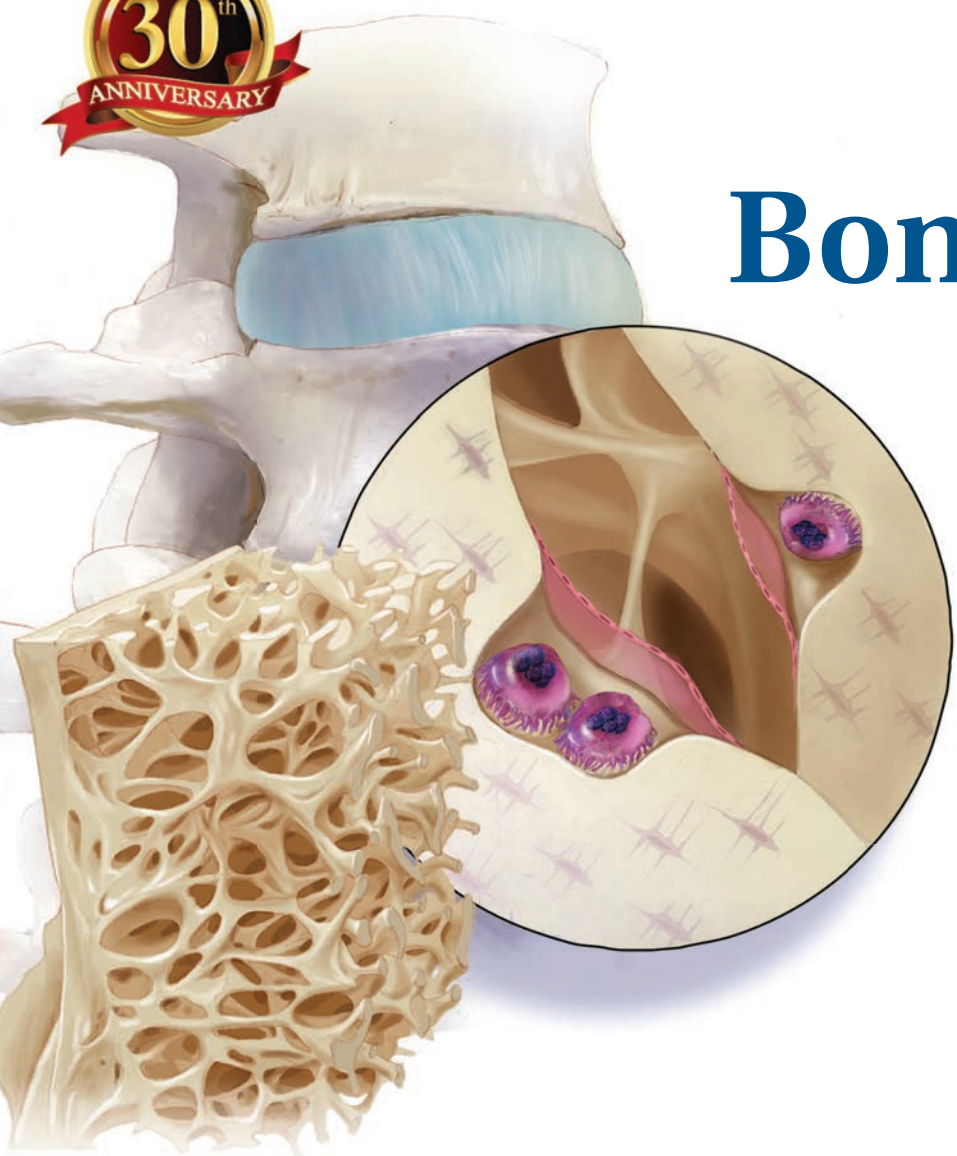
MDEDGE.COM/OBGYN | VOL 30, NO 12 | DECEMBER 2018

OBG MANAGEMENT

30th ANNIVERSARY



Does low-dose aspirin decrease risk of ovarian cancer?

Achieving holistic endometriosis treatment
Q&A with Andrea Rapkin, MD

Reimbursement 101: Maximizing payments

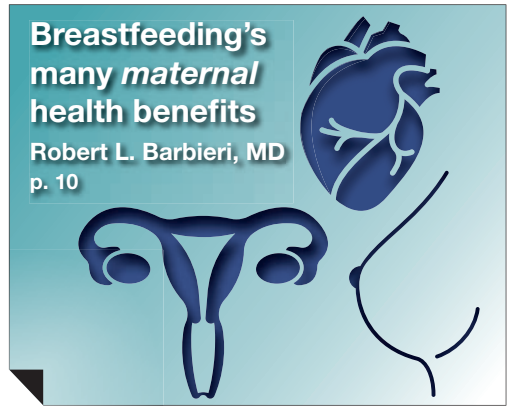
UPDATE ON
Bone health

Steven R. Goldstein, MD

- Does HT improve fracture risk?
- Practicing fracture-risk-appropriate BMD testing
- USPSTF screening recommendations

Cost-conscious minimally invasive hysterectomy: A case illustration

Zoledronic acid for osteopenia?



NOW APPROVED

A NEXT STEP IN ENDOMETRIOSIS PAIN RELIEF[1]

NEW

rilissa

elagolix tablets 150 mg 200 mg

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

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

abbvie

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

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

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

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

These are not all the possible side effects of ORILISSA.

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

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

Discover a next step at ORILISSA.com/hcp

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

Orilissa™
elagolix tablets 150 mg 200 mg

ORILISSA™ (elagolix) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Important Dosing Information

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

Table 1. Recommended Dosage and Duration of Use

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

Hepatic Impairment

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

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

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

Missed Dose

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

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

CONTRAINDICATIONS

ORILISSA is contraindicated in women:

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

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

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

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

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

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

Clinical Trials Experience

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

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

Serious Adverse Events

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

Adverse Reactions Leading to Study Discontinuation

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

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

Common Adverse Reactions:

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

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

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

Less Common Adverse Reactions:

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

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

Bone Loss

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

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

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

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

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

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

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

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

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

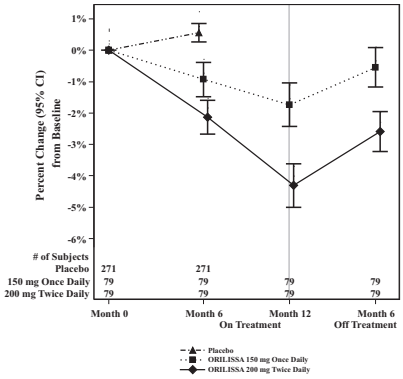
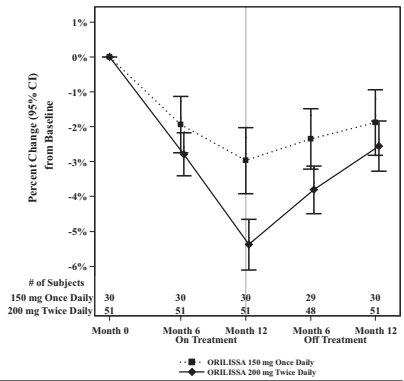


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

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

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

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

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

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

Hepatic Transaminase Elevations

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

Changes in Lipid Parameters

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

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

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

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

Hypersensitivity Reactions

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

Endometrial Effects

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

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

Effects on menstrual bleeding patterns

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

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

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

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

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

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

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

DRUG INTERACTIONS

Potential for ORILISSA to Affect Other Drugs

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

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

Potential for Other Drugs to Affect ORILISSA

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

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

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

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

Drug Interactions - Examples and Clinical Management

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

Table 7. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Plasma Exposure of Elagolix or Concomitant Drug	Clinical Recommendations
Antiarrhythmics digoxin	↑ digoxin	Clinical monitoring is recommended for digoxin when co-administered with ORILISSA.
Antimycobacteria rifampin	↑ elagolix	Concomitant use of ORILISSA 200 mg twice daily and rifampin is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and rifampin to 6 months.
Benzodiazepines oral midazolam	↓ midazolam	Consider increasing the dose of midazolam and individualize therapy based on the patient's response.
Statins rosuvastatin	↓ rosuvastatin	Consider increasing the dose of rosuvastatin.
The direction of the arrow indicates the direction of the change in the area under the curve (AUC) (↑= increase, ↓ = decrease).		

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

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

Data

Human Data

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

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

Animal Data

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

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

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

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

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

Lactation

Risk Summary

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

Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Renal Impairment

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

Hepatic Impairment

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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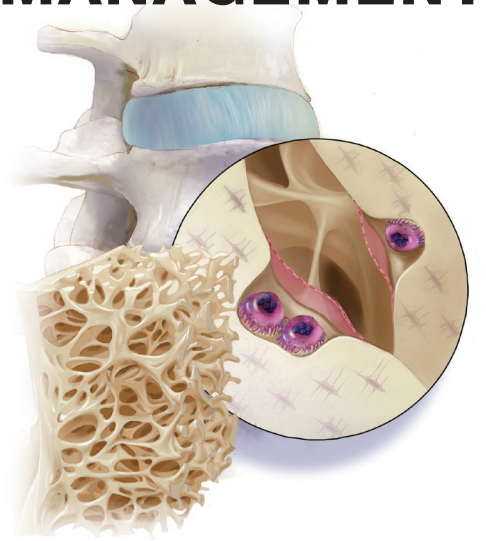

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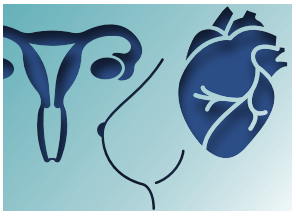

Maternal health and breastfeeding **10**

Considering surgical costs **30**

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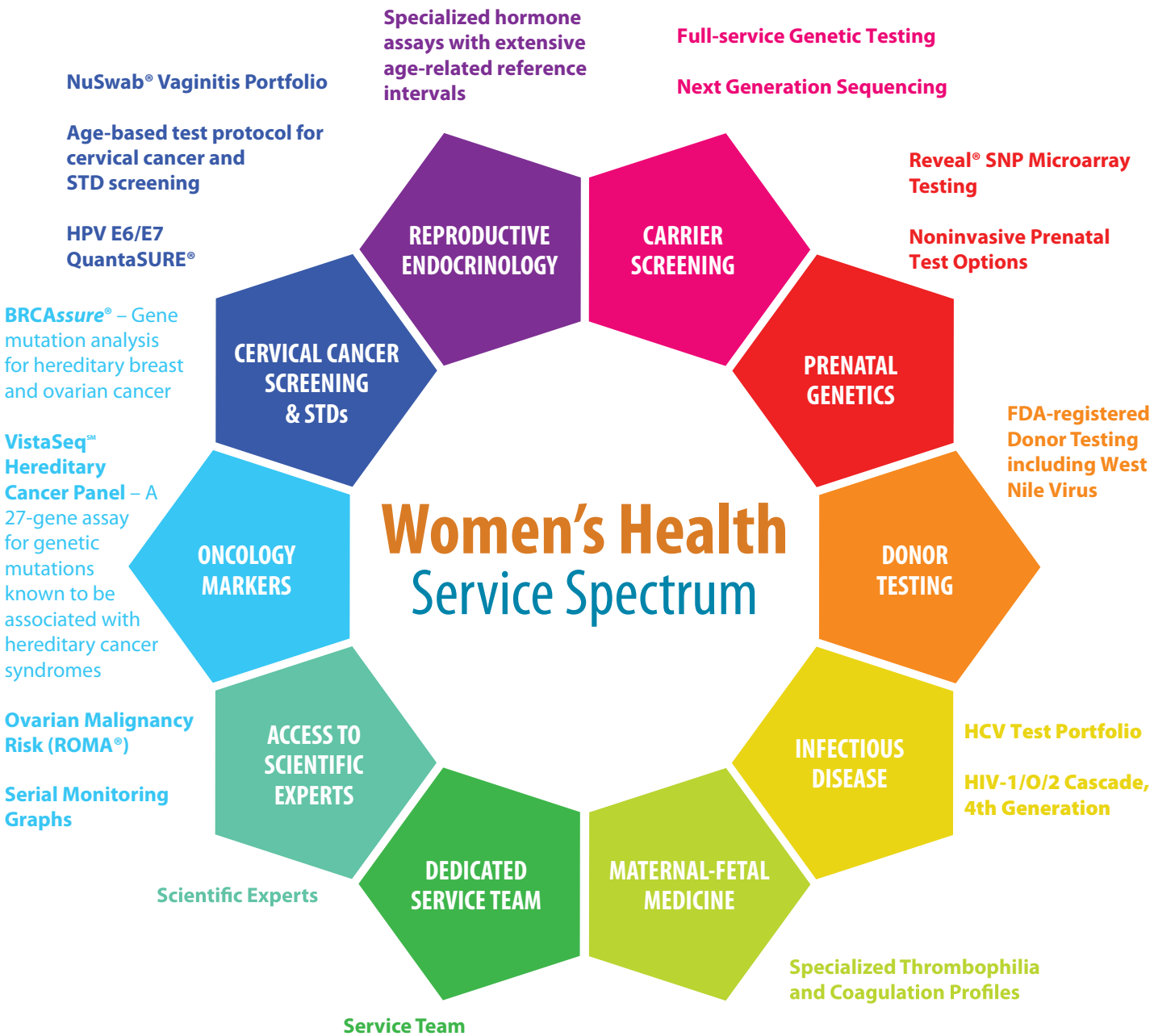

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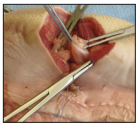

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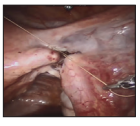

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EDITORIAL

Maternal health benefits of breastfeeding

Diseases highly prevalent among women include type 2 diabetes, hypertension, and coronary artery disease, as well as breast, ovarian, and endometrial cancers. What single intervention can obstetrician-gynecologists recommend to their patients to reduce the risk of these major diseases?

Robert L. Barbieri, MD
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In the past decade, breastfeeding rates have increased substantially. Between 2000 and 2015, the proportion of infants who continued to breastfeed at 12 months increased from 16% to 36%. The proportion of infants who had any breastfeeding increased from 71% to 83%.[1] While the infant health benefits of breastfeeding are widely recognized, the maternal health benefits of breastfeeding are many and likely underappreciated.

Infant health benefits of breastfeeding

There are no large-scale, randomized studies of the long-term health benefits of breastfeeding versus formula feeding. The evidence supporting the health benefits of breastfeeding is derived from case-control and cohort studies. Breastfeeding directly benefits newborn and infant nutrition, gastrointestinal function, host defense, and psychological well-being. Compared with formula-fed newborns, breastfed infants have a reduced risk of infectious diseases including otitis media, gastroenteritis, respiratory infections, sudden infant death syndrome, and metabolic disease. These benefits alone strongly support the public health benefit of breastfeeding.[2] In addition, breastfeeding greatly benefits maternal health.

Instant Poll

Which potential maternal health benefits of breastfeeding do you routinely discuss with your patients?

A. Decreased risk of diabetes
B. Decreased risk of endometrial cancer
C. Decreased risk of breast cancer
D. Decreased risk of cardiovascular disease
E. All of the above

To weigh in, visit **mdedge.com/obgyn** and answer the Poll on the home page.

Maternal health benefits of breastfeeding

Breastfeeding reduces a woman's risk for type 2 diabetes, hypertension, and coronary artery disease, myocardial infarction, as well as breast, ovarian, and endometrial cancer. There are few exposures that have such a multitude of positive health benefits.

Type 2 diabetes

In a prospective cohort study of 1,238 women without diabetes in 1985–1986, 182 women developed type 2 diabetes after 30 years of follow-up. Compared with never breastfeed-

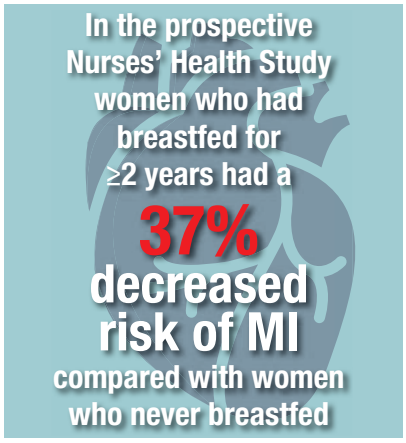
CONTINUED ON PAGE 12

CONTINUED FROM PAGE 10

ing, breastfeeding for 0 to 6 months, >6 months to <12 months, or ≥12 months reduced the risk of type 2 diabetes by 25%, 48%, and 69% respectively.[3] In the prospective Nurses' Health Study, among parous women, each additional year of breastfeeding decreased the risk of type 2 diabetes by 15% compared with women who did not breastfeed.[4]

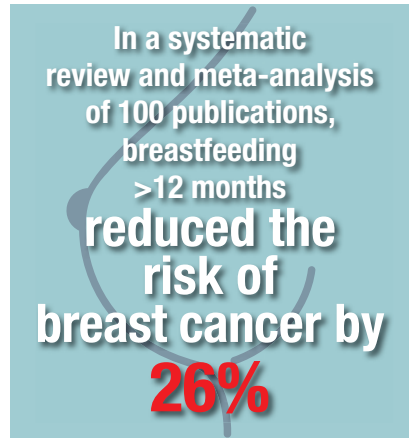
Hypertension

In the Women's Health Initiative (WHI) study of postmenopausal women, a lifetime history of breastfeeding for 12 months or more was associated with a 12% decrease in the risk of hypertension.[5] For parous women, the prevalence of hypertension among breastfeeding (≥12 months) and never breastfeeding women was estimated to be 38.6% versus 42.1%.[5] Similar results were observed in the Nurses' Health Study II.[6]



Myocardial infarction and coronary heart disease

In the prospective Nurses' Health Study, during 1,350,965 person-years of follow-up, 2,540 women had a myocardial infarction (MI). Women who had breastfed for ≥ 2 years had a 37% decreased risk of MI compared with women who never breastfed. After adjustment for family history, lifestyle factors, and adiposity, the observed reduction in risk was 23%.[7] In the WHI (observational study plus controlled trial), women with a single live birth who breastfed for 7 to 12 months had a lower risk of cardiovascular disease than women with a single live birth who did not breastfeed (hazard ratio, 0.72; 95% confidence interval, 0.53–97).[5]

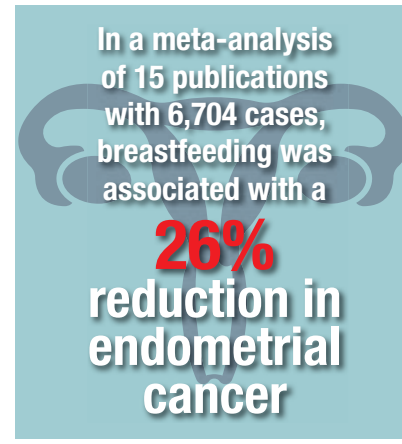


Breast cancer

In a systematic review and meta-analysis of 100 publications, breastfeeding >12 months reduced the risk of breast cancer by 26%.[8] In a systematic review of 47 studies, the relative risk of breast cancer decreased by 4.7% for every 12 months of breastfeeding.[9] In a systematic review and meta-analysis of 3 studies, ever breastfeeding was associated with a 28% reduced risk for triple-negative (ER-, PR-, HER2-) breast cancer among parous women.[10] Triple-negative breast cancer generally has a poorer prognosis than receptor-positive breast cancers.

Ovarian cancer

In a systematic review and meta-analysis of 40 publications, ever breastfeeding was associated with a 37% reduction in the risk of ovarian cancer.[8] In a prospective study of 1.1 million women in the United Kingdom, 8,719 developed ovarian cancer. Among parous women, ovarian cancer risk was reduced by 10% for every 12 months of breastfeeding.[11]



Endometrial cancer

In a meta-analysis of 17 publications, including 8,981 cases and 17,241 controls, ever breastfeeding was associated with an 11% reduction in breast cancer risk.[12] In a meta-analysis of 15 publications with 6,704 cases, breastfeeding was associated with a 26% reduction in endometrial cancer. After controlling for hormone use and body mass index, the reduced risk was in the range of 35%. A linear relationship between breastfeeding and reduced risk of endometrial cancer was observed, with 1 month of breastfeeding being associated with a 1.2% reduction in the risk of endometrial cancer.[13]

Let's support our patients' health by encouraging successful breastfeeding

Obstetrician-gynecologists play an important role in helping women make informed decisions about breastfeeding. Most professional organizations, including the American College of Obstetricians and Gynecologists, recommend exclusive breastfeeding for the first

6 months of life, with continued breastfeeding and introduction of complementary food from 6 to 12 months.[14,15] Birth practices that help to increase successful breastfeeding include:

- inform all pregnant women about the newborn and maternal health benefits and management of breastfeeding
- initiate skin-to-skin contact at birth
- encourage the initiation of breastfeeding within 1 hour of birth
- ensure that breastfeeding newborns do not receive any food or drink other than breast milk, unless medically indicated
- encourage breastfeeding women to not use pacifiers or artificial nipples.[15]

When women are discharged from the maternity center, providing information about community-based lactation support is helpful in ensuring continuation of successful breastfeeding.[16]

Most patients know that exercise and maintaining a healthy weight can reduce the risk of developing many prevalent diseases. However, far fewer patients know that breastfeeding can reduce the risk of developing type 2 diabetes, hypertension, and coronary artery disease, as well as breast, ovarian, and endometrial cancers. Educating our patients about these health benefits may help them to more fully commit to breastfeeding. ●

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

References

1. Centers for Disease Control and Prevention. Breastfeeding Among U.S. Children Born 2009–2015, CDC National Immunization Survey. https://www.cdc.gov/breastfeeding/data/nis_data/results.html. Updated August 2018. Accessed November 19, 2018.
2. Ip S, Chung M, Raman G, et al. A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries. *Breastfeed Med.* 2009;4 (suppl 1):S17.
3. Gunderson Ep, Lewis CE, Lin Y, et al. Lactation duration and progression to diabetes in women across the childbearing years: the 30-year CARDIA study. *JAMA Int Med.* 2018;178:328-337.
4. Stuebe AM, Rich-Edwards JW, Willett WC, et al. Duration of lactation and incidence of type 2 diabetes. *JAMA*. 2005;294:2601-2610.
5. Schwarz EB, Ray RM, Stuebe AM, et al. Duration of lactation and risk factors for maternal cardiovascular disease. *Obstet Gynecol.* 2009;113:974-982.
6. Stuebe Am, Schwarz EB, Grewen K, et al. Duration of lactation and incidence of maternal hypertension: a longitudinal cohort study. *Am J Epidemiol.* 2011;174:1147-1158.
7. Stuebe AM, Michels KB, Willett WC, et al. Duration of lactation and incidence of myocardial infarction in middle to late adulthood. *Am J Obstet Gynecol.* 2009;200:138.e1-e8.
8. Chowdhury R, Sinha B, Sankar MJ, et al. Breastfeeding and maternal health outcomes: a systematic review and meta-analysis. *Acta Paediatr.* 2015;104:96-113.
9. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries including 50,302 women with breast cancer and 96,973 women without the disease. *Lancet.* 2002;360:187-195.
10. Islami F, Liu Y, Jemal A, et al. Breastfeeding and breast cancer risk by receptor status—a systematic review and meta-analysis. *Ann Oncol.* 2015;26:2398-2407.
11. Gaitskell K, Green J, Pirie K, et al. Million Women Study Collaborators. Histological subtypes of ovarian cancer associated with parity and breastfeeding in the Million Women Study. *Int J Cancer.* 2018;142:281-289.
12. Jordan SJ, Na R, Johnatty SE, et al. Breastfeeding and endometrial cancer risk: an analysis from the epidemiology of endometrial cancer consortium. *Obstet Gynecol.* 2017;129:1059-1067.
13. Zhan B, Liu X, Li F, Zhang D, et al. Breastfeeding and the incidence of endometrial cancer: a meta-analysis. *Oncotarget.* 2015;6:38398-38409.
14. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database of Systematic Reviews.* 2012;CD003517.
15. ACOG Committee Opinion No. 756. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2018;132:e187-e196.
16. McFadden A, Gavine A, Renfrew M, et al. Support for healthy breastfeeding mothers with healthy term babies. *Cochrane Database Syst Rev.* 2017;CD001141.

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

LARC = long-acting reversible contraceptive

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

WARNINGS and PRECAUTIONS

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

WOMN-1267530-0000 09/18

NEXPLANON is the only non-uterine LARC option

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

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

Placed subdermally in the inner upper arm just under the skin

(Actual implant shown; actual implant is 4 cm)

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

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

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information

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

MERCK

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

The efficacy of NEXPLANON does not depend on daily, weekly or monthly administration. All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON. A single NEXPLANON implant is inserted subdermally in the upper arm. To reduce the risk of neural or vascular injury, the implant should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. The implant should be inserted subdermally just under the skin, avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissues. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult or impossible *[see Dosage and Administration and Warnings and Precautions]*. NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

1. **Complications of Insertion and Removal**

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

   If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. NEXPLANON should be inserted subdermally just under the skin avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissues. Deep insertions of NEXPLANON have been associated with paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

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

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

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

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

2. **Changes in Menstrual Bleeding Patterns**

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

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

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

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

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

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

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

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

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

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

3. **Ectopic Pregnancies**

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

4. **Thrombotic and Other Vascular Events**

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

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

5. **Ovarian Cysts**

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

6. **Carcinoma of the Breast and Reproductive Organs**

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

7. **Liver Disease**

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

8. **Weight Gain**

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

9. **Elevated Blood Pressure**

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

10. **Gallbladder Disease**

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

11. **Carbohydrate and Lipid Metabolic Effects**

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

12. **Depressed Mood**

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

13. **Return to Ovulation**

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

14. **Fluid Retention**
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.
15. **Contact Lenses**
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.
16. ***In Situ* Broken or Bent Implant**
There have been reports of broken or bent implants while in the patient's arm. Based on *in vitro* data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety *[see Dosage and Administration]*.
17. **Monitoring**
A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.
18. **Drug-Laboratory Test Interactions**
Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Effects of Other Drugs on Hormonal Contraceptives

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

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

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

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

Effects of Hormonal Contraceptives on Other Drugs

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

USE IN SPECIFIC POPULATIONS

1. **Pregnancy**
Risk Summary
NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant *[see Contraindications]*. Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 781 times the anticipated human dose (60 µg/day). NEXPLANON should be removed if maintaining a pregnancy.
2. **Nursing Mothers**
Lactation
Risk Summary
Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.
3. **Pediatric Use**
Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.
4. **Geriatric Use**
This product has not been studied in women over 65 years of age and is not indicated in this population.
5. **Hepatic Impairment**
No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated *[see Contraindications]*.
6. **Overweight Women**
The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

PATIENT COUNSELING INFORMATION *See FDA-Approved Patient Labeling.*

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

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

For more detailed information, please read the Prescribing Information.
USPI-MK8415-IPTX-1705r019
Revised: 05/17

OPTIMIZE THE MEDICAL TREATMENT OF ENDOMETRIOSIS—USE ALL AVAILABLE MEDICATIONS
ROBERT L. BARBIERI, MD
(AUGUST 2018)

Dienogest as an option for endometriosis pain

For treatment of endometriosis-related pain, what about the drug dienogest and the cyclic oral contraceptive Qlaira, which contains dienogest?

Chow Kah Kiong, MBBS
Singapore

Norethindrone's conversion to ethinyl estradiol

Dr. Barbieri's editorial on the medical treatment of endometriosis is excellent! Does norethindrone acetate metabolize to ethinyl estradiol in a higher percentage when the dose is higher, or is it still 1%? We were taught that at doses of greater than 15 mg daily, norethindrone can contribute significant amounts of estrogen.

Lauren Barnes, MD
Albuquerque, New Mexico

Endometriosis is a surgical, not a medical, disease

I read with some dismay Dr. Barbieri's editorial on medical treatment of endometriosis. As a long-time disciple of the eminent Dr. David Redwine, I have dedicated my practice focus over the past 28 years to minimally invasive curative solutions to many gynecologic problems. The data on the histology, qualitative hormonal differences, and inconsistent and poor long-term response of endometriosis to traditional hormonal suppressive therapies falls strongly in favor of complete and thorough laparoscopic excision—not "biopsy"—as the only truly curative treatment, certainly not medical therapy. Endometriosis is a surgical disease. The experience of the dedicated few in our field who have taken the time and effort to become experts in excision (not ablation) of endometriosis bears this out.

AUGUST 2018

The tragedy is that the only Current Procedural Terminology code that is usable for reimbursement is 58662. Sadly, this code was assigned a resource-based relative value scale "value" many years ago, when the operation consisted of putting a scope in the abdomen and taking a sampling biopsy (which took all of 10 minutes). Of course, we know that a prolonged, delicate procedure requiring retroperitoneal dissection, ureterolysis, excision of deeply infiltrating rectovaginal septum endometriosis, and discoid or segmental bowel resection requires the kind of surgical expertise developed only by those who put in the time and effort to get good at this type of surgery. The majority of ObGyns who have a full obstetric practice and low surgical volumes simply are not going to struggle in the operating room over the many cases that it takes to become good, and safe, at this procedure only to receive an insulting reimbursement.

It is emblematic of this travesty that many of the best minimally invasive surgery practitioners do not accept insurance or other third-party payment such as Medicaid as they would otherwise not cover their overhead.

Putting premenopausal women into a severely hypoestrogenic state with medication is cruel and, even worse, does not cure the disease.

Balanced information on surgical management should have been presented in the article. And physicians who are not capable of proper laparoscopic excision should refer the patient.

Hugo Ribot, MD
Cartersville, Georgia

Dr. Barbieri responds

I thank Drs. Chow, Barnes, and Ribot for their interest in my recent editorial on the medical treatment of endometriosis. I agree with Dr. Chow that dienogest, a synthetic progestin, is effective in the treatment of pelvic pain caused by endometriosis. In one observational study, norethindrone acetate 2.5 mg daily and dienogest 2 mg daily had similar efficacy in the treatment of pelvic pain. Dienogest treatment was associated with fewer side effects but was much more expensive than norethindrone acetate.[1] The US Food and Drug Administration has approved a combination estradiol-progestin pill (Natazia, Qlaira) as a contraceptive, and I have occasionally used this medication in my practice for women with pelvic pain caused by endometriosis. Dienogest monotherapy is not available in the United States.

Dr. Barnes reminds us that norethindrone is a substrate for the aromatase enzyme system and can be

CONTINUED ON PAGE 47

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

Does low-dose aspirin decrease a woman's risk of ovarian cancer?

While low-dose aspirin (ASA) is recommended as chemoprophylaxis for some cancers, **there are insufficient data to support its use to reduce ovarian cancer** incidence. Although recent prospective study of more than 200,000 women indicates a decreased risk of ovarian cancer with the use of low-dose ASA, the reported statistical significance recedes when controlling for clinically important confounders. The study findings are therefore not generalizable or clinically applicable. This lack of association is congruent with previously published prospective research.

FAST TRACK

The finding that current low-dose aspirin use was associated with decreased risk of ovarian cancer did not maintain significance after controlling for hypertension, autoimmune disease, etc.

EXPERT COMMENTARY

Mary M. Mullen, MD, is Fellow, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine and Alvin J. Siteman Cancer Center, St. Louis, Missouri.

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Barnard M, Poole EM, Curhan GC, et al. Association of analgesic use with risk of ovarian cancer in the Nurses' Health Studies. JAMA Oncol. October 4, 2018. doi: 10.1001/jamaoncol.2018.4149.

Epidemiologic studies conducted in ovarian cancer suggest an association between chronic inflammation and incidence of disease.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) work to decrease inflammation through the inhibition of cyclo-oxygenase (COX). Therefore, anti-inflammatory agents such as NSAIDs have been proposed to play a role in the pathophysiology of ovarian cancer.

Previous studies of this association show conflicting data. The majority of these studies are retrospective, and those that are prospective do not include detailed data regarding dosing and frequency of ASA use.[2-6]

The authors report no financial relationships relevant to this article.

Details of the study

This study by Barnard and colleagues is a prospective cohort study evaluating a total of 205,498 women from 1980–2015 from 2 separate cohorts (the Nurses' Health Study and the Nurses' Health Study II). The primary outcome was "to evaluate whether regular aspirin or nonaspirin NSAID use and patterns of use are associated with lower ovarian cancer risk." Analgesic use and data regarding covariates were obtained via self-reported questionnaires. Ovarian cancer diagnosis was confirmed via medical records.

Results demonstrated that current low-dose aspirin use was associated with a decreased risk of ovarian cancer (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.61–0.96). This significance was not maintained upon further controlling for inflammatory factors (hypertension, autoimmune disease, inflammatory diet scores, smoking, etc) (HR, 0.94; 95% CI, 0.69–1.26). Other significant findings included an increased risk of developing ovarian cancer with standard-dose ASA use of ≥5 years or standard-dose use at 6 to 9 tablets per week (HR, 1.77; 95% CI, 1.13–2.77 and HR, 2.00; 95% CI, 1.27–3.15, respectively). An increased risk of developing ovarian cancer also was found for >10-year use or use of >10 tablets per week of nonaspirin NSAIDs (HR, 2.00; 95% CI, 1.27–3.15 and HR, 1.35; 95% CI, 1.02–1.79, respectively).

The authors concluded that there was a slight inverse association for low-dose aspirin and ovarian cancer risk and that standard aspirin or NSAID use actually may be associated with an increased risk of ovarian cancer.

Study strengths and weaknesses

This study has many strengths. It was a large prospective cohort investigation with adequate power to detect clinically significant differences. The authors collected detailed exposure data, which was novel. They also considered a latency period prior to the diagnosis of ovarian cancer during which a patient may increase their analgesic use in order to treat pain caused by the impending cancer.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Based on these current data, there is insufficient evidence to suggest the use of low-dose aspirin for chemoprophylaxis of ovarian cancer. In order to suggest the use of a drug for prophylaxis the benefits must outweigh the risks, and in the case of NSAIDs, this has yet to be confirmed.

However, the conclusions of the authors seem to be overstated in the setting of the data. Specifically, the deduction regarding a decreased risk of ovarian cancer with low-dose aspirin use given the loss of the statistical significance when controlling for pertinent cofounders. Further, the study authors did not evaluate adverse effects associated with low-dose aspirin use, which would be clinically applicable when determining whether the results from this study should become formal recommendations. Lastly, other important clinical factors, such as the presence of genetic mutations or endometriosis, were not considered, and these considerations would greatly affect results.

In the setting of previous large prospective studies that suggest no association between ASA use and ovarian cancer risk,[4-6] data from this study are not compelling enough to recommend regular low-dose aspirin use to all women. ●

References

1. Poole EM, Lee IM, Ridker PM, et al. A prospective study of circulating C-reactive protein, interleukin-6, and tumor necrosis factor alpha receptor 2 levels and risk of ovarian cancer. *Am J Epidemiol*. 2013;178:1256-1264.
2. Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst*. 2014;106:djt431.
3. Peres LC, Camacho F, Abbott SE, et al. Analgesic medication use and risk of epithelial ovarian cancer in African American women. *Br J Cancer*. 2016;114(7):819-825.
4. Murphy MA, Trabert B, Yang HP, et al. Non-steroidal anti-inflammatory drug use and ovarian cancer risk: findings from the NIH-AARP Diet and Health Study and systematic review. *Cancer Causes Control*. 2012;23:1839-1852.
5. Brasky TM, Liu J, White E, et al. Non-steroidal anti-inflammatory drugs and cancer risk in women: results from the Women's Health Initiative. *Int J Cancer*. 2014;135:1869-1883.
6. Lacey JV Jr, Sherman ME, Hartge P, et al. Medication use and risk of ovarian carcinoma: a prospective study. *Int J Cancer*. 2004;108:281-286.

Coding and reimbursement 101: How to maximize your payments

Know these codes, modifiers, and bundles so you can submit reimbursement claims accurately and on time

Melanie Witt, RN, MA

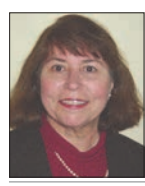
IN THIS ARTICLE

While reimbursement for ObGyn services seemingly should be a simple matter of putting codes on a claim form, the reality is that it is complex, and it requires a team approach to accomplish timely filing to receive fair and accurate reimbursement.

Reimbursement occurs over the length of the revenue cycle for a patient encounter and involves many steps. It starts when the patient makes an appointment for services and ends when the practice receives payment. Along the way, there must be good clinician documentation and sound knowledge about the billing process (including the Current Procedural Terminology [CPT] or Healthcare Common Procedure Coding System [HCPCS] codes for services), the *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM] codes that establish medical necessity, the modifiers that alter the meaning of the codes, and, of course, the bundling issues that now accompany many coding situations.

In addition, ObGyn practices must contend with a multitude of payers—from federal to commercial—and must understand and adhere to each payer's rules and policies to maximize and retain reimbursement.

In this article, I detail stumbling blocks to maximizing reimbursement and how to avoid them.



Ms. Witt is an independent coding and documentation consultant and former program manager, department of coding and nomenclature, American College of Obstetricians and Gynecologists.

The author reports no financial relationships relevant to this article.

Coding considerations for office services

Good documentation before, during, and after a patient's office visit is essential, along with accurate codes, modifiers, and order of services on the claims you submit.

Prep paperwork before the patient encounter

Once a patient makes an appointment, the front-end staff can handle some of the tasks in the cycle. This includes ensuring that the patient's insurance coverage information is current, informing the patient of any additional information to bring at the time of the visit (such as a patient history form for a new patient visit or a list of current prescriptions), or, if an established patient will be having a procedure, making sure that prior authorization is complete. This streamlines the process, assists the clinician with documentation housekeeping, and ensures that incorrect or missing information does not cause a claim to be denied or not be filed in a timely manner

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(many payers require submission of an initial claim 30 days from the date of service).

Document details of the clinician-patient interaction

At the time of the encounter, you are responsible for documenting your contact with the patient in enough detail to support billing a CPT evaluation and management (E/M) code at the level selected and/or any procedures or other services performed. The **TABLE** provides an overview of the requirements for each level of office service.

If both an E/M and a procedure are performed on the same date of service, the E/M must be documented to show it was separate from the procedure and that the work was significantly more than would be required to accomplish the procedure. Documentation of the procedure should include the indication, steps performed, findings, the patient's condition afterward, and instructions for aftercare or follow-up.

If you use an electronic health record for reporting, you may be the one responsible for selecting both the CPT code for services performed and an ICD-10-CM code(s) to establish the medical need for them. Select the most accurate CPT codes, and clearly link them to a supporting diagnosis for each service that will be billed. If more than one diagnosis is applicable, the first one linked to any given service should represent the most important justification, as not all payers will accept more than one diagnosis code on the claim per service billed.

If the billing staff is assigned the task of selecting the CPT and/or ICD-10-CM diagnostic codes based on your documentation, they should be well versed in the services, procedures, and diagnoses reported for their ObGyn practice.

The actual code selection may end up being a joint venture between the clinician and the staff to ensure that accurate information will be entered on the claim. Good and frequent clinician-staff communication on billing of services can transform average reimbursement into maximized reimbursement.

TABLE Requirements for each level of office service

Code	History	Exam	Medical decision-making complexity	Typical time reported when counseling time dominates the encounter
• New patient outpatient encounter				
• 3 of 3 elements required				
• Lowest documented element determines the level of service				
99201	PF	PF	Straightforward	10
99202	EPF	EPF	Straightforward	20
99203	D	D	Low	30
99204	C	C	Moderate	45
99205	C	C	High	60
• Established outpatient visit				
• 2 of 3 elements required; medical decision-making must be one of them				
• Lowest level of these 2 determines level of service				
99211	Minimal problem that may not require presence of clinician			5
99212	PF	PF	Straightforward	10
99213	EPF	EPF	Low	15
99214	D	D	Moderate	25
99215	C	C	High	40

Abbreviations: C, comprehensive; D, detailed; EPF, expanded problem focused; PF, problem focused.

Be aware of bundles

Sometimes more than one service or procedure is listed on a claim on the same date of service. However, it is important to identify all potential bundles before billing to ensure correct payment. For instance, payers like to bundle an E/M service and a procedure, or you may be in the global period (defined below) of a surgery but need to report an unrelated service.

You and your staff must work together to ensure the claim is submitted with the correct modifiers; on the other hand, you may decide that a better method of coding is in order. Some payers, for example, will not reimburse both an insertion and a removal of an intrauterine device (IUD) on the same date of service. If that does happen, a modifier on the removal code might save the day, rather than billing 2 codes.

Manage the modifiers

Sometimes the code billed requires a modifier to ensure payment. Typical modifiers used in an ObGyn office setting include the following:

- **22,** *Increased procedural services* (the clinician must assign a fee that is higher than the usual fee for the procedure and be able to document CPT equivalents to the work involved)
- **24,** *Unrelated E/M during the postoperative period* (note that this modifier does not apply during the antepartum period for pregnancy)
- **25,** *Significant and separate E/M on the same date as another service or minor procedure*
- **52,** *Reduced services* (generally, the payer will expect an explanation of the reduced service and will determine payment accordingly)
- **57,** *Decision to perform major surgery the day of or the day before the surgery*
- **59,** *Distinct procedural service* (used when 2 procedures are bundled and a modifier is allowed). Note that payment reductions for multiple procedures will still apply.
- **79,** *Unrelated procedure during the postoperative period* (usually paid at the full allowable).

Organize the order of services on the claim

For an outpatient claim that includes both an E/M service and procedures, the order of the services—not the order in which they were performed—may be important to obtaining maximum reimbursement. In general, payers will pay in full for a supported E/M service no matter where it appears on the claim, but they apply reductions only for multiple procedures.

For instance, if you insert levonorgestrel implants on the same date as you remove a large polyp from the cervix, you would want to report the code with the highest relative value unit (RVU) first. In this case, it would be 11981 (4.05 RVUs), 57500 (3.61 RVUs).

In the IUD case mentioned earlier (removal and insertion of IUDs on the same date), the order of the codes, assuming the payer reimburses for both, will be even more important since removal usually has a higher payment: 58301 (2.70 RUVs), 58300 (1.54 RVUs).

Coding considerations for surgical services

Surgical services performed in a hospital or ambulatory surgical center present another set of must-dos to ensure timely and fair reimbursement.

Grasp the 'global package' concept

Understanding this concept can be crucial to getting paid for additional services during this time period and correct billing for any E/M services performed prior to surgery. In general, the routine history and physical examination performed prior to a major surgery is considered included in the work and should not be billed separately. Surgical clearance for a patient's condition, such as hypertension, a heart condition, or lung issues, can be billed separately, but these generally are performed by someone other than the operating surgeon.

Procedures performed in the hospital setting generally will have a 10- or 90-day global period. During this time, any related

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FAST TRACK

Procedures performed in the hospital generally will have a 10- or 90-day global period

Meaningful endometriosis treatment requires a holistic approach and an understanding of chronic pain

Considering the pathways involved with chronic pelvic pain in endometriosis can pave the way toward whole body treatment focused on quality of life

Q&A with Andrea J. Rapkin, MD

IN THIS ARTICLE

Although it has been more than 100 years since endometriosis was first described in the literature, deciphering the mechanisms that cause pain in women with this enigmatic disease is an ongoing pursuit.

Pain is the most debilitating symptom of endometriosis.[1,2] In many cases, it has a profoundly negative impact on a patient's quality of life, and contributes significantly to disease burden, as well as to personal and societal costs from lost productivity.[3,4] Women with endometriosis often experience chronic pelvic pain, deep dyspareunia, dysmenorrhea, and subfertility.[5] The majority of women with the disease also have one or more comorbidities, including adenomyosis, adhesive disease, and other pelvic pain conditions such as interstitial cystitis, irritable bowel disease, inflammatory bowel disease, and pelvic floor myalgia.[6-8]

Recent studies have yielded new insights into the development of endometriosis-associated pelvic pain. The role of peritoneal inflammation, *de novo* innervation of endometriosis implants, and changes in the central nervous system are becoming increasingly clear.[5,9,10] These discoveries have important treatment implications.

In this article, Andrea J. Rapkin, MD, Professor of Obstetrics and Gynecology at the University of California, Los Angeles, and Founder and Director of the UCLA Pelvic Pain Center, offers her expert opinion on the findings of key studies and their clinical implications, including the importance of a multidisciplinary treatment approach that focuses on the whole patient.

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

Q What mechanisms underlie the chronic pain that many women with endometriosis feel?

Although pain is the primary symptom experienced by women with endometriosis, the disease burden and symptom severity do not often correlate.[11,12] "This was the first conundrum presented to clinicians," noted Dr. Rapkin. "In fact, we do not know the true prevalence of endometriosis because women with endometriosis only come to diagnosis either based on pain or infertility. When infertility is the problem, very often we are surprised by how much disease is present in an individual with either no pain or minimal pain. Conversely, in other individuals with very severe pain, upon laparoscopic surgery, have minimal or mild endometriosis."

Efforts to solve this clinical puzzle began decades ago. "Dr. Michael Vernon discovered that the small, red, endometriosis implants that looked like petechial hemorrhages produced more prostaglandin E2 (PGE2) in vitro

than the older black-brown lesions. PGE2 is a pain-producing (algesic) chemical produced after cytokines stimulation," said Dr. Rapkin. "This was the first evidence that, yes, there is a reason for pain in many individuals with lower-stage disease."

"Prostaglandins are known to be a major cause of dysmenorrhea. Prostaglandins induce uterine cramping, sensitize nerve endings, and promote other inflammatory factors responsible for attracting monocytes that become macrophages, further contributing to inflammation," Dr. Rapkin continued. "PGE2 also stimulates the enzyme aromatase, which allows androgens to be converted to estrogen, which promotes growth of endometriotic lesions. This is a self-feeding aspect of endometriosis."

These discoveries were followed by the realization that deeply infiltrating endometriosis (defined by disease infiltration of more than 5 mm, often in the uterosacral ligaments) was more likely to be painful than superficial disease, said Dr. Rapkin. "In some women with endometriosis, the disease we see laparoscopically is really the tip of the iceberg."

In 2005, landmark studies performed by Karen J. Berkley, PhD, were summarized in a paper coauthored by Dr. Berkley, Dr. Rapkin, and Raymond E. Papka, PhD.[13] "In a rodent model where endometriosis was developed by suturing pieces of endometrium in the mesentery, the endometriosis implants developed a vascular supply and a nerve supply. These nerves were not just functioning to govern the dilation and contraction of the blood vessels (in other words the sympathetic type nerves), but these nerves stained for neurotransmitters associated with pain (algesic agents, such as substance P and CGRP)," said Dr. Rapkin. "At UCLA, we acquired tissue from women with endometriosis and analyzed in Dr. Papka's lab. Those tissues also showed nerves staining for pain-producing chemicals." Other studies performed worldwide also demonstrated nerve endings with neurotrophic and algesic chemicals in endometriotic tissues. In addition to prostaglandins and cytokines, increased expression of various neuropeptides, neurotrophins, and alterations in ion channels contribute to hypersensitivity and pain.

Q What other chronic pain conditions might women with endometriosis experience?

Overlapping chronic pain conditions are common in women with endometriosis. "There is a very high co-occurrence of interstitial cystitis/painful bladder syndrome," said Dr. Rapkin. "Irritable bowel syndrome is more common in women with endometriosis, as is vulvodynia. Fibromyalgia, migraine headache, temporomandibular joint pain (TMJ), anxiety, and depression also commonly co-occur in women with endometriosis."

"Two concepts may be relevant to why these overlapping pain conditions develop," Dr. Rapkin continued. "First, visceral sensitization: If one organ or tissue is inflamed and becomes hyperalgesic then other organs in the adjacent region with shared thoracolumbar and sacral innervation can become sensitized through shared cell bodies in the spinal cord, cross-sensitization in the cord, or at higher regions of the CNS. In addition, visceral somatic conversion occurs, whereby somatic tissues such as muscles and subcutaneous tissues with the same nerve supply as the affected organs become sensitized. This process may explain why abdominal wall and pelvic floor muscles become painful. The involvement of surrounding musculature is an important contributor to the pain in many women with endometriosis."

"Finally, genetic studies of alterations in genes that encode for chemicals affecting the sensitivity and perception of pain are shedding light on the development of chronic pain. Ultimately these studies will advance our understanding of pain related to endometriosis."

Q How have new understandings about the pain mechanisms involved with endometriosis-caused pelvic pain improved treatment?

According to Dr. Rapkin, the increased understanding of the mechanisms involved in

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Deeply infiltrating endometriosis can be more painful than superficial disease; in some women, the disease is the tip of the iceberg

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endometriosis-associated pain gained from these key studies led to a paradigm shift, with endometriosis being viewed not just as a condition with mechanical hypersensitivity due to altered anatomy and inflammation but also as a neurologic condition, or a nerve pain condition with peripheral and central sensitization. "This means there is upregulation or hyperactivity both in the periphery (in the pelvis) and centrally (in the spinal cord and brain)," said Dr. Rapkin.

"In the periphery, the endometriotic lesions develop an afferent sensory innervation and communicate with the brain. Stimulation of these nerves by the inflammatory milieu contributes to pain." Dr. Rapkin noted research by Maria Adele Giamberardino, which demonstrated that women with endometriosis and pain have a lower threshold for feeling pain in the tissues overlying the pelvis (the abdominal wall and back).[14] This also has been shown by Dr. Berkley in rodents given endometriosis.

"The muscles develop trigger points and tender hyperalgesic points as part of the sensitization process. In addition, distant sensitization develops—women with pelvic pain and endometriosis have a lower threshold for sensing experimental pain in areas outside the pelvis, for example the back, leg, or shoulder. These discoveries clearly reflect up regulation for pain processing in the central nervous system."

Dr. Rapkin also pointed to research published in 2016 by Sawson As-Sanie, MD, MPH, that showed an association between endometriosis-associated pelvic pain and altered brain chemistry and function.[16] "Dr. As-Sanie demonstrated a decrease in gray matter volume in key neural pain processing areas in the brain in women with pain with endometriosis. This was not found in women with endometriosis who did not have pain," she said. "Altered connectivity in brain areas related to perception and inhibition of pain is important in maintaining pain. Dr. As-Sanie's studies also found that these changes are correlated with anxiety, depression, and pain intensity in patients with endometriosis and chronic pain."

FAST TRACK

It is now standard of care that medical therapy, not surgery, is the first approach to treatment

Q What are some newer treatment approaches to chronic pain with endometriosis?

"Multidisciplinary approaches to endometriosis-related pain are important," said Dr. Rapkin. "Although it is important to excise or cauterize endometriosis lesions, or debulk as much as can safely be removed during laparoscopic surgery, it is now standard of care that medical therapy, not surgery, is the first approach to treatment. Endometriosis is a chronic condition. Inflammatory factors will continue to proliferate in patients who menstruate and produce high levels of estrogen with ovulation. The goal of medical therapy is to decrease the levels of estrogen that contribute to maintenance and proliferation of the implants. We want to suppress estrogen in a way that is compatible with long-term quality of life for our patients. Wiping out estrogen and placing patients into a chemical or surgical menopause for most of their reproductive years is not desirable."

Approaches to hormonally modulate endometriosis include combined hormonal contraceptives and progestin-only medications, such as the levonogestrol-containing IUD, progestin-containing contraceptive implants, injections, or tablets. Second-line medical therapy consists of gonadotropin-releasing hormone agonists and antagonists that can be used for 6 months to 2 years and allows for further lowering of estrogen levels. These may not provide sufficient pain relief for some patients. "There is some evidence from Dr. Giamberadino's studies that after women with dysmenorrhea were treated with oral contraceptives, the abdominal wall hyperalgesia decreased," said Dr. Rapkin. "The question is, why don't we see this in all patients? We come to the realization that endometriosis has to be treated as a neurologically mediated disorder. We have to treat the peripheral and central sensitization in a multidisciplinary way."

A holistic approach to endometriosis is a new and exciting area for the field, said Dr. Rapkin. "We have to treat 'bottom-up,' and 'top-down.' Bottom-up means we are addressing the peripheral factors that contribute to

pain: endometriotic lesions, other pelvic organ pain, myofascial pain, trigger points, the tender points, and the muscle dysfunction in the abdominal wall, the back, and the pelvic floor. Pelvic floor physical therapists help women with pain and endometriosis. Often, women with endometriosis have myofascial pain and pain related to the other comorbid pain conditions they may have developed. Peripheral nerve blocks and medications used for neuropathic pain that alter nerve firing can be helpful in many situations. Pain can be augmented by cognitions and beliefs about pain, and by anxiety and depression. So the top-down approach addresses the cognitions, depression, and anxiety. We do not consider endometriosis a psychosomatic condition, but we know that if you do not address the central upregulation, including anxiety and depression, we may not get anywhere."

"Interestingly, neurotransmitters and brain regions governing mood contribute to nerve pain. Medications such as tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, anticonvulsants, and calcium channel blocking agents may prove fruitful. Cognitive behavioral therapy is another approach—to stimulate the prefrontal cortex, the area that is involved in pain inhibition, and other areas of the brain that may produce endogenous opioids to help with inhibiting pain. Bringing in complementary approaches is very important—for example, mindfulness-based meditation or yoga. There is growing evidence for acupuncture as well. Physical therapists, pain psychologists, anesthesiologists, or gynecologists who are facile with nerve blocks, to help tone down hyperalgesic tissues, in addition to medical and surgical therapy, have the possibility of really improving the lives of women with endometriosis."

Q What key pearls would you like to share with readers?

"It is important to evaluate the entire individual," she said. "Do not just viscerally focus on the uterus, the ovaries, fallopian tubes, and the peritoneum; investigate the adjacent organs and somatic tissues. Think about the abdominal wall, think about the pelvic floor. Learn how to evaluate these structures. There are simple evaluation techniques that gynecologists can learn and should include with every patient with pelvic pain, whether or not they are suspected of having endometriosis. You also want to get a complete history to determine if there are other co-occurring pain conditions. If there are, it is already a sign that there may be central sensitization."

"Very often, it is necessary to bring in a pain psychologist—not because the disease is psychosomatic but because therapy can help the patient to learn how to use their brain to erase pain memory, and of course to address the concomitant anxiety, depression, and social isolation that happens with pain." ●

FAST TRACK

A pain psychologist can provide therapy to help a patient learn how to use their brain to erase pain memory, and address the concomitant anxiety, depression, and social isolation that happens with pain

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References

1. Olive DL, Lindheim SR, Pritts EA. New medical treatments for endometriosis. *Best Pract Res Clin Obstet Gynaecol.* 2004;18(2):319-328.
2. Giudice LC, Kao LC. Endometriosis. *Lancet.* 2004;364(9447):1789-1799.
3. Nnoaham KE, Hummelshoj L, Webster P, et al; World Endometriosis Research Foundation Global Study of Women's Health consortium. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril.* 2011;96(2):366-373.e8.
4. Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod.* 2012;27(5):1292–1299.
5. Bruner-Tran KL, Mokshagundam S, Herington JL. Rodent models of experimental endometriosis: identifying mechanisms of disease and therapeutic targets. *Curr Womens Health Rev.* 2018;14(2):173-188.
6. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod.* 2002;17(10):2715-2724.
7. Struble J, Reid S, Bedaiwy MA. Adenomyosis: a clinical review of a challenging gynecologic condition. *J Minim Invasive Gynecol.* 2016;23(2):164-185.
8. Tirlapur SA, Kuhrt K, Chaliha C. The 'evil twin syndrome' in chronic pelvic pain: a systematic review of prevalence studies of bladder pain syndrome and endometriosis. *Int J Surg.* 2013;11(3):233-237.
9. Coxon L, Horne AW, Vincent K. Pathophysiology of endometriosis-associated pain: a review of pelvic and central nervous system mechanisms. *Best Pract Res Clin Obstet Gynaecol.* 2018 Feb 15. pii: S1521-6934(18)30032-4. doi: 10.1016/j.bpobgyn.2018.01.014. [Epub ahead of print]
10. Yan D, Liu X, Guo SW. Nerve fibers and endometriotic lesions: partners in crime in inflicting pains in women with endometriosis. *Eur J Obstet Gynecol Reprod Biol.* 2017;209:14-24.

Cost-conscious minimally invasive hysterectomy: A case illustration

This case demonstrates the importance of knowing which surgical tools are available to you and then providing value by considering cost without compromising safety or the best chance of a good outcome

Anupama Kotha, MD, MS, and Joseph S. Sanfilippo, MD, MBA

IN THIS ARTICLE

CASE Cost-conscious benign laparoscopic hysterectomy

A 43-year-old woman undergoes laparoscopic hysterectomy for treatment of presumed benign uterine fibroids and menorrhagia. Once she is prepped with ChloraPrep with tint, a RUMI II uterine manipulator is placed. Laparoscopic ports include a Kii Balloon Blunt Tip system, a Versaport Plus Pyramidal Bladed Trocar, and 2 Kii Fios First Entry trocars.

The surgeon uses the Harmonic ACE +7 device (a purely ultrasonic device) to perform most of the procedure. The uterus is morcellated and removed using the US Food and Drug Administration (FDA)-approved Olympus Contained Tissue Extraction System, and the vaginal cuff is closed using a series of 2-0 PDS II sutures. Skin incisions are closed using Dermabond skin adhesive.

Total cost of the products used in this case: $1,592.40. Could different product choices have reduced this figure?

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The authors report no financial relationships relevant to this article.

Health-care costs continue to rise faster than inflation: Total health-care expenditures account for approximately 18% of gross domestic product in the United States. Physicians therefore face increasing pressure to take cost into account in their care of patients.[1] Cost-effectiveness and outcome quality continue to increase in importance as measures in many clinical trials that compare standard and alternative therapies. And women's health—specifically, minimally invasive gynecologic surgery—invites such comparisons.

Overall, conventional laparoscopic gynecologic procedures tend to cost less than laparotomy, a consequence of shorter hospital stays, faster recovery, and fewer complications.[2-5] What is not fully appreciated, however, is how choice of laparoscopic instrumentation and associated products affects surgical costs. In this article, which revisits and updates a 2013 OBG MANAGEMENT examination of cost-consciousness in the selection of equipment and supplies for

minimally invasive gynecologic surgery,[6] we review these costs in 2018. Our goal is to raise awareness of the role of cost in care among minimally invasive gynecologic surgeons.

In the sections that follow, we highlight several aspects of laparoscopic gynecologic surgery that can affect your selection of instruments and products, describing differences in cost as well as some distinctive characteristics of products. Note that our comparisons focus *solely* on cost—not on ease of utility, effectiveness, surgical technique, risk of complications, or any other assessment. Note also that numerous other instruments and devices are commercially available besides those we list.

Importantly, 2013 and 2018 costs are included in **TABLE 1**. Unless otherwise noted, costs are per unit. Changes in manufacturers and material costs and technologic advances have contributed to some, but not all, of the changes in cost between 2013 and 2018.

Variables to keep in mind

Even when taking cost into consideration, tailor your selection of instruments and supplies to your capabilities and comfort, as well as to the particular characteristics of the patient and the planned procedure. Also, remember that your institution might have arrangements with companies that supply minimally invasive instruments, and that such arrangements might limit your options, to some degree. Last, be aware that reprocessed ports and instruments are now available at a reduced cost. In short, we believe that it is crucial for surgeons to be cognizant of all products available to them prior to attending a surgical case.

Skin preparation and other preop considerations

Multiple preoperative skin preparations are available (**TABLE 1**). Traditionally, a povidone–iodine topical antiseptic, such as Betadine, has been used for skin and vaginal preparation prior to gynecologic surgery. Hibiclens and ChloraPrep are different combinations of chlorhexidine gluconate and isopropyl alcohol that act as broad-spectrum antiseptics.

ChloraPrep is applied with a wand-like applicator and contains a much higher concentration of isopropyl alcohol than Hibiclens (70% and 4%, respectively), rendering it more flammable. It also requires longer drying time before surgery can be started. Clear and tinted ChloraPrep formulations are available.

Uterine manipulators

Cannulation of the cervical canal allows for uterine manipulation, increasing intraoperative traction and exposure as well as visualization of the adnexae and peritoneal surfaces.

The Hulka-Kenwick is a reusable uterine manipulator that is fairly standard and easy to apply. Specialized, single-use manipulators also are available, including the Advincula Delineator and VCare Plus uterine manipulator/elevator. The VCare Plus manipulator consists of 2 opposing cups: one cup (available in 4 sizes, small to extra-large) fits around the cervix and defines the site for colpotomy; the other helps maintain pneumoperitoneum once a colpotomy is created.

The ZUMI (Zinnanti Uterine Manipulator Injector) is a rigid, curved shaft with an intrauterine balloon to help prevent expulsion. It also has an integrated injection channel to allow for intraoperative chromotubation.

The RUMI II System fits individual patient anatomy with various tip lengths and colpotomy cup sizes. The Advincula Arch Uterine Manipulator Handle is a reusable alternative to the articulating RUMI II and works with the RUMI II System Disposable Tip (**TABLE 1**).

Entry style and ports

The peritoneal cavity can be entered using either a closed (Veress needle) or open (Hasson) technique.[7,8] Closed entry might allow for quicker access to the peritoneal cavity. A 2015 Cochrane review of 46 randomized, controlled trials of 7,389 patients undergoing laparoscopy compared outcomes between laparoscopic entry techniques and found no

FAST TRACK

Surgeons need to be cognizant of all products available to them prior to attending a surgical case

TABLE 1 Cost of commonly used equipment for minimally invasive gynecologic surgery: 2018 compared with 2013[a]

Skin preparations			
Product	**Manufacturer**	**2013 Cost**	**2018 Cost**
Betadine, 118 mL	Medline	$0.64	$0.64
Hibiclens, 118 mL	Mölnlycke Health Care	$2.13	$2.12
ChloraPrep with tint, 26 mL	Becton, Dickinson	$6	$5.93

Uterine manipulators					
Product	**Manufacturer**	**Reusable**	**Dye-instillation capability**	**2013 Cost**	**2018 Cost**
Hulka-Kenwick	Novo Surgical	Yes	No	$103.50 plus $13 reprocessing fee	$103.50 plus $40 reprocessing fee
VCare Plus (medium)	CONMED	No	No	$88.51	$88.51
ZUMI Zinnanti	CooperSurgical	No	Yes	$29	$378.97 (12/box); $31.58 each
RUMI II Koh-Efficient (all sizes)	CooperSurgical	No	No	$90	$496 (5/box); $99.20 each
RUMI II System Disposable Tip (all sizes)	CooperSurgical	No	No	$43.87	$235.50 (5/box); $47.10 each
Advincula Delineator	CooperSurgical	No	No	—	$315 (3/box); $105 each
Advincula Arch Uterine Manipulator Handle	CooperSurgical	Yes	No	—	$579.50 plus $40 reprocessing fee

Entry devices and ports (selected)			
Product	**Manufacturer**	**2013 Cost[b]**	**2018 Cost**
SurgiNeedle, 120 mm	Covidien	—	$71.23 each
Bluntport Plus, Hasson 5-12 mm	Owens & Minor	$49.46	$26.26 ea
Pediport Locking Trocar, 5.5 mm	Covidien	$37.13	$202 (5/box); $40.40 each
VersaOne Bladed Trocar, 5 mm	Covidien	—	$109.08 (6/box); $18.18 each
Versaport Plus Pyramidal Bladed Trocar, 10 mm-15 mm	Covidien	—	$43.43
Step Insufflation Needle, 14G	Covidien	$15.72	$12.12 each
VersaStep Bladeless Trocar, 5 mm	Covidien	$43.28	$40.40
VersaStep Plus Bladeless Trocar, 12 mm	Covidien	$51.51	$151.50 (3/box); $50.50 each
Kii Fios First Entry, 5 mm × 100 mm	Applied Medical	$26.50	$360 (6/box); $60 each
Kii Balloon Blunt Tip, 12 mm × 100 mm	Applied Medical	$36.50	$420 (6/box); $70 each
ENDOPATH XCEL Bladeless Trocar, 5 mm × 100 mm	Ethicon	$160c	$180 (6/box); $30 each

[a]Costs are those at a typical large academic medical center.
[b]Prices are per unit, unless otherwise noted.
[c]The 2013 OBG MANAGEMENT article[6] included the price for the box but not for the individual unit.

TABLE 1 Cost of commonly used equipment for minimally invasive gynecologic surgery: 2018 compared with 2013[a] (continued)

Cutting and coagulation devices (selected)			
Product	**Manufacturer**	**2013 Cost[b]**	**2018 Cost**
Endo Shears (reprocessed)	Stryker Sustainability Solutions	—	$150 (6/box); $25 each
LigaSure Maryland LF1937	Covidien	—	$2,610 (6/box); $435 each
LigaSure Dolphin Tip, 5 mm/37 cm	Covidien	$395	$395
LigaSure Blunt Tip, 5 mm/37 cm	Covidien	$435	$1,920 (6/box); $320 each
Laparoscopic L Hook	ConMed Corp.	—	$172.80 (5/box); $34.56 each
PKS LYONS Dissecting Forceps	Olympus America	$221[c]	$221 (5/box); $44.20 each
HALO PKS Cutting Forceps, 5-mm/ 33-cm	Olympus America	—	$2,501.25 (5/box); $500.25 each
Thunderbeat	Olympus	$550	$1,900 (5/box); $380 each
Harmonic ACE +7, 5-mm/ 36-cm	Ethicon	—	$3,119.20 (6/box); $519.87 each
Enseal Curved Jaw, 5-mm/35-cm	Ethicon	$444.60	$2,481.69 (6/box); $413.62 each
Enseal Straight Jaw, 5-mm/45-cm	Ethicon	$446.47	$2,603.86 (6/box); $433.98 each

Tissue-removal devices				
Product	**Manufacturer**	**Reusability**	**2013 Cost**	**2018 Cost**
Olympus Contained Tissue Extraction System (PK Morcellator with Pneumoliner)	Olympus	Morcellator Yes Pneumoliner No	—	Morcellator $2,750 (5/box); $550 each (plus $40 reprocessing fee) Pneumoliner $2,750 (5/box); $550 each
Endo Catch	Covidien	No	$70	$35.35
LapSac Surgical Tissue Pouch	Cook Medical	No	—	$74.25

Sutures and skin adhesives (selected)			
Product	**Manufacturer**	**2013 Cost**	**2018 Cost**
2-0 PDS II, 27 in	Ethicon	$5.79	$340.63 (36/box); $9.44 each
2-0 V-Loc, 9 in	Covidien	$4.08	$208.20 (12/box); $17.35 each
4-0 Polysorb, 18 in	Covidien	$1.29	$2.75
4-0 Caprosyn, 18 in	Covidien	$3.21	$3.35
LiquiBand, 0.8 mL	CardinalHealth	$13.75	$13.88
DERMABOND Advanced, 0.7 mL	Ethicon	$23.25 (0.5 mL)	$241.37 (6/box); $40.23 each

[a]Costs are those at a typical large academic medical center.
[b]Prices are per unit, unless otherwise noted.
[c]The 2013 OBG MANAGEMENT article[6] included the price for the box but not for the individual unit.

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difference in major vascular or visceral injury between closed and open techniques at the umbilicus.[9] However, open entry was associated with a greater likelihood of successful entry into the peritoneal cavity.[9]

Left upper-quadrant (Palmer's point) entry is another option when adhesions are anticipated or abnormal anatomy is encountered at the umbilicus.

In general, complications related to laparoscopic entry are rare in gynecologic surgery, ranging from 0.18% to 0.5% of cases in studies.[8,10,11] A minimally invasive surgeon might prefer one entry technique over another but should be able to perform both methods competently and recognize when a particular technique is warranted.

Choosing a port

Laparoscopic ports usually range from 5 mm to 12 mm and can be fixed or variable in size.

The primary port, usually placed through the umbilicus, can be a standard, blunt, 10-mm (Bluntport Plus Hasson) port, or it can be specialized to ease entry of the port or stabilize the port once it is introduced through the skin incision.

Optical trocars have a transparent tip that allows the surgeon to visualize the abdominal wall entry layer by layer using a 0° laparoscope, sometimes after pneumoperitoneum is created with a Veress needle. Other specialized ports include those that have balloons or foam collars, or both, to secure the port without traditional stay sutures on the fascia and to minimize leakage of pneumoperitoneum.

Accessory ports

When choosing an accessory port type and size, it is important to anticipate which instruments and devices, such as an Endo Catch bag, suture, or needle, will need to pass through it. Also, know whether 5-mm and 10-mm laparoscopes are available, and anticipate whether a second port with insufflation capabilities will be required.

The Pediport Locking Trocar is a user-friendly, 5-mm bladed port that deploys a mushroom-shaped stabilizer to prevent dislodgement. The Versaport bladed trocar has a spring-loaded entry shield, which slides over the blade to protect it once the peritoneal cavity is entered.

VersaStep Bladeless Trocars are introduced after a Step Insufflation Needle has been inserted. These trocars create a smaller fascial defect than conventional bladed trocars for an equivalent cannula size (**TABLE 1**).

Cutting and coagulating

Both monopolar and bipolar electrosurgical techniques are commonly employed in gynecologic laparoscopy. A wide variety of disposable and reusable instruments are available for monopolar energy, such as scissors, a hook, and a spatula.

Bipolar devices also can be disposable or reusable. Although bipolar electrosurgery minimizes injury to surrounding tissues by containing the current within the jaws of the forceps, it cannot cut or seal large vessels. As a result, several advanced bipolar devices with sealing and transecting capabilities have emerged (the LigaSure line of devices, Enseal). Ultrasonic devices, such as the Harmonic ACE, also can coagulate and cut at lower temperatures by converting electrical energy to mechanical energy (**TABLE 1**).

Suture material

Aspects of minimally invasive gynecologic surgery that require the use of suture include, but are not limited to, closure of the vaginal cuff, oophoropexy, and reapproximation of the ovarian cortex after cystectomy. Synthetic and delayed absorbable sutures, such as PDS II, are used frequently. The barbed suture also has gained popularity because it anchors to tissue without the need for intracorporeal or extracorporeal knots (**TABLE 1**).

Tissue removal

Adnexae and pathologic tissue, such as dermoid cysts, can be removed intact from the peritoneal cavity using an Endo Catch Single Use Specimen Pouch, a polyurethane sac. Careful use, with placement of the ovary with the cyst into the pouch prior to cystectomy, can contain or prevent spillage outside the bag.

FAST TRACK

When choosing port type and size, anticipate needed instruments and devices (such as an Endo Catch bag, suture, or needle) will need to pass through it

A large uterus that cannot be extracted through a colpotomy can be manually morcellated. Appropriate candidates can undergo power morcellation using an FDA-approved device. (**TABLE 1**), allowing for the removal of smaller pieces through a small laparoscopic incision or the colpotomy.

Issues surrounding morcellation continue to require that gynecologic surgeons understand FDA recommendations. In 2014, the FDA issued a safety communication that morcellation is "contraindicated in gynecologic surgery if tissue is known or suspected to be malignant; it is contraindicated for uterine tissue removal with presumed benign fibroids in perimenopausal women."[12] A black-box warning was issued that uterine tissue might contain unsuspected cancer.

A task force created by AAGL addressed key issues in this controversy.

AAGL then provided guidelines related to morcellation[13]:

- Do not use morcellate in the setting of known malignancy.
- Provide appropriate preoperative evaluation with up-to-date Pap smear screening and image analysis.
- Increasing age significantly increases the risk of leiomyosarcoma, especially in a postmenopausal woman.
- Fibroid growth is not a reliable sign of malignancy.
- Do not use a morcellator if the patient is at high risk for malignancy.
- If leiomyosarcoma is the presumed pathology, await the final pathology report before proceeding with hysterectomy.
- Concomitant use of a bag might mitigate the risk of tissue spread.
- Obtain informed consent before proceeding with morcellation.

Skin closure

Final subcuticular closure can be accomplished using sutures or skin adhesive. Sutures can be synthetic, absorbable monofilament (Caprosyn), or synthetic, absorbable, braided multifilament (Polysorb).

Skin adhesive closes incisions quickly, avoids inflammation related to foreign bodies, and can ease patients' concerns that sometimes arise when absorbable suture persists postoperatively (**TABLE 1**).

The impact of physician experience

Physician experience has been shown to reduce cost while maintaining quality of care.[14] That was the conclusion of researchers who undertook a retrospective study, addressing cost and clinical outcomes, of senior and junior attending physicians who performed laparoscopic-assisted vaginal hysterectomy on 120 patients. Studies such as these often lead to clinical pathways to facilitate cost-effective quality care.

CASE Same outcome at lower cost

The hypothetical 43-year-old patient in the opening case undergoes laparoscopic hysterectomy for treatment of uterine fibroids and menorrhagia. In this scenario, however, the surgeon makes the following product choices:

- **The patient is prepped with Hibiclens.**
- **A VCare Plus uterine manipulator is placed.**
- **Laparoscopic ports include a VersaStep Plus Bladeless Trocar with Step Insufflation Needle; Versaport Plus Pyramidal Bladed Trocar; and 2 VersaOne Bladed trocars.**
- **The surgeon uses the PKS LYONS Dissecting Forceps and reprocessed Endo Shears to perform the hysterectomy.**
- **The uterus is enclosed in an Endo Catch bag and removed through the minilaparotomy site.**
- **The vaginal cuff is closed using 2-0 V-Loc barbed suture. Skin incisions are closed with 4-0 Polysorb, a polyglycolic acid absorbable suture.**

The cost of this set of products? $360.44 or, roughly, $1,231.96 less than the set-up described in the case at the beginning of this article (**TABLE 2**).

Summing up

Here are key points to take away from this analysis and discussion:

FAST TRACK

Physician experience reduces cost while maintaining quality of care

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- As third-party payers and hospitals continue to evaluate surgeons individually and compare procedures from surgeon to surgeon, reimbursement might be stratified—thereby favoring physicians who demonstrate both quality outcomes *and* cost containment.
- There are many ways a minimally invasive surgeon can implement cost-conscious choices that have little or no impact on the quality of outcome.
- Surgeons who are familiar with surgical instruments and models available at their institution are better prepared to make wise cost-conscious decisions. (See "Caregivers should keep cost in mind: Here's why," in the Web version of this article at https://www.mdedge.com/obgyn.)

TABLE 2 Cost, and savings, for surgical products used in the opening and concluding cases[a]

Opening case		Concluding case		Savings
Tool	**Cost**	**Tool**	**Cost**	
Skin preparation				
ChloraPrep with tint, 26 mL	$5.93	Hibiclens, 118 mL	$2.12	$3.81
Uterine manipulator				
RUMI II system	$146.30 ($99.20 [cup] + $47.10 [tip])	VCare Plus (medium)	$88.51	$57.79
Laparoscopic ports				
Kii Balloon Blunt-Tip, 12 mm × 100 mm	$70	VersaStep Plus, 12mm + Step Insufflation Needle, 14G	$62.62 ($50.50 + $12.12)	$7.38
Versaport Plus Pyramidal Bladed Trocar, 10 mm-15 mm	$43.43	Versaport Plus Pyramidal Bladed Trocar, 10 mm-15 mm	$43.43	equal
Kii Fios First Entry, 5 x 100 mm	$120 (2 × $60)[b]	VersaOne Bladed Trocar, 5 mm	$36.36 (2 × $18.18)	$83.64
Energy devices				
Harmonic ACE +7, 5 mm/36 cm	$519.87	PKS LYONS Dissecting Forceps	$44.20	$450.67
—	—	Endo Shears (reprocessed)	$25	—
Tissue extraction				
Olympus Contained Tissue Extraction System (PK Morcellator with Pneumoliner)	$1,140 Morcellator $550 plus $40 reprocessing fee Pneumoliner $550	Endo Catch	$35.35	$554.65[c]
Sutures and skin adhesives				
2-0 PDS II, 27 in (6 interrupted sutures)	$56.64 (6 × $9.44)	2-0 V-Loc barbed suture, 9 in	$17.35	$39.29
DERMABOND Advanced, 0.7 mL	$40.23	4-0 Polysorb, 18 in (2 sutures)	$2.75 x 2 = $5.50	$34.73
Cost and savings				
Total cost	$1,592.40		$360.44	
Total savings				$1,231.96

[a]Costs are those at a typical large academic medical center.

[b]Two ports were used in this case.

[c]Because the initial purchase price of the reusable morcellator has been covered.

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- Cost is not the only indicator of value: The surgeon must know how to apply tools correctly and be familiar with their limitations, and should choose instruments and products for their safety and ease of use. More often than not, a surgeon's training and personal experience define—and sometimes restrict—the choice of devices.
- Last, it makes sense to have instruments and devices readily available in the operating room at the start of a case, to avoid unnecessary surgical delays. However, we recommend that you refrain from opening these tools until they are required intraoperatively. It is possible that the case will require conversion to laparotomy or that, after direct visualization of the pathology, different ports or instruments are required.

Acknowledgments

The authors would like to thank Meredith Snook, MD, who was coauthor of the original 2013 article[6] and Kathleen Riordan, BSN, RN, for assistance in gathering specific cost-related information for this article.

References

1. Centers for Medicare & Medicaid Services. National health expenditure projections 2017-2026: Forecast summary. www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/ForecastSummary.pdf. Accessed November 3, 2018.
2. Vilos GA, Alshimmiri MM. Cost-benefit analysis of laparoscopic versus laparotomy salpingo-oophorectomy for benign tubo-ovarian disease. *J Am Assoc Gynecol Laparosc*. 1995;2(3):299-303.
3. Gray DT, Thorburn J, Lundor P, et al. A cost-effectiveness study of a randomised trial of laparoscopy versus laparotomy for ectopic pregnancy. *Lancet*. 1995;345(8958):1139-1143.
4. Chapron C, Fauconnier A, Goffinet F, et al. Laparoscopic surgery is not inherently dangerous for patients presenting with benign gynaecologic pathology. Results of a meta-analysis. *Hum Reprod*. 2002;17(5):1334-1342.
5. Benezra V, Verma U, Whitted RW. Comparison of laparoscopy versus laparotomy for the surgical treatment of ovarian dermoid cysts. *Obstet Gynecol Surv*. 2006;61(1):20-21.
6. Sanfilippo JS, Snook ML. Cost-conscious choices for minimally invasive gynecologic surgery. *OBG Manag*. 2013;25(11):40-41,44,46-48,72.
7. Hasson HM. A modified instrument and method for laparoscopy. *Am J Obstet Gynecol*. 1971;110(6):886-887.
8. Ott J, Jaeger-Lansky A, Poschalko G, et al. Entry techniques in gynecologic laparoscopy—a review. *Gynecol Surg*. 2012;9(2):139-146.
9. Ahmad G, Gent D, Henderson D, et al. Laparoscopic entry techniques. Cochrane Database Syst Rev. 2015;8:CD006583.
10. Hasson HM, Rotman C, Rana N, et al. Open laparoscopy: 29-year experience. *Obstet Gynecol*. 2000;96(5 Pt 1):763-766.
11. Schäfer M, Lauper M, Krähenbühl L. Trocar and Veress needle injuries during laparoscopy. *Surg Endosc*. 2001;15(3):275-280.
12. Immediately in effect guidance document: product labeling for laparoscopic power morcellators. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration Center for Devices and Radiological Health; November 25, 2014. www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM424123.pdf. Accessed November 3, 2018.
13. Tissue Extraction Task Force Members. Morcellation during uterine tissue extraction: an update. *J Minim Invasive Gynecol*. 2018;25(4):543-550.
14. Chang WC, Li TC, Lin CC. The effect of physician experience on costs and clinical outcomes of laparoscopic-assisted vaginal hysterectomy: a multivariate analysis. *J Am Assoc Gynecol Laparosc*. 2003;10(3):356-359.

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E/M service should not be billed separately, and the use of modifiers becomes even more important than with office services.

Applicable modifiers for use with hospital surgery can include all those for outpatient services plus:

- **50,** *Bilateral procedure* (for which you may be paid up to 150% of the allowable)
- **58,** *Staged or related procedure during the postoperative period* (this may be paid at the full allowable)
- **62,** *Co-surgeons* (both surgeons bill the same CPT code and both document their involvement in the surgery). Medicare will reimburse each surgeon 62.5% of the allowable.
- **78,** *Return to the operating room for an unplanned related procedure* (the full allowable may be reduced by some payers owing to their belief that this is soon after the original procedure so intraoperative time only is considered).

FAST TRACK

If you receive a denial or unfair payment reduction, analyze the rejection for the cause and change your billing and reporting practices to improve future reimbursements

Be savvy about surgical bundles

Here, it is important to understand all published bundling edits for multiple procedures performed by the same surgeon at the same surgical session. If a code combination is never allowed but the surgery is more intense due to additional work required, a modifier **-22** may be your only option. Again, clear, concise documentation of the additional work is imperative to receive the additional payment.

When a modifier is allowed, it generally will be one that denotes a procedure done on bilateral organs (such as the ovaries) when there is no extensive code to cover all of the work or when the additional procedure is "distinct" and meets the criteria for using a modifier **59**.

Medicare has expanded the modifier **-59** into additional modifiers to further explain the situation. These additional modifiers are:

- **XE,** *A service that is distinct because it occurred during a separate encounter on the same date of service*
- **XS**, *A service that is distinct because it was performed on a separate organ/structure*
- **XP,** *A service that is distinct because it was performed by a different practitioner*
- **XU,** *The use of a service that is distinct because it does not overlap usual components of the main service.*

Standards of care: Some steps are inherent to the surgery

Expect to receive claim denials if you bill separately for adhesiolysis during a surgical procedure. Every payer considers this procedure related to access to the surgical site and will deny separate coding. If the lysis was truly significant in terms of work, try reporting the modifier **22** and provide adequate documentation.

Other procedures at the time of surgery that generally are not paid for include 1) examination under anesthesia, 2) any procedure done to check the surgeon's work (for example, cystoscopy, especially when done after urinary or pelvic reconstruction procedures, or chromotubation following extensive ovariolysis), 3) placement of catheters, and 4) placement of devices to alleviate postsurgical pain.

Bottom line

Maximizing reimbursement involves good documentation, correct CPT codes linked to specific and accurate medical indications, the use of appropriate modifiers, and listing codes in order of their relative values from highest to lowest.

Should a denial or unfair reduction in payment come your way, analyze the rejection to determine the cause and make billing and reporting changes as needed to improve your future reimbursements. ●

To prevent fractures, treating only women with osteoporosis is not enough

In older osteopenic women, intravenous zoledronic acid effectively prevents fragility fractures

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The conventional bone mineral density threshold for initiating treatment to prevent fragility fractures is a T-score of less than -2.5 (the World Health Organization criteria for osteoporosis).[1] However, most fractures experienced by postmenopausal women occur not in osteoporotic women but in those with low bone mass (osteopenia).[2]

Investigators in New Zealand recently published the results of a randomized controlled trial they conducted to determine the efficacy of zoledronate (zoledronic acid) in preventing fractures in postmenopausal women.[3] They enrolled women age 65 years or older with osteopenia of the hip and randomly assigned the participants to 4 intravenous infusions of 5 mg zoledronic acid or placebo at 18-month intervals for 6 years.

Zoledronic acid reduced fracture risk

The trial included 2,000 postmenopausal women (mean age at baseline, 71 years; 94% European ethnicity) with a T-score of -1.0 to -2.5 at either the total hip or the femoral neck on either side. Both hips were assessed. The women received either zoledronic acid treatment or placebo in a 1:1 ratio. Candidates were excluded if they regularly used bone-active drugs in the previous year.

Fragility fractures were noted in 190 women in the placebo group and in 122 women treated with zoledronic acid (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.50–0.79, $P<.001$). The number of women that would need to be treated to prevent the occurrence of a fracture in 1 woman was 15.

Compared with placebo, zoledronic acid also lowered the risk of nonvertebral, symptomatic, and vertebral fractures as well as height loss ($P\leq.003$ for these 4 comparisons). Relatively few adverse events occurred with zoledronic acid treatment. No atypical femoral fractures or cases of osteonecrosis of the jaw occurred in either group.

Trial closes the knowledge gap regarding treatment thresholds

This trial's findings underscore the importance of age as a risk factor for fragility fracture and clarify that pharmacologic treatment is appropriate not only for women with osteoporosis but also for older postmenopausal women with osteopenia.

As the authors point out, administration of zoledronic acid less often than annually can be highly effective in preventing fractures; they recommend future trials of administration of this intravenous bisphosphonate at intervals less frequent than 18 months. Although the absence of atypical femoral fractures or cases of osteonecrosis of the jaw is reassuring, the authors note that their trial was underpowered to assess these uncommon events. ●

The author reports no financial relationships relevant to this article.

References

1. World Health Organization. WHO Scientific Group on the assessment of osteoporosis at primary health care level. Summary meeting report, Brussels, Belgium, 5-7 May 2004. https://www.who.int/chp/topics/Osteoporosis.pdf. Accessed November 19, 2018.
2. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med.* 2004;164:1108-1112.
3. Reid IR, Horne AM, Mihov B, et al. Fracture prevention with zoledronate in older women with osteopenia. *N Engl J Med.* 2018. doi:10.1056/NEJMoa1808082.

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The author reports no financial relationships relevant to this article.

More than one-quarter of women with a hip fracture will be dead within 12 months; maintaining and protecting bone health postmenopause is paramount. In this article: WHI findings on hip fracture, treatment-level fracture scores in women older and younger than age 65, and updated USPSTF recommendations for screening.

IN THIS ARTICLE

As ObGyns, we are the first-line health care providers for our menopausal patients in terms of identifying, preventing, and initiating treatment for women at risk for fragility fractures. Osteoporosis is probably the most important risk factor for bone health, although sarcopenia, frailty, poor eyesight, and falls also play a significant role in bone health and fragility fracture.

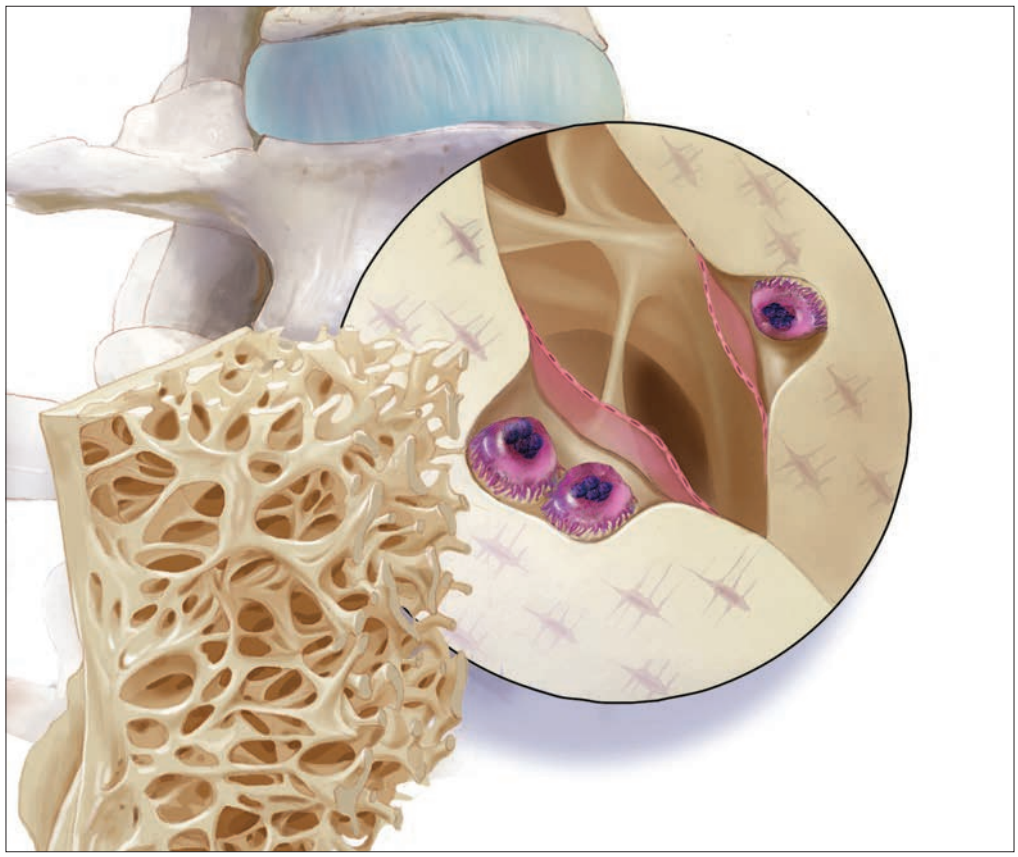
In 2005, more than 2 million incident fractures were reported in the United States, with a total cost of $17 billion.[1] By 2025, annual fractures and costs are expected to rise by almost 50%. People who are 65 to 74 years of age will likely experience the largest increase in fracture—greater than 87%.[1]

Findings from the Women's Health Initiative study showed that the number of women who had a clinical fracture in 1 year exceeded all the cases of myocardial infarction, stroke, and breast cancer combined.[2] Furthermore, the morbidity and mortality rates for fractures are staggering. Thirty percent of women with a hip fracture will be dead within 1 year.[3] So, although many patients fear developing breast cancer, and cardiovascular disease remains the number 1 cause of death, the impact of maintaining and protecting bone health cannot be emphasized enough.

WHI incidental findings: Hormone-treated menopausal women had decreased hip fracture rate

Manson JE, Aragaki AK, Rossouw JE, et al; WHI Investigators. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. JAMA. 2017;318:927-938.

Manson and colleagues examined the total and cause-specific cumulative mortality of the 2 Women's Health Initiative (WHI) hormone therapy trials. This was an observational follow-up of



US multiethnic postmenopausal women aged 50 to 79 years (mean age at baseline, 63.4 years) enrolled in 2 randomized clinical trials between 1993 and 1998 and followed up through December 31, 2014. A total of 27,347 women were randomly assigned to treatment.

Treatment groups

Depending on the presence or absence of a uterus, women received conjugated equine estrogens (CEE, 0.625 mg/d) plus medroxyprogesterone acetate (MPA, 2.5 mg/d) (n = 8,506) or placebo (n = 8,102) for a median of 5.6 years or CEE alone (n = 5,310) versus placebo (n = 5,429) for a median of 7.2 years. All-cause mortality (the primary outcome) and cause-specific mortality (cardiovascular disease mortality, cancer mortality, and other major causes of mortality) were analyzed in the 2 trials pooled and in each trial individually.

All-cause and cause-specific mortality findings

Mortality follow-up was available for more than 98% of participants. During the cumulative 18-year follow-up, 7,489 deaths occurred. In the overall pooled cohort, all-cause mortality in the hormone therapy group was 27.1% compared with 27.6% in the placebo group (hazard ratio [HR], 0.99 [95% confidence interval (CI), 0.94–1.03]). In the CEE plus MPA group, the HR was 1.02 (95% CI, 0.96–1.08). For those in the CEE-alone group, the HR was 0.94 (95% CI, 0.88–1.01).

In the pooled cohort for cardiovascular mortality, the HR was 1.00 (95% CI, 0.92–1.08 [8.9% with hormone therapy vs 9.0% with placebo]). For total cancer mortality, the HR was 1.03 (95% CI, 0.95–1.12 [8.2% with hormone therapy vs 8.0% with placebo]). For other causes, the HR was 0.95 (95% CI, 0.88–1.02 [10.0% with hormone therapy vs 10.7% with placebo]). Results did not differ significantly between trials.

FAST TRACK

The 2017 WHI investigators observed 27,347 women aged 50 to 79 years who were treated with hormone therapy or placebo and followed for a median of 5.6 years (CEE plus MPA) or 7.2 years (CEE alone)

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ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Postmenopausal hormone therapy is arguably the most effective "bone drug" available. While all other antiresorptive agents show hip fracture efficacy only in subgroup analyses of the highest-risk patients (women with established osteoporosis, who often already have pre-existing vertebral fractures), the hormone-treated women in the WHI—who were not chosen for having low bone mass (in fact, dual-energy x-ray absorptiometry [DXA] scores were not even recorded)—still had a statistically significant decrease in hip fracture as an adverse event when compared with placebo-treated women. Increasing data on the long-term safety of hormone therapy in menopausal patients will perhaps encourage its greater use from a bone health perspective.

Key takeaway

The study authors concluded that among postmenopausal women, hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.

Appropriate to defer DXA testing to age 65 when baseline FRAX score is below treatment level

FAST TRACK

In a study of 4,957 women ≥67 years with normal BMD or osteopenia, the estimated time for 10% of women to transition to osteoporosis was 16.8 years for those with normal BMD

Gourlay ML, Overman RA, Fine JP, et al; Women's Health Initiative Investigators. Time to clinically relevant fracture risk scores in postmenopausal women. Am J Med. 2017;130:862.e15-862.e23.

Gourlay ML, Fine JP, Preisser JS, et al; Study of Osteoporotic Fractures Research Group. Bone-density testing interval and transition to osteoporosis in older women. N Engl J Med. 2012;366:225-233.

Many clinicians used to (and still do) order bone mineral density (BMD) testing at 23-month intervals because that was what insurance would allow. Gourlay and colleagues previously published a study on BMD testing intervals and the time it takes to develop osteoporosis. I covered that information in previous Updates.[4,5]

To recap, Gourlay and colleagues studied 4,957 women, 67 years of age or older, with normal BMD or osteopenia and with no history of hip or clinical vertebral fracture or of treatment for osteoporosis; the women were followed prospectively for up to 15 years. The estimated time for 10% of women to make the transition to osteoporosis was 16.8 years for those with normal BMD, 4.7 years for those with moderate osteopenia, and 1.1 years for women with advanced osteopenia.

Today, FRAX is recommended to assess need for treatment

Older treatment recommendations involved determining various osteopenic BMD levels and the presence or absence of certain risk factors. More recently, the National Osteoporosis Foundation and many medical societies, including the American College of Obstetricians and Gynecologists, have recommended using the FRAX fracture prediction algorithm (available at https://www.shef.ac.uk/FRAX) instead of T-scores to consider initiating pharmacotherapy.

The FRAX calculation tool uses information such as the country where the patient lives, age, sex, height, weight, history of previous fracture, parental fracture, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, alcohol use of 3 or more units per day, and, if available,

BMD determination at the femoral neck. It then yields the 10-year absolute risk of hip fracture and any major osteoporotic fracture for that individual or, more precisely, for an individual like that.

In the United States, accepted levels for cost-effective pharmacotherapy are a 10-year absolute risk of hip fracture of 3% or major osteoporotic fracture of 20%.

Age also is a key factor in fracture risk assessment

Gourlay and colleagues more recently conducted a retrospective analysis of new occurrence of treatment-level fracture risk scores in postmenopausal women (50 years of age and older) before they received pharmacologic treatment and before they experienced a first hip or clinical vertebral fracture.

In 54,280 postmenopausal women aged 50 to 64 without a BMD test, the time for 10% to develop a treatment-level FRAX score could not be estimated accurately because of the rarity of treatment-level scores. In 6,096 women who had FRAX scores calculated *with* their BMD score, the estimated time to treatment-level FRAX was 7.6 years for those 65 to 69 and 5.1 years for 75 to 79 year olds. Furthermore, of 17,967 women aged 50 to 64 with a screening-level FRAX at baseline, only 100 (0.6%) experienced a hip or clinical vertebral fracture by age 65.

The investigators concluded that, "Postmenopausal women with sub-threshold fracture risk scores at baseline were unlikely to develop a treatment-level FRAX score between ages 50 and 64 years. After age 65, the increased incidence of treatment-level fracture risk scores, osteoporosis, and major osteoporotic fracture supports more frequent consideration of FRAX and bone mineral density testing."

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Many health care providers begin BMD testing early in menopause. Bone mass results may motivate patients to initiate healthy lifestyle choices, such as adequate dietary calcium, vitamin D supplementation, exercise, moderate alcohol use, smoking cessation, and fall prevention strategies. However, providers and their patients should be aware that if the fracture risk is beneath the threshold score at baseline, the risk of experiencing an osteoporotic fracture prior to age 65 is extremely low, and this should be taken into account before prescribing pharmacotherapy. Furthermore, as stated, FRAX can be performed without a DXA score. When the result is beneath a treatment level in a woman under 65, DXA testing may be deferred until age 65.

FAST TRACK

Providers and their patients should be aware that if the fracture risk is beneath the BMD threshold score at baseline, the risk of an osteoporotic fracture prior to age 65 is extremely low

USPSTF offers updated recommendations for osteoporosis screening

US Preventive Services Task Force, Curry SJ, Krist AH, Owens DK, et al. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:2521-2531.

The 2018 updated osteoporosis screening recommendations from the United States Preventative Services Task Force (USPSTF) may seem contradictory to the conclusions of Gourlay and colleagues discussed above. They are not.

The USPSTF authors point out that by 2020, about 12.3 million US individuals older than 50 years are expected to have osteoporosis. Osteoporotic fractures (especially hip fractures) are associated with limitations in ambulation, chronic pain and disability, loss of independence, and decreased quality of life. In fact, 21% to 30% of people who sustain a hip fracture die within 1 year. As the US population continues to age, the potential preventable burden will likely increase.

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Evidence on bone measurement tests, risk assessment tools, and drug therapy efficacy

The USPSTF conducted an evidence review on screening for and treatment of osteoporotic fractures in women as well as risk assessment tools. The task force found the evidence convincing that bone measurement tests are accurate for detecting osteoporosis and predicting osteoporotic fractures. In addition, there is adequate evidence that clinical risk assessment tools are moderately accurate in identifying risk of osteoporosis and osteoporotic fractures. Furthermore, there is convincing evidence that drug therapies reduce subsequent fracture rates in postmenopausal women.

The USPSTF recommends the following:

- For women aged 65 and older, screen for osteoporosis with bone measurement testing to prevent osteoporotic fractures.
- For women younger than 65 who are at increased risk for osteoporosis based on formal clinical risk assessment tools, screen for osteoporosis with bone measurement testing to prevent osteoporotic fractures. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

We all agree that women older than 65 years of age should be screened with DXA measurements of bone mass. The USPSTF says that in women under 65, a fracture assessment tool like FRAX, which does not require bone density testing to yield an individual's absolute 10-year fracture risk, should be used to determine *if* bone mass measurement by DXA is, in fact, warranted. This recommendation is further supported by the article by Gourlay and colleagues, in which women aged 50 to 64 with subthreshold FRAX scores had a very low risk of fracture prior to age 65.

FAST TRACK

The USPSTF found the evidence convincing that bone measurement tests are accurate for detecting osteoporosis and predicting osteoporotic fractures

References

1. Burge R, Dawson-Hughes B, Solomon DH, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res.* 2007;22:465-475.
2. Cauley JA, Wampler NS, Barnhart JM, et al; Women's Health Initiative Observational Study. Incidence of fractures compared to cardiovascular disease and breast cancer: the Women's Health Initiative Observational Study. *Osteoporos Int.* 2008;19:1717-1723.
3. Brauer CA, Coca-Perraillon M, Cutler DM, et al. Incidence and mortality of hip fractures in the United States. *JAMA.* 2009;302:1573-1579.
4. Goldstein SR. Update on osteoporosis. *OBG Manag.* 2012;24:16-21.
5. Goldstein SR. 2017 update on bone health. *OBG Manag.* 2017;29-32, 48.

Coming soon...

- **FDA approves HPV vaccine for men and women aged 27–45 years. How should we counsel our patients?**
  Anupama Kotha, MD; Joseph Sanfilippo, MD
- **Update on obstetrics**
  Jaimey Paulie, MD
- **Should we abandon minimally invasive surgery for cervical cancer?**
  Mary M. Mullen, MD; David G. Mutch, MD
- **Managing vasomotor and genitourinary symptoms in breast cancer survivors**
  JoAnn Pinkerton, MD

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converted to ethinyl estradiol.[2] The conversion occurs at a very low rate, likely less than 0.4%.[3] At a norethindrone acetate dose of 5 mg daily, aromatization would result in the production of less than 2 µg of ethinyl estradiol daily.

Dr. Ribot advocates for surgery as the primary treatment of pelvic pain caused by endometriosis. I agree with Dr. Ribot that, for severe pain caused by deep infiltrating endometriosis, surgery is an optimal approach. However, for women with pelvic pain and Stage I endometriosis, hormonal treatment after initial surgical diagnosis and treatment reduces pain recurrence and repetitive surgical procedures.[4]

References

1. Vercellini P, Bracco B, Mosconi P, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. *Fertil Steril*. 2016;105:734-743.
2. Barbieri RL, Petro Z, Canick JA, et al. Aromatization of norethindrone to ethinyl estradiol by human placental microsomes. *J Clin Endocrinol Metab*. 1983;57:299-303.
3. Chu MC, Zhang X, Gentzschein E, et al. Formation of ethinyl estradiol in women during treatment with norethindrone acetate. *J Clin Endocrinol Metab*. 2007;92:2205-2207.
4. Soliman AM, Bonafede M, Farr AM, et al. Analysis of subsequent surgery rates among endometriosis patients who underwent surgery with and without concomitant leuprolide acetate therapy. *Curr Med Res Opin*. 2016;32:1073-1082.

Treating endometriosis pain: Not just one and done

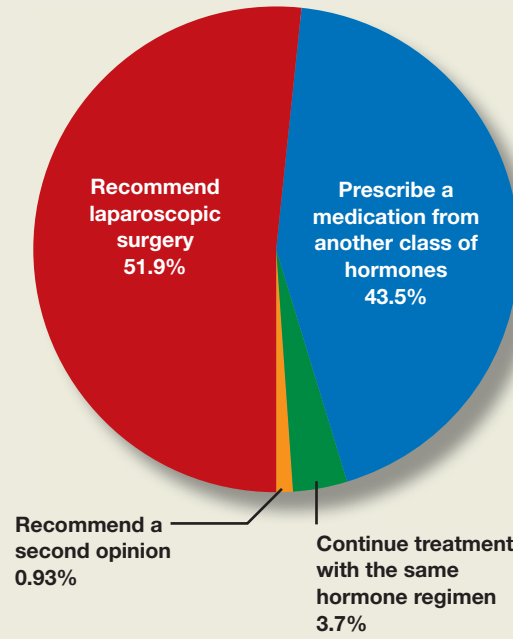
In his article, "Optimize the medical treatment of endometriosis—Use all available medications" (August 2016), OBG MANAGEMENT Editor in Chief Robert L. Barbieri, MD, discussed the various hormonal options ObGyns can prescribe for endometriosis pain when use of one drug has stopped being efficacious. Alternatives to a first-line treatment, such as continuous low-dose estrogen-progestin contraceptives, include progestin-only medications, gonadotropin-releasing hormone analogues, and androgens.

Recently, OBG MANAGEMENT posed this query to readers in a website poll: "Continued endometriosis-related pelvic pain: What's your next step?" Here's how they responded.

Poll results

More than 100 readers cast their vote:

- **51.9% (56 readers)** recommend laparoscopic surgery
- **43.5% (47 readers)** would prescribe a medication from another class of hormones
- **3.7% (4 readers)** would continue treatment with the same hormone regimen
- **0.93% (1 reader)** recommended a second opinion



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Please include the city and state in which you practice.

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11. Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: a multivariate analysis of over 1000 patients. *Hum Reprod.* 2007;22(1):266-271.
12. Fedele L, Parazzini F, Bianchi S. Stage and localization of pelvic endometriosis and pain. *Fertil Steril.* 1990;53(1):155-158.
13. Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. *Science.* 2005;308(5728):1587-1589.
14. Giamberardino MA, Tana C, Costantini R. Pain thresholds in women with chronic pelvic pain. *Curr Opin Obstet Gynecol.* 2014;26(4):253-259.
15. Giamberardino MA, Berkley KJ, Affaitati G. Influence of endometriosis on pain behaviors and muscle hyperalgesia induced by a ureteral calculosis in female rats. *Pain.* 2002;95(3):247-257.
16. As-Sanie S, Kim J, Schmidt-Wilcke T. Functional connectivity is associated with altered brain chemistry in women with endometriosis-associated chronic pelvic pain. *J Pain.* 2016;17(1):1-13.

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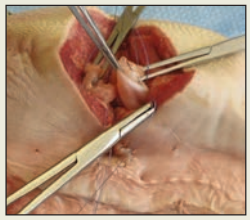
OBG MANAGEMENT

Instructional video for fourth-degree obstetric laceration repair using modified beef tongue model

JOSEPH MALEK, MD; JANA D. ILLSTON, MD; ALICIA C. BALLARD, MD; HOLLY E. RICHTER, PHD, MD



In this video, the authors demonstrate anatomic considerations and outline the steps in the repair of a fourth-degree obstetric laceration. Proper technique for repair, as well as each step of the repair, is demonstrated, including repair of: the anal epithelium with a second imbricating layer through the anorectal muscularis and submucosa; the internal anal sphincter; the external anal sphincter in posterior, inferior, superior, and anterior fashion; and the second-degree portion of the vaginal laceration and perineal body.

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enrolled 524 women into a cohort study in which they received their desired SARC method. In addition, 392 women agreed to be enrolled in a randomized clinical trial comparing women beginning a LARC method for the first time with a group receiving 1 of the 2 SARC methods.

Importance of covered costs. Of note, the women in the randomized trial had the costs of the insertion or removal of the LARC method covered; those randomly assigned to the comparative SARC arm had the costs of their oral contraceptives (OCs) or depot medroxyprogesterone acetate (DMPA) covered for the first year of use. Underwriting the costs in the randomized study was likely important for study recruitment, since 47% of participants who were randomized to the LARC group cited cost as one of the reasons they did not try a LARC method previously.

Satisfaction with contraceptive method. In addition to the differences in continuation rates and pregnancy rates noted, it is interesting that, among women who tried a LARC method and who had some persistent negative feelings about the method, 65.9% would try the method again.

Satisfaction levels were estimated using 3 choices, with "happiness" being the highest level of satisfaction, followed by "neutral" and "unhappy." At 24 months, the number of women indicating happiness was similar among the 3 study groups: 71.4% for the LARC randomized group, 75.0% for the randomized SARC group, and 77.6% for the preferred SARC cohort group.

Among women who discontinued their LARC method, occurrence of adverse effects was the reason given 74.2% of the time, while among SARC method users in both groups there was no dominant reason for discontinuation. Also, among women who discontinued their method, the percentage indicating happiness was 32.2% for the LARC randomized group compared with 69.9% and 68.2% for the randomized and preference cohort SARC groups, respectively.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Women who use LARC methods, even if they have reservations about using them, have high efficacy and continuation rates compared with women using OCs or DMPA, as well as a high level of satisfaction, particularly when cost and access barriers are removed. Adequate balanced counseling about the advantages and disadvantages of LARC methods may convince some women who harbor concerns to try a LARC method if cost is not a significant barrier. Since adverse effects are the major reason for discontinuation, potential users should be counseled adequately about their occurrence and about the potential approaches that can be used to try to ameliorate them should they occur.

RONALD T. BURKMAN, MD

Study strengths and weaknesses

This study had several strengths. The population from which the study groups were obtained was demographically diverse and was appropriate for determining if women with reservations about LARC methods could have satisfactory outcomes similar to women who self-select LARC methods. Further, the 24 months of observations indicate that, for the most part, satisfaction persisted.

One of the study's shortcomings is the limited data on the subsets, that is, the specific method chosen, within each of the study groups. ●

Reference

1. Foster DG, Barar R, Gould H, et al. Projections and opinions from 100 experts in long-acting reversible contraception. Contraception. 2015;92:543-552.

Are women seeking short-acting contraception satisfied with LARC after giving it a try?

Yes—and their chances of continuing contraception at 2 years are greater and their chances of unintended pregnancy at 2 years are less than their SARC-using counterparts.

This study included women randomly assigned to receive a LARC (long-acting reversible contraceptive) method (copper or levonorgestrel intrauterine device or subdermal implant) or a SARC (short-acting reversible contraceptive) method (oral contraceptives or depot medroxyprogesterone acetate); a separate cohort of women received a SARC method of preference. At 24 months, the randomized LARC users had a continuation probability of 64.3% compared with SARC users who were randomized or were in the preference group (25.5% and 40.0%, respectively). The unintended pregnancy probability was 3.6% in the randomized LARC group, while SARC users in either the randomized group or in the preferred methods group had pregnancy probability rates of 6.9% and 9.9%, respectively.

FAST TRACK

Underwriting cost in the study was important for recruitment, since nearly half of participants in the LARC group cited cost as a reason they did not try a LARC method previously

Hubacher D, Spector H, Monteith C, et al. Not seeking yet trying long-acting reversible contraception: a 24-month randomized trial on continuation, unintended pregnancy and satisfaction. Contraception. 2018;97:524-532.

EXPERT COMMENTARY
Ronald T. Burkman, MD is Emeritus Professor of Obstetrics and Gynecology, Tufts University School of Medicine, Baystate Medical Center, Springfield, Massachusetts.

Because of women's personal preference and aversion, for various reasons, to LARC methods, the current estimated use rate of 17% for LARC methods would increase only to 24% to 29% even if major barriers, such as cost and availability, were removed.[1] To gain more insight into this issue, Hubacher and colleagues sought to determine if LARC methods would meet the contraceptive needs and be acceptable to a population of women who were not seeking these methods actively and who might have some reservation about using them.

The author reports no financial relationships relevant to this article.

Details of the study

The authors approached women actively seeking 1 of the 2 SARC methods but not a LARC method for contraception. They

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OBG MANAGEMENT

TOP 2018 WEB-ACCESSED CONTENT

TOP 10 ARTICLES

1. Postpartum hemorrhage: Aortic compression to reduce pelvic bleeding
2. 2018 Update on obstetrics
3. Ovarian masses: Surgery or surveillance?
4. How ovarian reserve testing can (and cannot) address your patients' fertility concerns
5. 2018 Update on abnormal uterine bleeding
6. Diagnosing placenta accreta spectrum with prenatal ultrasound
7. Importance of providing standardized management of hypertension in pregnancy
8. 2018 Update on contraception
9. Optimal surgical management of stage 3 and 4 pelvic organ prolapse
10. The techno vagina: The laser and radiofrequency device boom in gynecology

TOP 5 VIDEOS

1. Excision of a Bartholin gland cyst
2. Common skin diseases of the vulva: Red down there
3. Size can matter: Laparoscopic hysterectomy for the very large uterus
4. Morcellation at the time of vaginal hysterectomy
5. Basic technique of vaginal hysterectomy

TOP 5 AUDIOS

1. New single-dose treatment for bacterial vaginosis
2. Which IUD is right for me? Answering your patients' questions about differences in LNG-IUDs
3. Managing menopausal symptoms in breast cancer survivors
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Some examples of these tools include the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire-9 (PHQ-9).

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

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

SAGE THERAPEUTICS