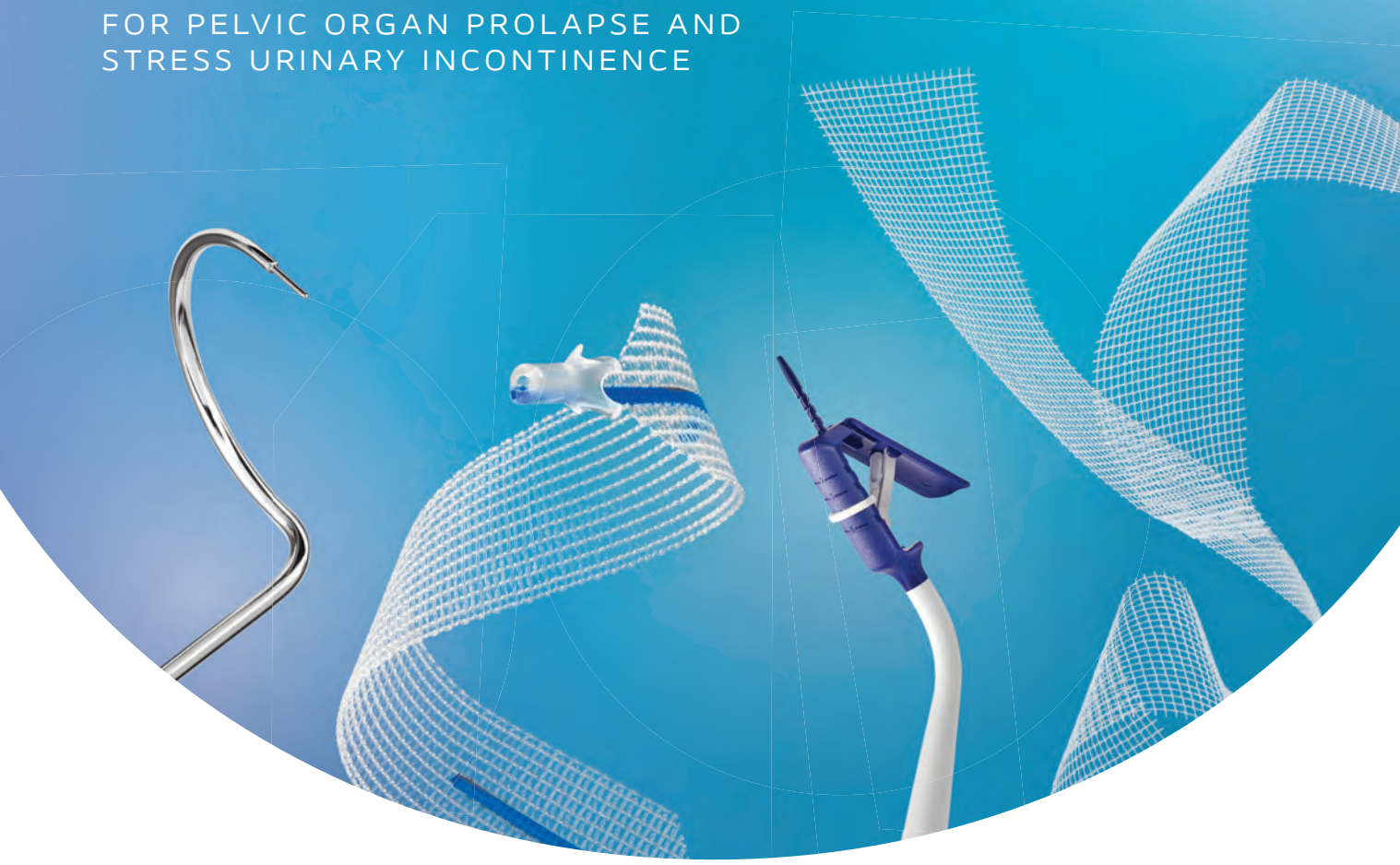

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women referred for evaluation and treatment.[19]

Clinical judgment and screening

Screening for prevalent depression and screening for women at increased risk for perinatal depression is challenging. ACOG highlights two important clinical issues[1]:

"Women with current depression or anxiety, a history of perinatal mood disorders, risk factors for perinatal mood disorders or suicidal thoughts warrant particularly close monitoring, evaluation and assessment."

When screening for perinatal depression, screening test results should be interpreted within the clinical context. "A normal score for a tearful patient with a flat affect does not exclude depression; an elevated score in the context of an acute stressful event may resolve with close follow-up."

In addition, women who screen-positive for prevalent depression and are subsequently evaluated by a mental health specialist may be identified as having mental health problems such as an anxiety disorder, substance misuse, or borderline personality disorder.[20]

Policy changes that support pregnant women and mothers could help to reduce the stress of pregnancy, birth, and childrearing, thereby reducing the risk of perinatal depression. The United States stands alone among rich nations in not providing paid parental leave. Paid maternity and parental leave would help many families respond more effectively to the initial stresses of parenthood.[21] For women and families living in poverty, improved social support, including secure housing, protection from abusive partners, transportation resources, and access to healthy foods likely will reduce both stress and the risk of depression.

The ultimate goal: A healthy pregnancy

Clinicians have been phenomenally successful in screening for perinatal depression. The new USPSTF recommendation adds the prevention of perinatal depression to the goals of a healthy pregnancy. This recommendation builds upon the foundation of screening for acute illness (depression), pivoting to the public health perspective of disease prevention. ●

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

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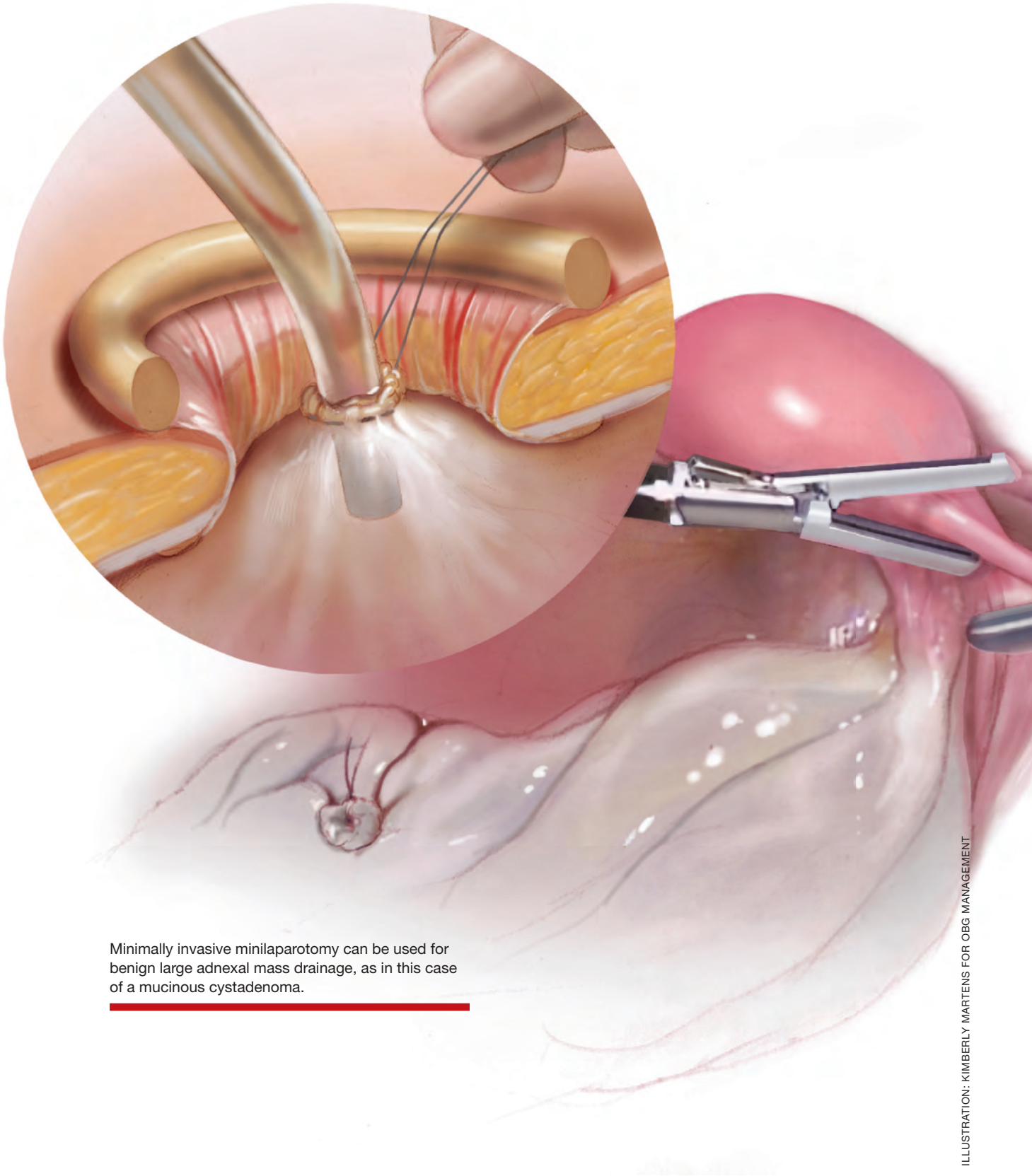
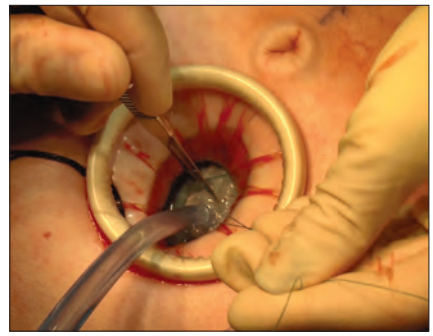


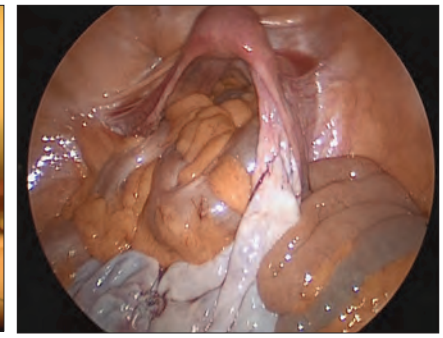
Minimally invasive minilaparotomy can be used for benign large adnexal mass drainage, as in this case of a mucinous cystadenoma.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

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





To view the video
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Large adnexal masses traditionally are removed surgically via laparotomy through a midline vertical incision to achieve adequate exposure and to avoid spillage of cyst contents. However, large laparotomies carry significant morbidity compared with minimally invasive techniques. Minilaparotomy is a minimally invasive approach that is associated with shorter operating times and lower estimated blood loss compared with laparoscopy in gynecologic surgery.[1] The procedure also provides adequate exposure and can be used for carefully selected patients with a large adnexal mass.[2,3] Preoperative assessment for the risk of malignancy typically includes an evaluation of risk factors, physical examination, imaging, and tumor markers.[4]

In this video, we illustrate a minimally invasive technique for the removal of a massively enlarged adnexal mass through laparoscopic bilateral salpingo-oophorectomy with minilaparotomy assistance. We conclude that this procedure is a safe and feasible option for women with a large benign adnexal mass, such as the highlighted patient whose final pathology resulted in a mucinous cystadenoma. Careful patient selection and preoperative assessment of malignancy risk is critical.[5,6]

We hope that you find this innovative approach useful in your clinical practice. ●

›› DR. ARNOLD P. ADVINCULA AND COLLEAGUES

Dr. Cui is Resident, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York.

Dr. Dubin is Fellow, Minimally Invasive Gynecologic Surgery, Columbia University Irving Medical Center.

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

Dr. Advincula reports serving as a consultant to ConMed, CooperSurgical, Intuitive Surgical, and Titan Medical and receiving royalties from CooperSurgical. The other authors report no financial relationships relevant to this article.

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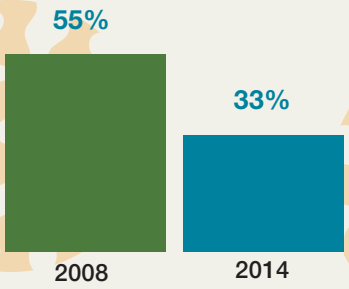
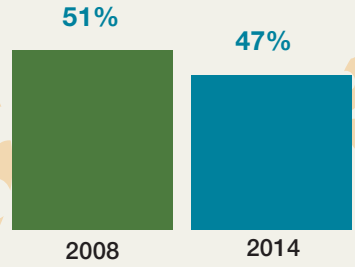
Impact of the HPV vaccine on cervical precancers among US women

The HPV vaccine is working to reduce cervical precancers[a,b]



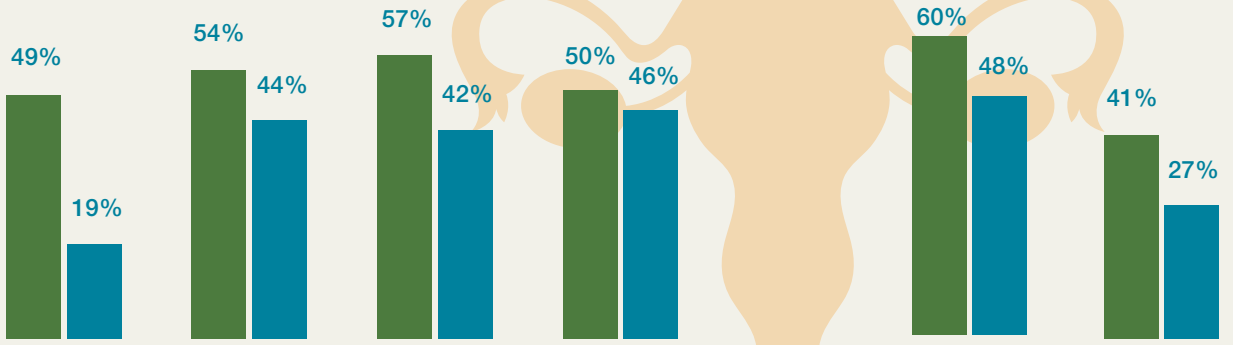
22% drop in HPV 16/18-positive CIN2+

The estimated number of HPV 16/18-positive CIN2+ cases also has declined in unvaccinated women, suggesting herd protection



4% drop in HPV 16/18-positive CIN2+

From 2008 to 2014, the percentage of cervical precancers was reduced in the following groups[c]:



In 2017

66%

of adolescents aged 13–17 years received the first dose to start the HPV vaccine series

49%

of adolescents received all recommended doses to complete the HPV vaccine series

[a]HPV vaccination was included in the routine immunization program for females in 2006.

[b]Researchers looked at more than 10,000 laboratory samples of cervical tissue obtained from women aged 18 to 39 diagnosed with cervical intraepithelial neoplasia (CIN) grades 2–3 or adenocarcinoma in situ (CIN2+) between 2008 and 2014. Trends in HPV16/18-positive CIN2+ were examined, overall and by vaccination status, age, histologic grade, and race/ethnicity, using Cochrane–Armitage tests.

[c]Among both vaccinated and unvaccinated women.

Sources:

McClung NM, Gargano JW, Bennett NM, et al; HPV-IMPACT Working Group. Trends in human papillomavirus vaccine types 16 and 18 in cervical precancers, 2008–2014. *Cancer Epidmiol Biomarkers Prev.* 2019;28:602-609.

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