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OBG MANAGEMENT

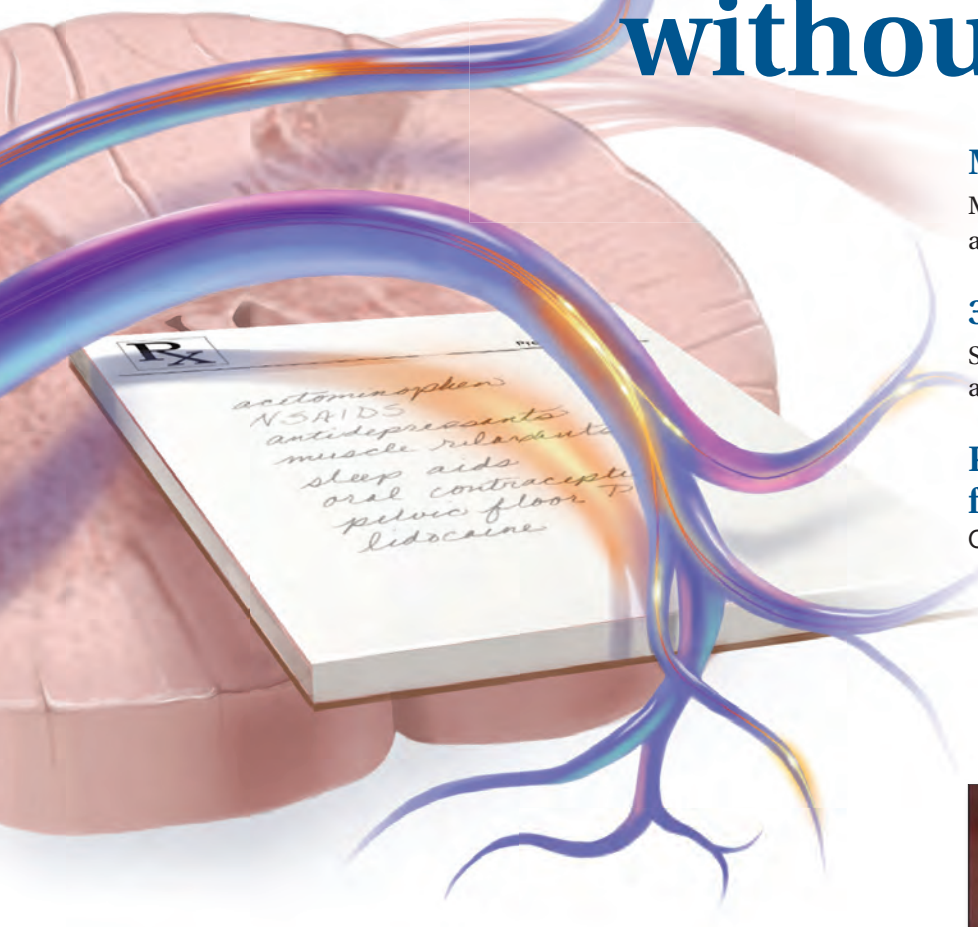
30th ANNIVERSARY

The new normal in blood pressure diagnosis
Robert L. Barbieri, MD

The beginning of the end of the Pap?

In collaboration with ACOG
What makes a quality "quality measure"?

Addressing pain without opioids



Managing postsurgical pain
Mikio Nihira, MD, MPH,
and Adam C. Steinberg, DO

3 cases of chronic pelvic pain
Sara R. Till, MD, MPH,
and Sawsan As-Sanie, MD, MPH

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EVEN WHEN IT'S NOT YOUR PATIENT'S PERIOD

HER ENDOMETRIOSIS IS PART OF THE FAMILY[1,2]

In an international multicenter survey of patients treated in tertiary care centers, it was reported that

7 out of 10 endometriosis patients experience **unresolved pain despite management**[2]

Could your endometriosis patients be suffering in silence?
Discover resources at **HerEndometriosisReality.com** that can help your patients open up about the true impact of their endometriosis pain.

References:

1. Fourquet J, Gao X, Zavala D, et al. Patients' report on how endometriosis affects health, work, and daily life. *Fertil Steril*. 2010;93(7):2424-2428.
2. De Graaff AA, D'Hooghe TM, Dunselman GAJ, Dirksen CD, Hummelshoj L; WERF EndoCost Consortium, Simoens S. The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey. *Hum Reprod*. 2013;28(10):2677-2685.

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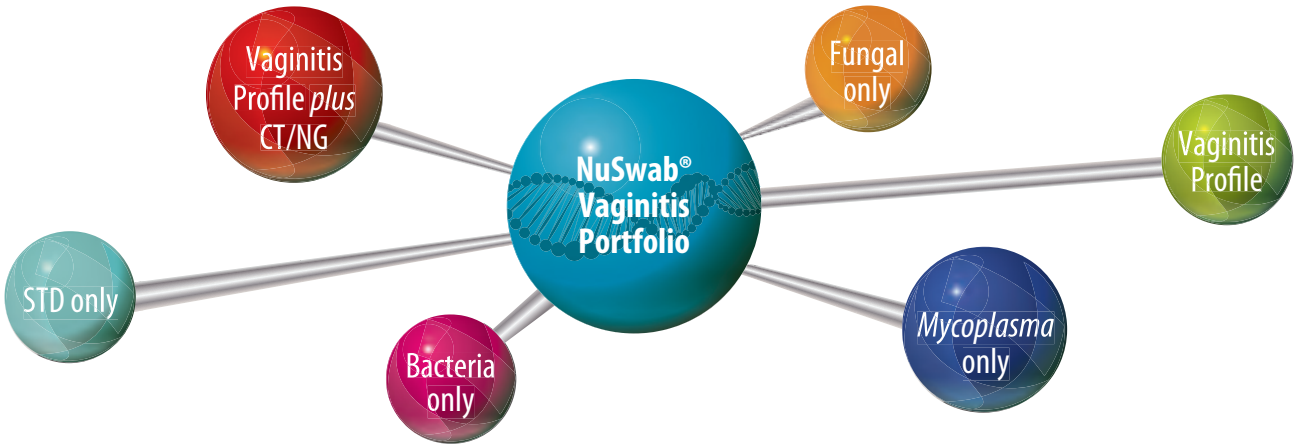
Enhancing the quality of women's health care and the professional development of ObGyns and all women's health care clinicians

*Source: Kantar Media, Medical Surgical Study December 2017, Obstetrics/Gynecology Combined Office & Hospital Readers.



Everything **she** needs

with the services **you** expect.

Vaginitis accounts for approximately 10 million office visits each year.[1] Most women will experience vaginitis symptoms.[2] Recurrence is common.[3] This condition commands a great deal of your daily patient care time. You need a test with diagnostic accuracy to help treat patients properly on the first visit and help reduce recurrence.

Tests **She** Needs - Bacterial

The NuSwab Bacterial Vaginosis (BV) test:

- uses 3 quantitative organisms: *Atopobium vaginae*, BVAB-2, *Megasphaera-1*
- distinguishes normal flora from BV
- is 97% sensitive and 92% specific according to a published clinical study[4]

Tests **She** Needs - Fungal

The NuSwab C *albicans* and C *glabrata* test:

- targets the 2 most common *Candida* species
- helps guide treatment – C *glabrata* is often resistant to fluconazole[5]
- six species test options and add-on testing of 4 additional *Candida* species in refractory or recurrent cases

Tests **She** Needs - Parasitic

The NuSwab *Trichomonas vaginalis* (Tv) test:

- is 100% sensitive and 99% specific for Tv diagnosis[6]
- shown to be more sensitive than culture, microscopy, and Affirm™ VPIII[7]
- can be used as a follow-up test to confirm negative wet mounts[8]

1. Willett LL, Centor RM. Evaluating vaginitis. The importance of patient factors. *J Gen Intern Med.* 2005 Sept;20(9): 871.
2. Centers for Disease Control and Prevention. Recommendations and Reports: Sexually transmitted diseases treatment guidelines, 2015. *MMWR.* 2015;64(3):1-137.
3. The American College of Obstetricians and Gynecologists. Vaginitis. ACOG Practice Bulletin No. 72. *Obstet Gynecol.* 2006;107:1195-1206.
4. Cartwright CP, Lembke BD, Ramachandran K, et al. Development and validation of a semiquantitative multitarget PCR assay for diagnosis of bacterial vaginosis. *J Clin Microbiol.* 2012;50(7):2321-2329.
5. Richter SS, Galask RP, Messer SA, Hollis RJ, Diekema DJ, Pfaller MA. Antifungal susceptibilities of Candida species causing vulvovaginitis and epidemiology of recurrent cases. *J Clin Microbiol.* 2005 May; 43(5):2155-2162.
6. APTIMA® *Trichomonas vaginalis* Assay [package insert]. San Diego, Calif: Gen-Probe Incorporated; 2009-2011.
7. Chapin K, Andrea S. APTIMA *Trichomonas vaginalis*, a transcription-mediated amplification assay for detection of *Trichomonas vaginalis* in urogenital specimens. *Expert Rev Mol Diagn.* 2011; 11(7):679-688.
8. Nye MB, Schwebke JR, Body BA. Comparison of APTIMA *Trichomonas vaginalis* transcription-mediated amplification to wet mount microscopy, culture, and polymerase chain reaction for the diagnosis of trichomoniasis in men and women. *Am J Obstet Gynecol.* 2009;200:188.e1-188.e7.9.

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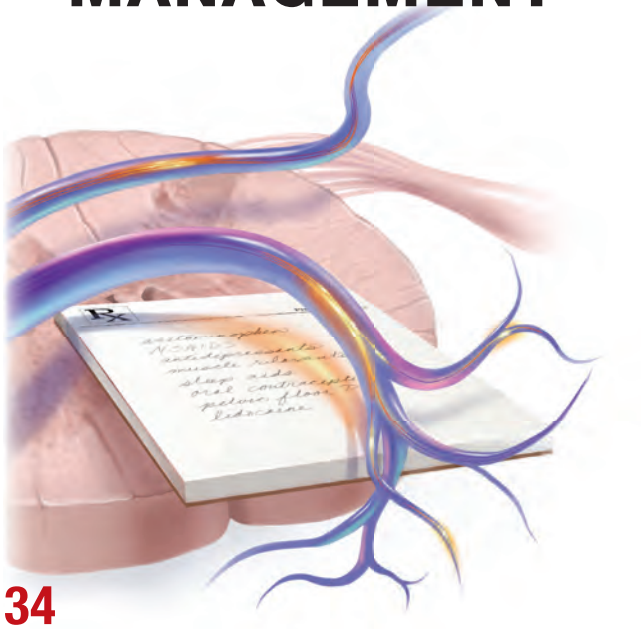

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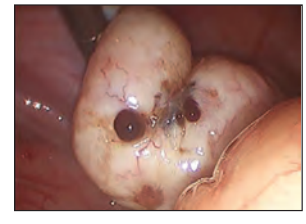

Endometriosis and fertility **18**

Quality measures **30**

FAST TRACK is a system to enable you as a reader to move quickly through each issue of **OBG MANAGEMENT**, identifying articles or sections of articles to read in depth.

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For more product information visit Methergine.com

Severe maternal morbidity affects over 60,000 women each year[1]

Every ***10 minutes*** a woman in the US nearly dies of pregnancy-related complications[1]

THINK TWICE

Start with IM and transition to Oral Tablets*

Ensure your patients are protected *from Hospital to Home*

*In appropriate patients who are at risk of PPH.

Methergine®

(methylergonovine maleate) tablets, USP 0.2mg

METHYLERGONOVINE MALEATE TABLETS

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

INDICATIONS AND USAGES

Methylergonovine Maleate is a semi-synthetic ergot alkaloid used for the prevention and control of postpartum hemorrhage. It is used following delivery of placenta, for routine management of uterine atony, hemorrhage, and subinvolution of the uterus as well as for control of uterine hemorrhage in the second stage of labor following delivery of the anterior shoulder.

CONTRAINDICATIONS

Hypertension, toxemia, pregnancy, and hypersensitivity are contraindications to Methylergonovine Maleate Tablets.

WARNINGS

General: This drug should not be administered intravenously routinely because of the possibility of inducing sudden hypertensive and cerebrovascular accidents. If intravenous administration is considered essential as a lifesaving measure, methylergonovine maleate should be given slowly over a period of no less than 60 seconds with careful monitoring of blood pressure. Intra-arterial or periarterial injection should be strictly avoided. Caution should be exercised in presence of impaired hepatic or renal function.

Breast-Feeding: Mothers should not breast-feed during treatment with Methylergonovine Maleate Tablets, USP. Milk secreted during this period should be discarded. Methylergonovine Maleate Tablets, USP may produce adverse effects in the breast-feeding infant. Methylergonovine Maleate Tablets, USP may also reduce the yield of breast milk. Mothers should wait at least 12 hours after administration of the last dose of Methylergonovine Maleate Tablets, USP before initiating or resuming breast-feeding.

Coronary Artery Disease: Patients with coronary artery disease or risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with methylergonovine-induced vasospasm.

Medication Errors: Inadvertent administration of Methylergonovine Maleate Tablets, USP to newborn infants has been reported. In these cases of inadvertent neonatal exposure, symptoms such as respiratory depression, convulsions, cyanosis, and oliguria have been reported. Usual treatment is symptomatic. However, in severe cases, respiratory and cardiovascular support is required. Methylergonovine Maleate Tablets, USP has been administered instead of vitamin K and Hepatitis B vaccine, medications which are routinely administered to the newborn. Due to the potential for accidental neonatal exposure, methylergonovine maleate should be stored separately from medications intended for neonatal administration.

PRECAUTIONS

General: Caution should be exercised in the presence of sepsis, obliterative vascular disease. Also use with caution during the second stage of labor. The necessity for manual removal of a retained placenta should occur only rarely with proper technique and adequate allowance of time for its spontaneous separation.

Drug Interactions

CYP3A4 Inhibitors (e.g., Macrolide Antibiotics and Protease Inhibitors): There have been rare reports of serious adverse events in connection with the coadministration of certain ergot alkaloid drugs (e.g., dihydroergotamine and ergotamine) and potent CYP3A4 inhibitors, resulting in vasospasm leading to cerebral ischemia and/or ischemia of the extremities. Although there have been no reports of such interactions with methylergonovine alone, potent CYP3A4 inhibitors should not be coadministered with methylergonovine. Examples of some of the more potent CYP3A4 inhibitors include macrolide antibiotics (e.g., erythromycin, troleandomycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g., ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g., ketoconazole, itraconazole, voriconazole). Less potent CYP3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with methylergonovine.

CYP3A4 Inducers: Drugs (e.g. nevirapine, rifampicin) that are strong inducers of CYP3A4 are likely to decrease the pharmacological action of Methylergonovine Maleate Tablets, USP.

Beta-Blockers: Caution should be exercised when Methylergonovine Maleate Tablets, USP is used concurrently with beta-blockers. Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

Anesthetics: Anesthetics like halothan and methoxyfluran may reduce the oxytocic potency of Methylergonovine Maleate Tablets, USP.

Glyceryl Trinitrate and Other Antianginal Drugs: Methylergonovine maleate produces vasoconstriction and can be expected to reduce the effect of glyceryl trinitrate and other antianginal drugs. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known. Caution should be exercised when methylergonovine maleate is used concurrently with other vasoconstrictors, ergot alkaloids, or prostaglandins.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies have been performed in animals to evaluate carcinogenic potential. The effect of the drug on mutagenesis or fertility has not been determined.

Pregnancy: Category C: Animal reproductive studies have not been conducted with methylergonovine maleate. It is also not known whether methylergonovine maleate can cause fetal harm or can affect reproductive capacity. Use of methylergonovine maleate is contraindicated during pregnancy because of its uterotonic effects. (See INDICATIONS AND USAGE).

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clinical studies of methylergonovine maleate did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most common adverse reaction is hypertension associated in several cases with seizure and/or headache. Hypotension has also been reported. Abdominal pain (caused by uterine contractions), nausea and vomiting have occurred occasionally. Rarely observed reactions have included: acute myocardial infarction, transient chest pains, vasoconstriction, vasospasm, coronary arterial spasm, bradycardia, tachycardia, dyspnea, hematuria, thrombophlebitis, water intoxication, hallucinations, leg cramps, dizziness, tinnitus, nasal congestion, diarrhea, diaphoresis, palpitation, rash, and foul taste. There have been rare isolated reports of anaphylaxis, without a proven causal relationship to the drug product.

Nervous System Disorders: Cerebrovascular accident, paraesthesia.

Cardiac Disorders: Ventricular fibrillation, ventricular tachycardia, angina pectoris, atrioventricular block.

DRUG ABUSE AND DEPENDENCE

Methylergonovine maleate has not been associated with drug abuse or dependence of either a physical or psychological nature.

OVERDOSAGE

Symptoms of acute overdose may include: nausea, vomiting, abdominal pain, numbness, tingling of the extremities, rise in blood pressure, in severe cases followed by hypotension, respiratory depression, hypothermia, convulsions, and coma.

Because reports of overdosage with methylergonovine maleate are infrequent, the lethal dose in humans has not been established. The oral LD50 (in mg/kg) for the mouse is 187, the rat 93, and the rabbit 4.5. Several cases of accidental methylergonovine maleate injection in newborn infants have been reported, and in such cases 0.2 mg represents an overdose of great magnitude. However, recovery occurred in all but one case following a period of respiratory depression, hypothermia, hypertonicity with jerking movements, and convulsions.

Also, several children 1-3 years of age have accidentally ingested up to 10 tablets (2 mg) with no apparent ill effects. A postpartum patient took 4 tablets at one time in error and reported paresthesias and clamminess as her only symptoms.

Treatment of acute overdosage is symptomatic and includes the usual procedures of: 1. Removal of offending drug by inducing emesis, gastric lavage, catharsis, and supportive diuresis. 2. Maintenance of adequate pulmonary ventilation, especially if convulsions or coma develop. 3. Correction of hypotension with pressor drugs as needed. 4. Control of convulsions with standard anticonvulsant agents. 5. Control of peripheral vasospasm with warmth to the extremities if needed.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088, or call Lupin Pharmaceuticals, Inc. at 1-800-399-2561.

Please note that this information is not comprehensive. Please see the full prescribing information at www.methergine.com.

Reference: 1. Creanga AA, Berg CJ, Ko JY, et al. Maternal mortality and morbidity in the United States: Where are we now? *J Women's Health.* 2014; 23(1):3-9.

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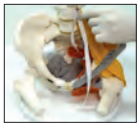

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NEXPLANON is indicated for use by women to prevent pregnancy.

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.

NEXPLANON — 1 ARM IMPLANT provides up to 3 years of pregnancy prevention*

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

(Actual implant shown;
actual implant size is 4cm)

>99% effective†

Placed subdermally in the inner upper arm just under the skin

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

Please read the adjacent Brief Summary of the Prescribing Information.

MERCK

Nexplanon®

(etonogestrel implant) 68mg

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.

Nexplanon®
(etonogestrel implant) 68mg

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 increase breakthrough bleeding.

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

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

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

Effects of Hormonal Contraceptives on Other Drugs

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

USE IN SPECIFIC POPULATIONS

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.

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EDITORIAL

The new normal in blood pressure diagnosis and management: Lower is better

The revised definition of normal blood pressure (systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg) will result in major changes in the clinical care of mid-life women

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For many years, the approach to the diagnosis of hypertension was straight-forward—multiple blood pressure (BP) measurements ≥140/90 mm Hg established the diagnosis of hypertension, a disease associated with an increased risk of adverse cardiovascular events, including myocardial infarction and stroke. For more than a decade, hypertension experts have argued that a BP ≥130/80 mm Hg should establish the diagnosis of hypertension. Many clinicians resisted the change because it would markedly increase the number of asymptomatic adults with the diagnosis, increasing the number needing treatment. However, the findings of the Systolic Blood Pressure Intervention Trial (SPRINT) and other observational studies have catalyzed the American College of Cardiology (ACC) and the American Heart Association (AHA) to redefine normal BP as <120/80 mm Hg.[1] This change will expand the diagnosis of hypertension to include up to 50% of American adults.[1] In addition, the new definition of normal BP will result in the greater use of lifestyle interventions and antihypertensive medications to achieve the new normal, a BP of <120/80 mm Hg.

The new definition of hypertension

The new definition of hypertension is of particular importance for people at risk for developing cardiovascular disease (CVD)[1,2] and is summarized here.

- Normal BP: systolic BP (SBP) <120 mm Hg **and** diastolic BP (DBP) <80 mm Hg
- Elevated BP: SBP 120–129 mm Hg **and** DBP <80 mm Hg
- Stage 1 hypertension: SBP 130–139 mm Hg **or** DBP 80–89 mm Hg.
- Stage 2 hypertension: SBP ≥140 mm Hg **or** DBP ≥90 mm Hg.

The new definition of hypertension will markedly increase the number of mid-life adults eligible to be treated for hypertension. I summarize the approach to treating hypertension in this article.

For mid-life adults, a SBP of <120 mm Hg is better for the heart

The heart is a pump, and not surprisingly, if a pump can achieve its job at a lower rather than a higher pressure, it is likely to last longer. The SPRINT study clearly demonstrated that in elderly hypertensive adults, an SBP target of <120 mm Hg is associated with fewer deaths than a SBP in the range of 130 to 140 mm Hg.[3]

In the SPRINT trial, 9,361 people with a mean age, body mass index, and BP of 68 years, 30 kg/m^2 and 140/78 mm Hg, respectively, were randomly assigned to intensive treatment of SBP to a goal of <120 mm Hg or to a target of <140 mm Hg. After 1 year of treatment, the intensive treatment group had a mean SBP of 121 mm Hg and the standard treatment group had a mean SBP of 136 mm Hg. To achieve a SBP <120 mm Hg, most patients required 3 antihypertensive medications, in contrast to the 2 antihypertensive medications typically needed to achieve a SBP in the range of 130 to 140 mm Hg.

After a median of 3.3 years of follow-up, significantly fewer deaths occurred in the intensive treatment group than in the standard treatment group, including deaths from all causes (3.3% vs 4.5%, P = .003) and deaths from CVD (0.8% vs 1.4%; P = .005). In addition, the risk of developing heart failure was lower in the intensive treatment than in the

CONTINUED ON PAGE 14

NOW AVAILABLE

DEMONSTRATED TO SIGNIFICANTLY DECREASE MODERATE TO SEVERE **DYSPAREUNIA DUE TO MENOPAUSE**[1]

Not actual size.

NON-ESTROGEN BASED, CONVERTS TO ESTROGENS AND ANDROGENS*

Prasterone is a precursor that is locally converted to estrogens and androgens with minimal systemic exposure.[1,2] *The mechanism of action of INTRAROSA is not fully established[1]

ONCE-DAILY TREATMENT

Individually wrapped vaginal inserts with disposable applicators[1]

NO FDA BOXED WARNING[2]

No restrictions on duration of use[2,3]

To order samples and learn more about INTRAROSA, including our patient savings program, visit IntrarosaHCP.com

Indication

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

Important Safety Information

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS Current or Past History of Breast Cancer

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

ADVERSE REACTIONS Clinical Trials Experience

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

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

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

References: 1. Intrarosa [package insert]. Waltham, MA: AMAG Pharmaceuticals, Inc.; 2017. **2.** Archer DF, Labrie F, Bouchard C, et al; VVA Prasterone Group. *Menopause*. 2015;22(9):950-963. **3.** Labrie F, Archer DF, Koltun W, et al; VVA Prasterone Research Group. *Menopause*. 2016;23(3):243-256.

Intrarosa™ Prasterone VAGINAL INSERTS

amag PHARMACEUTICALS

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standard treatment group (1.3% vs 2.1%, P = .002). There was no difference between the 2 groups in the risk of stroke (1.3% vs 1.5%, P = .50) or myocardial infarction (2.1% vs 2.5%, P = .19). The rate of syncope was higher in the intensive treatment group (2.3% vs 1.7% in the standard treatment group, P = .05).[3] Self-reported mental and physical health and satisfaction with treatment was similar in both groups.[4]

The investigators concluded that among people at risk for CVD, targeting a SBP of <120 mm Hg as compared to <140 mm Hg resulted in lower rates of heart failure and death, two clinically meaningful endpoints.

Diet and exercise

Nonpharmacologic interventions, including diet and exercise, are recommended for all people with a BP >120/80 mm Hg. In most situations, antihypertensive medications are not necessary if the patient has elevated BP (SBP 120–129 mm Hg and DBP <80 mm Hg) or Stage 1 hypertension (SBP 130–139 mm Hg or DBP 80–89 mm Hg) and a 10-year CVD risk of less than 10% using the ACC/AHA cardiovascular risk calculator[5] (see http://www.cvriskcalculator.com/). For people at low risk for CVD, nonpharmacologic interventions, including diet and exercise, are often sufficient treatment.

The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes increasing consumption of fruits, vegetables, low-fat dairy, whole-grains, fish, poultry, and nuts and decreasing the consumption of red meats, sugary drinks, sweets, sodium, and saturated and trans-fats. In randomized trials, the DASH diet is associated with a reduction in BP of approximately 5 mm Hg systolic and 3 mm Hg diastolic.[6] The DASH trial monitored weight changes and adjusted calorie intake to ensure a stabilized weight throughout the study. Hence, the positive effect of the DASH diet was observed in the absence of any weight loss. Weight loss also can decrease BP with every 1- to 2-lb weight loss, reducing SBP by approximately 1 mm Hg.[7] Combining the DASH diet with a low-sodium diet is especially important in people with high sodium intake, and is reported to reduce SBP by 5 to 20 mm Hg.[8] Reducing the consumption of alcohol can result in a reduction of SBP and DBP in the range of 3 and 2 mm Hg, respectively.[9]

Exercising for 40 minutes, 3 to 4 times per week is associated with a reduction of SBP and DBP of approximately 5 and 3 mm Hg, respectively.[10] Although the studies are of low quality, meditation is reported to decrease SBP and DBP by 4 and 2 mm Hg, respectively.[11]

Antihypertensive medications

For all mid-life adults with Stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg) or with both clinical CVD and Stage 1 hypertension, antihypertensive medications are recommended.[1] For people with Stage 1 hypertension and a 10-year CVD risk of ≥10%, antihypertensive medications are recommended. The target BP is <130/80 mm Hg for most people.

The recommended antihypertensive medications include thiazide diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs). Many patients with Stage 2 hypertension will need treatment with 2 agents of different classes to achieve a BP <130/80 mm Hg. Some experts believe that an optimal 2-agent regimen includes an ACE or ARB plus a CCB based on the results of the ACCOMPLISH trial.[12] In this trial, 11,506 adults with hypertension and at very high risk for CVD, were randomly assigned to treatment with an ACE inhibitor plus CCB or with an ACE inhibitor plus hydrochlorothiazide. The BP achieved in both groups was approximately 132/73 mm Hg. The study was stopped after 3 years because participants in the ACE/thiazide group had a higher rate of adverse cardiovascular events (myocardial infarction, stroke, or death) than those in the ACE/CCB group (11.8% vs 9.6%; hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.72–0.90; P<.001). Compared to the ACE/thiazide group, the ACE/CCB group had a significantly lower rate of fatal and nonfatal myocardial infarction (2.2% vs 2.8%; HR, 0.78; 95% CI, 0.62–0.99; P = .04) and a lower rate of death from cardiovascular causes (1.9% vs 2.3%; HR, 0.80; 95% CI, 0.62–1.03, P = .08).

Worldwide, approximately 1 billion adults have a SBP ≥140 mm Hg.[13] In the United States, 32% of adult women have Stage 2 hypertension or are taking an antihypertensive medication (TABLE).[1] There is a generally linear relationship between increasing SBP and DBP and an increased risk of a cardiovascular event, including heart failure, myocardial infarction, and stroke. An increase of SBP of 20 mm Hg or DBP of 10 mm Hg above a baseline BP of 115/75 mm Hg doubles the risk of death from CVD.[14] For adults at risk for CVD, intensive treatment of hypertension clearly reduces the risk of a life-changing cardiovascular event.

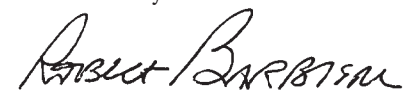
It will probably take many years for the new SBP target of <120 mm Hg to be fully accepted by clinicians and patients because, although achieving

TABLE Prevalence of Stage 2 hypertension or self-reported use of antihypertension medication among US women by age and race-ethnicity[1,a]

Age group, y	SBP ≥140 or DBP ≥90 mm Hg or self-reported use of antihypertension medication
20–44	10%
45–54	27%
55–64	52%
65–74	63%
≥75	78%
Race-Ethnicity	
Non-Hispanic white	30%
Non-Hispanic black	46%
Non-Hispanic Asian	27%
Hispanic	32%

[a]Sample size = 4,906, National Health and Nutrition Examination Survey 2011–2014.

a SBP of <120 mm Hg will decrease cardiovascular events, it is a very difficult target to achieve, requiring treatment with 3 antihypertensive medications for most patients. The early diagnosis and intensive treatment of hypertension is challenging because it requires clinicians to initiate a multi-decade course of treatment of asymptomatic people with the goal of preventing a life-altering cardiovascular event, including stroke and myocardial infarction. ●



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

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COMMENTARY

Does hormonal contraception increase the risk of breast cancer?

These experts analyze the data from a recent large study and provide counseling points for your patients

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Hormonal contraception (HC) has long been utilized safely in this country for a variety of indications, including pregnancy prevention, timing pregnancy appropriately, management of symptoms (dysmenorrhea, irregular menstrual cycles, heavy menstrual bleeding), and to prevent serious diseases (such as ovarian cancer, uterine cancer, osteoporosis in women with premature menopause). Like most prescription medications, there are potential adverse effects. With HC, side effects such as venous thromboembolism, a slight increase in liver cancer, and a possible increase in breast cancer risk have long been recognized.

Danish study compared HC use with breast cancer risk

In the December 7, 2017, issue of *New England Journal of Medicine*,[1] investigators in Denmark published a study of women using HC (oral, transdermal, intravaginal routes, and levonorgestrel intrauterine device [LNG-IUD]) and breast cancer risk compared with women who did not use HC. This retrospective observational country-wide study was very large (1.8 million women followed over an average of 10.9 years), which allowed for the detection of even small changes in breast cancer risk.

The authors report no financial relationships relevant to this article.

Putting results in perspective

It is important to point out that this is an observational study, and small effect sizes (1 in 7,600) should be interpreted with caution. Observational studies can introduce many different types of bias (prescribing bias, confounding bias, etc). Of note, while the LNG-IUD was associated with a small increased risk of breast cancer (relative risk [RR], 1.21; 95% confidence interval [CI], 1.11–1.33]), the higher dose continuous progestin administration (medroxyprogesterone) was not (RR, 0.95; 95% CI, 0.40–2.29).[1]

Nonetheless, providing patients with a balanced summary of this new study along with other published and reliable information about HC that conveys both benefits and risks is important to assure that each woman makes a decision regarding HC that achieves her health and life goals. See "Counseling talking points."

Bottom line

This recent study demonstrated that in Denmark, a woman's risk of *developing breast cancer* is very slightly elevated on HC[1]:

- 1 in 7,690 users overall
- 1 in 50,000 women older than age 35 years.

By comparison, the risk of maternal mortality in the United States is 1 in 3,788.[2] A substantial reduction in HC use would likely increase unintended and mistimed pregnancies with a potential substantial negative impact on quality of life and personal/societal cost.

The best available data indicate that a woman's risk of *developing any cancer* is **slightly less** on HC than not on HC, even with this incremental breast cancer increase.[3,4]

Counseling talking points

Breast cancer risk relative to benefits of pregnancy prevention

There was a very slight increase in breast cancer in women using HC in the Danish study.[1]

Risk of breast cancer

- Overall, the number needed to harm (NNH) was approximately 1 in 7,690, which equates to 13 incremental breast cancers for every 100,000 women using HC (0.013%).
- Breast cancer risk was not evenly distributed across the different age groups. In women younger than 35 years, the risk was 1 extra case for every 50,000 women using HC (0.002%).

Risk of pregnancy prevention failure: Maternal mortality

- By comparison, the rate of maternal mortality is considerably higher than either of these risks in the United States. Specifically, the most recently available rate of maternal mortality (2015) in the United States was 26.4 for every 100,000 women, essentially double that of developing breast cancer on HC.[2]
  - Most women who develop breast cancer while on HC will survive their cancer long-term.[5] And most would agree that while neither is desirable, death is a worse outcome than the development of breast cancer.

Risk of pregnancy prevention failure other than maternal mortality

- Other than the copper IUD and sterilization methods, all other nonhormonal contraceptive methods are by far inferior in terms of the ability to prevent unintended pregnancy.
- Unintended pregnancy has substantial health, social, and economic consequences to women and infants, and contraception use is a well-accepted proximate determinant of unintended pregnancy.[6]
- Unintended pregnancy is a serious maternal-child health problem with potentially long-term burdens not only for women and families[7–10] but also for society.[11–13]
- Unintended pregnancies generate an estimated $21 billion direct and indirect costs for the US health care system per year,[14] and approximately 42% of these pregnancies end in abortion.[15]

HC cancer risk and HC cancer prevention

- HC use increases risk of breast and liver cancer but reduces risk of ovarian, endometrial, and colorectal cancer; the net effect is a modest reduction in total cancer.[3,4]
- In addition, there appears to be additional cervical cancer prevention benefit from IUD use.[16]
- In a recent meta-analysis, IUDs (including LNG-IUD) have been associated with a 33% reduction in cervical cancer.[16]

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These experts spotlight an international consensus on endometriosis-associated infertility and a revised international glossary on infertility that should help ensure consistent use of terminology and accurate outcomes reporting. Plus, they report on study results that suggest one particular contrast medium with hysterosalpingography may be better than another for improving pregnancy rates.

IN THIS ARTICLE

Clinicians always should consider endometriosis in the diagnostic work-up of an infertility patient. But the diagnosis of endometriosis is often difficult, and management is complex. In this Update, we summarize international consensus documents on endometriosis with the aim of enhancing clinicians' ability to make evidence-based decisions. In addition, we explore the interesting results of a large hysterosalpingography trial in which 2 different contrast mediums were used. Finally, we urge all clinicians to adapt the new standardized lexicon of infertility and fertility care terms that comprise the recently revised international glossary.

Endometriosis and infertility: The knowns and unknowns

Johnson NP, Hummelshoj L, Adamson GD, et al; World Endometriosis Society Sao Paulo Consortium. World Endometriosis Society consensus on the classification of endometriosis. Hum Reprod. 2017;32(2):315–324.

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Rogers PA, Adamson GD, Al-Jefout M, et al; WES/WERF Consortium for Research Priorities in Endometriosis. Research priorities for endometriosis. Reprod Sci. 2017;24(2):202–226.

Endometriosis is defined as "a disease characterized by the presence of endometrium-like epithelium and stroma outside the endometrium and myometrium.

Intrapelvic endometriosis can be located superficially on the peritoneum (peritoneal endometriosis), can extend 5 mm or more beneath the peritoneum (deep endometriosis) or can be present as an ovarian endometriotic cyst (endometrioma)."[1] Always consider endometriosis in the infertile patient.

Although many professional societies and numerous Cochrane Database Systematic Reviews have provided guidelines on endometriosis, controversy and uncertainty remain. The World Endometriosis Society (WES) and the World Endometriosis Research Foundation (WERF), however, have now published several consensus documents that assess the global literature and professional organization guidelines in a structured, consensus-driven process.[2–4] These WES and WERF documents consolidate known information and can be used to inform the clinician in making evidence-linked diagnostic and treatment decisions. Recommendations offered in this discussion are based on those documents.

Establishing the diagnosis can be difficult

Diagnosis of endometriosis is often difficult and is delayed an average of 7 years from onset of symptoms. These include severe dysmenorrhea, deep dyspareunia, chronic pelvic pain, ovulation pain, cyclical or perimenstrual symptoms (bowel or bladder associated) with or without abnormal bleeding, chronic fatigue, and infertility. A major difficulty is that the predictive value of any one symptom or set of symptoms remains uncertain, as each of these symptoms can have other causes, and a significant proportion of affected women are asymptomatic.

For a definitive diagnosis of endometriosis, visual inspection of the pelvis at laparoscopy is the gold standard investigation, unless disease is visible in the vagina or elsewhere. Positive histology confirms the diagnosis of endometriosis; negative histology does not exclude it. Whether histology should be obtained if peritoneal disease alone is present is controversial: visual inspection usually is adequate, but histologic confirmation of at least one lesion is ideal. In cases of ovarian endometrioma (>4 cm in diameter) and in deeply infiltrating disease, histology should be obtained to identify endometriosis and to exclude rare instances of malignancy.

Compared with laparoscopy, transvaginal ultrasonography (TVUS) has no value in diagnosing peritoneal endometriosis, but it is a useful tool for both making and excluding the diagnosis of an ovarian endometrioma. TVUS may have a role in the diagnosis of disease involving the bladder or rectum.

At present, evidence is insufficient to indicate that magnetic resonance imaging (MRI) is useful for diagnosing or excluding endometriosis compared with laparoscopy. MRI should be reserved for when ultrasound results are equivocal in cases of rectovaginal or bladder endometriosis.

Serum cancer antigen 125 (CA 125) levels may be elevated in endometriosis. However, measuring serum CA 125 levels has no value as a diagnostic tool.

No fertility benefit with ovarian suppression

More than 2 dozen randomized controlled trials (RCTs) provide strong evidence that there is no fertility benefit from ovarian suppression. The drug costs and delayed time to pregnancy mean that ovarian suppression with oral contraceptives, other progestational agents, or gonadotropin-releasing hormone (GnRH) agonists before fertility treatment is not indicated, with the possible exception of using it prior to in vitro fertilization (IVF).

Ovarian suppression also has been suggested as beneficial in conjunction with surgery. However, at least 16 RCTs have failed to show fertility improvement when ovarian suppression is given either preoperatively or postoperatively. Again, the delay in attempting pregnancy, drug costs, and adverse effects render ovarian suppression not appropriate.

While ovarian suppression has not been shown to increase pregnancy rates, ovarian stimulation (OS) likely does, especially

FAST TRACK

Endometriosis must always be considered in the infertile patient

CONTINUED ON PAGE 25

Are your adult patients with iron deficiency anemia (IDA) getting what they need from oral iron therapy?

Typical oral iron dose*

Ferrous sulfate tablets 325 mg, taken 3x daily for 30 days (dose may vary depending on patient condition)[1,2]

*Not intended to represent all possible oral iron regimens.

Typical oral iron absorption

Even in healthy subjects, less than 10% of oral iron is absorbed[3]

INDICATIONS

Injectafer® (ferric carboxymaltose injection) is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, and in adult patients with non-dialysis dependent chronic kidney disease.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Injectafer is contraindicated in patients with hypersensitivity to Injectafer or any of its inactive components.

WARNINGS AND PRECAUTIONS

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but were not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

In clinical studies, hypertension was reported in 3.8% (67/1775) of subjects. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1775) of subjects. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration.

In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

ADVERSE REACTIONS

In two randomized clinical studies, a total of 1775 patients were exposed to Injectafer, 15 mg/kg of body weight, up to a single maximum dose of 750 mg of iron on two occasions, separated by at least 7 days, up to a cumulative dose of 1500 mg of iron. Adverse reactions reported by ≥2% of Injectafer-treated patients were nausea (7.2%); hypertension (3.8%); flushing/hot flush (3.6%); blood phosphorus decrease (2.1%); and dizziness (2.0%).

The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports: urticaria, dyspnea, pruritus, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope.

To report adverse events, please contact American Regent† at 1-800-734-9236. You may also contact the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

Please see brief summary of Full Prescribing Information on the following pages.

Help your patients access the iron they need‡
www.injectafercopay.com
Restrictions apply§

Injectafer provides up to 1500 mg of iron in just 2 administrations separated by at least 7 days[4]

Up to 750 mg in a single dose‖¶

+

Up to 750 mg in a single dose‖¶

=

Total cumulative dose **up to 1500 mg** per course

At least 7 days apart

IV infusion over at least 15 minutes or Slow IV push over 7.5 minutes

injectafer®
ferric carboxymaltose injection

Many IDA patients have iron deficits of approximately 1500 mg[5#]

Monitor your patients. When oral fails, it's time to consider Injectafer.

To learn more, visit **www.injectaferHCP.com**

Injectafer has not been studied in pregnant women. Injectafer should be prescribed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

†American Regent® is a registered trademark of Luitpold Pharmaceuticals, Inc.

‡For appropriate adult IDA patients (see INDICATIONS). Not all patients need 1500 mg of iron. The amount of iron needed for each patient must be determined by the prescribing clinician.

§The Injectafer Savings Program is only available for adults 18 years or older who are commercially insured or cash-paying patients. It provides up to a maximum savings limit of $500 per dose and a $1000 program limit for coverage up to 2 doses. Insurance out of pocket must be over $50. Additional restrictions may apply. Please see full Terms and Conditions.

‖For adult patients weighing less than 50 kg (110 lb), give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course of treatment.

¶When administered via IV infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not <2 mg of iron per mL and administer over at least 15 minutes. When administered as a slow IV push, give at the rate of approximately 100 mg (2 mL) per minute.

#Calculated iron deficit based on the modified Ganzoni formula: Subject weight in kg x (15 - current hemoglobin g/dL) x 2.4 + 500. If subject TSAT >20% and ferritin >50 ng/mL, the 500-mg constant is not needed.

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Daiichi-Sankyo

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
INJECTAFER® (ferric carboxymaltose injection)
Please see package insert for Full Prescribing Information

Rx Only

INDICATIONS AND USAGE: Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non–dialysis-dependent chronic kidney disease.

DOSAGE AND ADMINISTRATION: For patients weighing 50 kg (110 lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose not to exceed 1500 mg of iron per course.

For patients weighing less than 50 kg (110 lb): Give Injectafer in two doses separated by at least 7 days. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

The dosage of Injectafer is expressed in mg of elemental iron. Each mL of Injectafer contains 50 mg of elemental iron. Injectafer treatment may be repeated if iron deficiency anemia reoccurs.

Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes.

When added to an infusion bag containing 0.9% sodium chloride injection, USP, at concentrations ranging from 2 mg to 4 mg of iron per mL, Injectafer solution is physically and chemically stable for 72 hours when stored at room temperature. To maintain stability, do not dilute to concentrations less than 2 mg iron/mL.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration. The product contains no preservatives. Each vial of Injectafer is intended for single-use only. Any unused drug remaining after injection must be discarded.

Avoid extravasation of Injectafer since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectafer administration at that site.

DOSAGE FORMS AND STRENGTHS: 750 mg iron / 15 mL single-use vial

CONTRAINDICATIONS: Hypersensitivity to Injectafer or any of its components.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions: Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

Hypertension: In clinical studies, hypertension was reported in 3.8% (67/1,775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1,775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration.

Laboratory Test Alterations: In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

ADVERSE REACTIONS

Adverse Reactions in Clinical Trials: Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

In two randomized clinical studies [Studies 1 and 2, *See Clinical Studies*], a total of 1,775 patients were exposed to Injectafer 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Adverse reactions reported by ≥1% of treated patients are shown in the following table.

Table 1. Adverse reactions reported in ≥1% of Study Patients in Clinical Trials 1 and 2

Term	Injectafer (N=1775) %	Pooled Comparators[a] (N=1783) %	Oral iron (N=253) %
Nausea	7.2	1.8	1.2
Hypertension	3.8	1.9	0.4
Flushing/Hot Flush	3.6	0.2	0.0
Blood Phosphorus Decrease	2.1	0.1	0.0
Dizziness	2.0	1.2	0.0
Vomiting	1.7	0.5	0.4
Injection Site Discoloration	1.4	0.3	0.0
Headache	1.2	0.9	0.0
Alanine Aminotransferase Increase	1.1	0.2	0.0
Dysgeusia	1.1	2.1	0.0
Hypotension	1.0	1.9	0.0
Constipation	0.5	0.9	3.2

[a]Includes oral iron and all formulations of IV iron other than Injectafer

Other adverse reactions reported by ≥0.5% of treated patients include abdominal pain, diarrhea, gamma glutamyl transferase increased, injection site pain/irritation, rash, paraesthesia, sneezing. Transient decreases in laboratory blood phosphorus levels (<2 mg/dL) have been observed in 27% (440/1638) patients in clinical trials.

Post-marketing Experience: Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports with Injectafer: urticaria, dyspnea, pruritus, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope. One case of hypophosphatemic osteomalacia was reported in a subject who received 500 mg of Injectafer every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectafer.

DRUG INTERACTIONS: Formal drug interaction studies have not been performed with Injectafer.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.

Risk Summary

Adequate and well controlled studies in pregnant women have not been conducted. However, animal reproduction studies have been conducted with ferric carboxymaltose. In these studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused fetal malformations and increased implantation loss at maternally toxic doses of approximately 12% to 23% of the human weekly dose of 750 mg (based on body surface area). The incidence of major malformations in human pregnancies has not been established for Injectafer. However, all pregnancies, regardless of exposure to any drug, has a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Administration of ferric carboxymaltose to rats as a one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryofetal findings. This daily dose in rats is approximately 40% of the human weekly dose of 750 mg based on body surface area. In rabbits, ferric carboxymaltose was administered as a one-hour infusion on gestation days 6 to 19 at iron doses of 4.5, 9, 13.5, and 18 mg/kg/day. Malformations were seen starting at the daily dose of 9 mg/kg (23% of the human weekly dose of 750 mg). Spontaneous abortions occurred starting at the daily iron dose of 4.5 mg/kg (12% of the human weekly dose based on body surface area). Pre-implantation loss was at the highest dose. Adverse embryofetal effects were observed in the presence of maternal toxicity.

A pre- and post-natal development study was conducted in rats at intravenous doses up to 18 mg/kg/day of iron (approximately 23% of the weekly human dose of 750 mg on a body surface area basis). There were no adverse effects on survival of offspring, their behavior, sexual maturation or reproductive parameters.

Nursing Mothers: A study to determine iron concentrations in breast milk after administration of Injectafer (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving Injectafer than in lactating women receiving oral ferrous sulfate.

Pediatric Use: Safety and effectiveness have not been established in pediatric patients.

Geriatric Use: Of the 1775 subjects in clinical studies of Injectafer, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE: Excessive dosages of Injectafer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. A patient who received Injectafer 18,000 mg over 6 months developed hemosiderosis with multiple joint disorder, walking disability and asthenia. Hypophosphatemic osteomalacia was reported in a patient who received Injectafer 4000 mg over 4 months. Partial recovery followed discontinuation of Injectafer.

DESCRIPTION: Ferric carboxymaltose, an iron replacement product, is an iron carbohydrate complex with the chemical name of polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Da corresponding to the following empirical formula:

$[FeO_x(OH)_y(H_2O)_z]_n\ [\{(C_6H_{10}O_5)_m\ (C_6H_{12}O_7)\}_l]_k$,

where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$

(l represents the mean branching degree of the ligand).

Injectafer (ferric carboxymaltose injection) is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Each mL contains 50 mg iron as ferric carboxymaltose in water for injection. Injectafer is available in 15 mL single-use vials. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH to 5.0-7.0.

Vial closure is not made with natural rubber latex.

CLINICAL PHARMACOLOGY

Mechanism of Action: Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.

Pharmacodynamics: Using positron emission tomography (PET) it was demonstrated that red cell uptake of ^{59}Fe and ^{52}Fe from Injectafer ranged from 61% to 99%. In patients with iron deficiency, red cell uptake of radio-labeled iron ranged from 91% to 99% at 24 days after Injectafer dose. In patients with renal anemia red cell uptake of radio-labeled iron ranged from 61% to 84% after 24 days Injectafer dose.

Pharmacokinetics: After administration of a single dose of Injectafer of 100 to 1000 mg of iron in iron deficient patients, maximum iron levels of 37 µg/mL to 333 µg/mL were obtained respectively after 15 minutes to 1.21 hours post dose. The volume of distribution was estimated to be 3 L.

The iron injected or infused was rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours. Renal elimination of iron was negligible.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies have not been performed with ferric carboxymaltose.

Ferric carboxymaltose was not genotoxic in the following genetic toxicology studies: *in vitro* microbial mutagenesis (Ames) assay, *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, *in vivo* mouse micronucleus test at single intravenous doses up to 500 mg/kg.

In a combined male and female fertility study, ferric carboxymaltose was administered intravenously over one hour to male and female rats at iron doses of up to 30 mg/kg. Animals were dosed 3 times per week (on Days 0, 3, and 7). There was no effect on mating function, fertility or early embryonic development. The dose of 30 mg/kg in animals is approximately 40% of the human dose of 750 mg based on body surface area.

CLINICAL STUDIES: The safety and efficacy of Injectafer for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectafer was administered at a dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Trial 1: Iron Deficiency Anemia in Patients Who Are Intolerant to Oral Iron or Have Had Unsatisfactory Response to Oral Iron

Trial 1 was a randomized, open-label, controlled clinical study in patients with iron deficiency anemia who had an unsatisfactory response to oral iron (Cohort 1) or who were intolerant to oral iron (Cohort 2) during the 14 day oral iron run-in period. Inclusion criteria prior to randomization included hemoglobin (Hb) <12 g/dL, ferritin ≤100 ng/mL or ferritin ≤300 ng/mL when transferrin saturation (TSAT) ≤30%. Cohort 1 subjects were randomized to Injectafer or oral iron for 14 more days. Cohort 2 subjects were randomized to Injectafer or another IV iron per standard of care [90% of subjects received iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)

	Cohort 1		Cohort 2	
Hemoglobin (g/dL) Mean (SD)	Injectafer (N=244)	Oral Iron (N=251)	Injectafer (N=245)	IV SC[a] (N=237)
Baseline	10.6 (1.0)	10.6 (1.0)	9.1 (1.6)	9.0 (1.5)
Highest Value	12.2 (1.1)	11.4 (1.2)	12.0 (1.2)	11.2 (1.3)
Change (from baseline to highest value)	1.6 (1.2)	0.8 (0.8)	2.9 (1.6)	2.2 (1.3)
p-value	0.001		0.001	

SD=standard deviation; [a]:Intravenous iron per standard of care

Increases from baseline in mean ferritin (264.2 ± 224.2 ng/mL in Cohort 1 and 218.2 ± 211.4 ng/mL in Cohort 2), and transferrin saturation (13 ± 16% in Cohort 1 and 20 ± 15% in Cohort 2) were observed at Day 35 in Injectafer-treated patients.

Trial 2: Iron Deficiency Anemia in Patients with Non–Dialysis-Dependent Chronic Kidney Disease

Trial 2 was a randomized, open-label, controlled clinical study in patients with non–dialysis-dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) ≤11.5 g/dL, ferritin ≤100 ng/mL or ferritin ≤300 ng/mL when transferrin saturation (TSAT) ≤30%. Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 96); 64% were female; 54% were Caucasian, 26% were African American, 18% Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

Table 3. Mean Change in Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Injectafer (N=1249)	Venofer (N=1244)
Baseline	10.3 (0.8)	10.3 (0.8)
Highest Value	11.4 (1.2)	11.3 (1.1)
Change (from baseline to highest value)	1.1 (1.0)	0.9 (0.92)
Treatment Difference (95% CI)	0.21 (0.13, 0.28)	

Increases from baseline in mean ferritin (734.7 ± 337.8 ng/mL), and transferrin saturation (30 ± 17%) were observed at Day 56 in Injectafer-treated patients.

PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems.

Daiichi-Sankyo

This is not all the risk information for Injectafer.
Please see www.injectafer.com for Full Prescribing Information.

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when combined with intrauterine insemination (IUI).[5]

Laparoscopy: Appropriate for selected patients

A major decision for clinicians and patients dealing with infertility is whether to perform a laparoscopy, both for diagnostic and for treatment reasons. Currently, data are insufficient to recommend laparoscopic surgery prior to OS/IUI unless there is a history of evidence of anatomic disease and/or the patient has sufficient pain to justify the physical, emotional, financial, and time costs of laparoscopy. Laparoscopy therefore can be considered as possibly appropriate in younger women (<37 years of age) with short duration of infertility (<4 years), normal male factor, normal or treatable uterus, normal or treatable ovulation disorder, and limited prior treatment.

It is important to consider what disease might be found and how much of an increase in fertility can be obtained by treatment, so that the number needed to treat (NNT) can be used as an estimate of the potential value of laparoscopy in a given patient. A patient also should have no contraindications to laparoscopy and accept 9 to 15 months of attempting pregnancy before undergoing IVF treatment.

When laparoscopy is performed for minimal to mild disease, the odds ratio for pregnancy is 1.66 with treatment. It is important to remove all visible disease without injuring healthy tissue. When disease is moderate to severe, there is often severe anatomic distortion and a very low background pregnancy rate. Numerous uncontrolled trials show benefit of operative laparoscopy, especially for invasive, adhesive, and cystic endometriosis. However, repeat surgery is rarely indicated. After surgery, the Endometriosis Fertility Index (EFI) can be used to determine prognosis and plan management.[6] An easy-to-use electronic EFI calculator is available online at www.endometriosisefi.com. (See **FIGURE 1** in the online version of this article.)

Management of endometriomas

Endometriomas are often operated on because of pain. Initial pain relief occurs in 60% to 100% of patients, but cysts recur following stripping about 10% of the time, and drainage without stripping, about 20%. With recurrence, pain is present about 75% of the time.

Pregnancy rates following endometrioma treatment depend on patient age and the status of the pelvis following operative intervention. This can be determined from the EFI. Often, the dilemma with endometriomas is how aggressive to be in removing them. The principles involved are to remove all the cyst wall if possible, but absolutely to minimize ovarian tissue damage, because reduced ovarian reserve is a possible major negative consequence of ovarian surgery.

Recommendations

While endometriosis is often a cause of infertility, often infertile patients do not have endometriosis. A careful history, physical examination, and ultrasonography, and possibly other imaging studies, are prerequisites to careful clinical judgment in diagnosing and treating infertile patients who might or do have endometriosis.

When pelvic pain is present, initially nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives (OCs), progestational agents, or an intrauterine device can be helpful. These ovarian suppression medications do not increase fertility, however, and should be stopped in any patient who desires to get pregnant.

When pelvic and male fertility factors appear reasonably normal (even if minimal or mild endometriosis is suspected), treatment with clomiphene 100 mg on cycle days 3 through 7 and IUI for 3 to 6 cycles is an effective first step. However, if the patient has persistent pain and/or infertility without other significant infertility factors, then diagnostic laparoscopy with intraoperative treatment of disease is indicated.

Surgery well performed is effective treatment for all stages of endometriosis

FAST TRACK

If the patient has persistent pain and/or infertility without other significant factors, diagnostic laparoscopy with intraoperative treatment is indicated

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Endometriosis is a complex disease that can cause infertility. Its diagnosis and management are frequently difficult, requiring knowledge, experience, and good medical judgment and surgical skills. However, if evidence-linked principles are followed, effective treatment plans and good outcomes can be obtained for most patients.

and endometriomas, both for infertility and for pain. Repeat surgery, however, is rarely indicated because of limited results, so it is important to obtain the best possible result on the first surgery. Surgery is indicated for large endometriomas (>4 cm). Endometriosis has almost no effect on the IVF live birth rate unless ovarian reserve has been reduced by endometriomas or surgery, so endometriosis surgery should be performed by skilled and experienced surgeons.

Oil-based contrast medium use in hysterosalpingography is associated with higher pregnancy rates compared with water-based contrast

FAST TRACK

A multicenter RCT compared ongoing pregnancy rates and other outcomes among 1,294 women who had HSG with oil versus water contrast medium

Dreyer K, van Rijswijk J, Mijatovic V, et al. Oil-based or water-based contrast for hysterosalpingography in infertile women. N Engl J Med. 2017;376(21):2043–2052.

Hysterosalpingography (HSG) to assess tubal patency has been a mainstay of infertility diagnosis for decades. Some, but not all, studies also have suggested that pregnancy rates are higher after this tubal flushing procedure, especially if performed with oil contrast.[7,8] A recent multicenter, randomized, controlled trial by Dreyer and colleagues that compared ongoing pregnancy rates and other outcomes among women who had HSG with oil contrast versus with water contrast provides additional valuable information.[9]

Trial details

In this study, 1,294 infertile women in 27 academic, teaching and nonteaching hospitals were screened for trial eligibility; 1,119 women provided written informed consent. Of these, 557 women were randomly assigned to HSG with oil contrast and 562 to water contrast. The women had spontaneous menstrual cycles, had been attempting pregnancy for at least 1 year, and had indications for HSG.

Exclusion criteria were known endocrine disorders, fewer than 8 menstrual cycles per year, a high risk of tubal disease, iodine allergy, and a total motile sperm count after sperm wash of less than 3 million/mL in the male partner (or a total motile sperm count of less than 1 million/mL when an analysis after sperm wash was not performed).

Just prior to undergoing HSG, the women were randomly assigned to receive either oil contrast or water contrast medium. (The trial was not blinded to participants or caregivers.) HSG was performed according to local protocols using cervical vacuum cup, metal cannula (hysterophore), or balloon catheter and approximately 5 to 10 mL of contrast medium.

After HSG, couples received expectant management when the predicted likelihood of pregnancy within 12 months, based on the prognostic model of Hunault, was 30% or greater.[10] IUI was offered for pregnancy likelihood less than 30%, mild male infertility, or failure after a period of expectant

management. IUI with or without mild ovarian stimulation (2–3 follicles) with clomiphene or gonadotropins was initiated after a minimum of 2 months of expectant management after HSG.

The primary outcome measure was ongoing pregnancy, defined as a positive fetal heartbeat on ultrasonographic examination after 12 weeks of gestation, with the first day of the last menstrual cycle for the pregnancy within 6 months after randomization. Secondary outcome measures were clinical pregnancy, live birth, miscarriage, ectopic pregnancy, time to pregnancy, and pain scores after HSG. All data were analyzed according to intention-to-treat.

Pregnancy rates increased with oil-contrast HSG

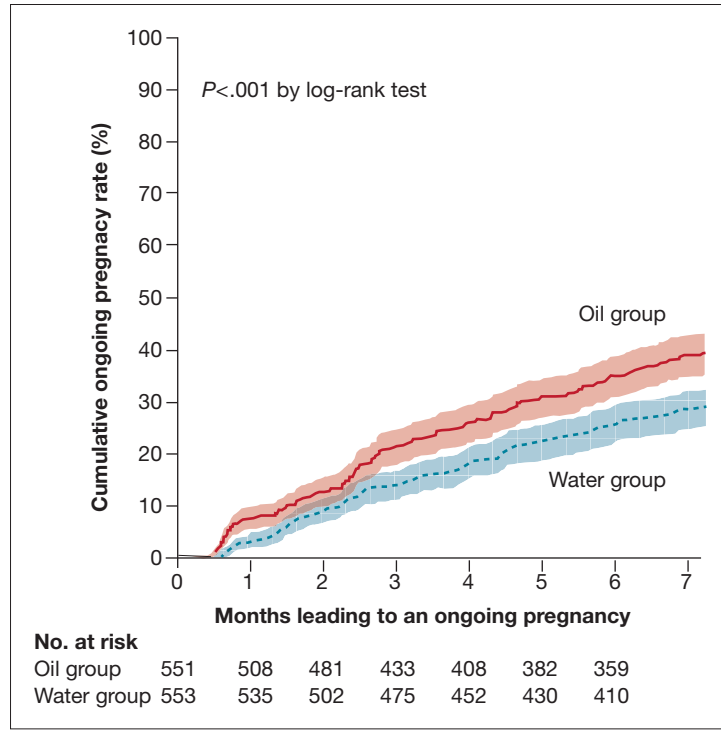
The baseline characteristics of the 2 groups were similar. HSG showed bilateral tubal patency in 477 of 554 women (86.1%) in the oil contrast group and in 491 of 554 women (88.6%) who received the water contrast (rate ratio, 0.97; 95% confidence interval [CI], 0.93–1.02). Bilateral tubal occlusion occurred in 9 women in the oil group (1.6%) and in 13 in the water group (2.3%) (relative risk, 0.69; 95% CI, 0.30–1.61).

A total of 58.3% of the women assigned to oil contrast and 57.2% of those assigned to water contrast received expectant management. Similar percentages of women in the oil group and in the water group underwent IUI (39.7% and 41.0%, respectively), IVF or intracytoplasmic sperm injection (ICSI) (2.3% and 2.2%), laparoscopy (6.2% in each group), and hysteroscopy (4.4% and 4.2%).

Ongoing pregnancy occurred in 220 of 554 women (39.7%) in the oil contrast group and in 161 of 554 women (29.1%) in the water contrast group (rate ratio, 1.37; 95% CI, 1.16–1.61; *P*<.001). The median time to the onset of pregnancy in the oil group was 2.7 months (interquartile range, 1.5–4.7) (**FIGURE**), while in the water group it was 3.1 months (interquartile range, 1.6–4.8) (*P* = .44).

While the proportion of women getting pregnant with or without the different interventions was similar in both groups, the live birth rate was 38.8% in the oil group versus 28.1% in the water group (rate ratio, 1.38; 95% CI, 1.17–1.64; *P*<.001). Three of 554 women (0.5%) assigned to oil contrast and 4 of 554 women (0.7%) in the water contrast group had an adverse event during the trial period. Three women (1.4%), all in the oil group, delivered a child with a congenital anomaly.

FIGURE Ongoing pregnancy rate in women who had hysterosalpingography with oil-based or water-based contrast medium[9]



Why this study is important

This is the largest and best methodologic study on this clinical issue. It showed higher pregnancy and live birth rates within 6 months of HSG performed with oil compared with water. Although the study was not blinded, the group similarities and objective outcomes support minimal bias. Importantly, these results can be generalized only to women with similar inclusion characteristics.

It is unclear why oil HSG might enhance fertility. Suggested mechanisms include flushing of debris and/or mucous plugs or an effect

WHAT THIS EVIDENCE MEANS FOR PRACTICE

HSG is an important diagnostic test for most infertility patients. The fact that a therapeutic benefit probably also is associated with oil-based HSG increases the clinical indications for this test.

on peritoneal macrophages or endometrial receptivity. Since HSG is minimally invasive and inexpensive, and the 10% increase in pregnancy rates corresponds to an NNT of 10, it is reasonable to consider, although formal cost-effectiveness data are lacking.

Concerns include the rare theoretical risk of intravasation with subsequent allergic reaction or fat embolism. Three infants in the oil group and none in the water group had congenital anomalies. This is likely due to chance, since this rate is not higher than that in the general population and no other data suggest an increased risk. Comparison of these results with other new techniques, such as sonohysterography (saline infusion sonogram), awaits further studies.

Recommendation

HSG with oil contrast should be considered a potential therapeutic as well as diagnostic intervention in selected patients.

Infertility glossary is newly updated

FAST TRACK

The revised evidence-base driven glossary provides definitions that now set the standard for international communication

Zegers-Hochchild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. Fertil Steril. 2017;108(3):393–406.

Terms and definitions used in infertility and fertility care frequently have had different meanings for different stakeholders, especially on a global basis. This can result in misunderstandings and inappropriate interpretation and comparison of published information and research. To help address these issues, international fertility organizations recently developed an updated glossary on infertility terminology.

The consensus process for updating the glossary

The International Glossary on Infertility and Fertility Care, 2017, was recently published simultaneously in *Fertility and Sterility* and *Human Reproduction*. This is the second revision; the first glossary was published in 2006 and revised in 2009. This revision's 25 lead experts began work in 2014. Their teams of professionals interacted by electronic mail, at international and regional society meetings, and at 2 consultations held in Geneva, Switzerland. This glossary represents consensus agreement reached on 283 evidence-driven terms and definitions.

The work was led by the International Committee for Monitoring Assisted Reproductive Technologies in partnership with the American Society for Reproductive Medicine, European Society of Human Reproduction and Embryology, International Federation of Fertility Societies, March of Dimes, African Fertility Society, Groupe Inter-africain d'Etude de Recherche et d'Application sur la Fertilité, Asian Pacific Initiative on Reproduction, Middle East Fertility Society, Red Latinoamericana de Reproducción Asistida, and the International Federation of Gynecology and Obstetrics.

All together, 108 international professional experts (clinicians, basic scientists, epidemiologists, and social scientists), along with national and regional representatives of infertile persons, participated in the development of this evidence-base driven glossary. As such, these definitions now set the standard for international communication among clinicians, scientists, and policymakers.

Definition of infertility is broadened

The definitions take account of ethics, human

rights, cultural sensitivities, ethnic minorities, and gender equality. For example, the first modification included broadening the concept of infertility to be an "impairment of individuals" in their capacity to reproduce, irrespective of whether the individual has a partner. Reproductive rights are individual human rights and do not depend on a relationship with another individual. The revised definition also reinforces the concept of infertility as a disease that can generate an impairment of function.

New—and changed—definitions

Certain terms need to be consistent with those used currently internationally, for example, at which gestational age a miscarriage/abortion becomes a stillbirth.

Some terms are confusing, such as *subfertility,* which does not define a different or less severe fertility status than infertility, does not exist before infertility is diagnosed, and should not be confused with sterility, which is a permanent state of infertility. The term *subfertility* therefore is redundant and has been removed and replaced by *infertility.*

In a different context, the term *conception,* and its derivatives such as *conceiving* or *conceived,* was removed because it cannot be described biologically during the process of reproduction. Instead, terms such as *fertilization, implantation, pregnancy,* and *live birth* should be used.

Important male terms also changed: *oligospermia* is a term for low semen volume that is now replaced by *hypospermia* to avoid confusion with *oligozoospermia,* which is low concentration of spermatozoa in the ejaculate below the lower reference limit. When reporting results, the reference criteria should be specified.

Lastly, owing to the lack of standardization in determining the burden of infertility, and to better ensure comparability of prevalence data published globally, this glossary includes definitions for terms frequently used in epidemiology and public health. Examples include *voluntary* and *involuntary childlessness, primary* and *secondary infertility, fertility care, fecundity,* and *fecundability,* among others.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The language we use determines our individual and collective understanding of the scientific and clinical care of our patients. This glossary provides an essential and comprehensive standardization of terms and definitions essential to quality reproductive health care.

Getting the word out

The glossary has been approved by all of the participating organizations who are assisting in its distribution. It is being presented at national and international meetings and is used in The FIGO Fertility Toolbox (www.fertilitytool.com). It is hoped that all professionals and other stakeholders will begin to use its terminology globally to provide quality care and ensure consistency in registering specific fertility care interventions and more accurate reporting of their outcomes. ●

FAST TRACK

The updated glossary is available in the FIGO Fertility Toolbox at www.fertilitytool.com

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VALUE-BASED MEDICINE: PART 2

What makes a quality "quality measure"?

As we move away from fee-for-service medicine, we need to understand the brave new world of value-based care so we can successfully adapt our practices to the new payment model

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IN THIS ARTICLE

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The future of health care is value-based care. If Value equals Quality divided by Cost, then a defined, validated way to measure Quality is paramount to that equation. (Fortunately, Cost comes with convenient measurement units called *dollars*.) Payers now are asking health care providers to shift from a fee-for-service to a value-based reimbursement structure to encourage providers to deliver the best care at the lowest cost. Providers who can embrace this data-driven paradigm will succeed in this new environment.

So how do we define high-quality care? What makes a good quality measure? How do you actually measure what happens in a clinical encounter that impacts health outcomes?

To answer these questions, organizations have constructed standardized clinical quality measures. Clinical quality measures facilitate value-based care by providing a metric on which to measure a patient's quality of care. They can be used 1) to decrease the overuse, underuse, and misuse of health care services and 2) to measure patient engagement and satisfaction with care.

What are quality measures?

The Academy of Medicine (formerly named the Institute of Medicine) defines health care quality as "the degree to which health services for individuals and populations increase the likelihood of desired health

outcomes and are consistent with current professional knowledge."[1]

Clearly defined components and terminology. From a quantitative standpoint, quality measures must have a clearly defined numerator and denominator and appropriate inclusions, exclusions, and exceptions. These components need to be expressed clearly in terms of publicly available terminologies, such as ICD (International Classification of Diseases) codes or SNOMED CT (Systematized Nomenclature of Medicine—Clinical Terms) terms. A measure that asks if "antihypertensive meds" have been given will not nearly be as specific as one that asks if "labetalol IV, *or* hydralazine IV, *or* nifedipine SL" has been administered. The decision to tie the data elements in a measure to administrative data, such as ICD codes, or to clinical data, such as SNOMED CT, also affects how these measures can be calculated.

Moving targets. The target of the measure also must carefully be considered. Quality measures can be used to evaluate care across the full range of health care settings—from individual providers, to care teams, to hospitals and hospital systems, to health plans. While some measures easily can be assigned to a specific provider, others are not as straightforward. For example, who gets assigned the cesarean delivery when a midwife turns the case over to an obstetrician?

Timeframe in outcomes measurement. The data infrastructure is currently set up to support measurement of immediate events, 30-day or 90-day episodes, and health insurance plan member years. Longer-term outcomes, such as over 5- and 10- year periods, are out of reach for most measures. To obtain an accurate view of the impact of medical interventions or disease conditions, however, it will be important to follow patients over time. For example, to know the failure rate of intrauterine systems, sterilization, or hormonal contraceptives, it is important to be able to track pregnancy occurrence during use of these methods for longer than 90 days. Failures can occur years after a method is initiated.

Another example is to create a performance measure focused on the overall improvement in quality of life and costs related to different treatments for abnormal uterine bleeding. How does the patient experience vary over time between treatment with hormonal contraception, endometrial ablation, or hysterectomy? Which option is most "valuable" over time when the patient experience and the cost are assessed for more than a 90-day episode? These important questions need to be answered as we maneuver into a value-based health system.

Risk adjustment. Quality measures also may need to be risk adjusted. The "My patients are sicker" refrain must be accounted for with full transparency and based on the best available data. Quality measures can be adjusted using an Observed/Expected factor, which helps to account for complicated cases.[2]

Clearly, social and behavioral determinants of health also play a role in these adjustments, but it can be more challenging to acquire the data elements needed for those types of adjustments. Including these data enables us to evaluate health disparities between populations, both demographically and socioeconomically.[3] This is important for future development of minority inclusive quality measures. Some racial and ethnic minority populations have poorer health outcomes from preventable and treatable diseases. Evidence shows that these groups have differences in access to health care, quality of care, and health measures, including life expectancy and maternal mortality. Access to clinical data through quality measures allows for these health disparities to be brought into quantifiable perspective and assists in the development of future incentive programs to combat health inequalities and provide improved delivery of care.

Developing quality measures

Quality measures generally fall into 4 broad categories: structure, process, outcome, and patient experience (**TABLE,** page 33).[4,5] Quality measure development begins with an assessment of the evidence, which is usually derived from clinical guidelines that link a particular process, structure, or outcome with improved

FAST TRACK

Quality measures must have a clearly defined numerator and denominator and appropriate inclusions, exclusions, and exceptions

patient health or experience of care. For example, the American College of Obstetricians and Gynecologists (ACOG) has developed a clinical practice guideline for screening, diagnosing, and managing gestational diabetes. The guideline addresses drug therapies, such as insulin, and alternative treatments, such as nutrition therapy. Much like the process for creating the guideline itself, translating the guideline into a quality measure requires a thoughtful, transparent, and well-defined process.

Role of the quality measure steward. Coordinating the process of translating evidence-based guidelines into quality measures requires a measure steward. Measure stewards usually are government agencies, nonprofit organizations, and/or for-profit companies. During the development process, the steward usually reaches out to additional stakeholders for feedback and consensus. Development process steps include:

- evaluation of the evidence, including the clinical practice guideline(s)
- consensus on the best measurement approach (consider the feasibility of the measurement and how it will be collected)
- development of detailed measure specifications (that is, what will be measured and how)
- feedback on the specifications from stakeholders, including professional societies and patient advocates
- testing of the measure logic and clinical validity against clinical data
- final approval by the measure steward.

Endorsement of quality measures. After a quality measure is developed, it is often endorsed by government agencies, professional societies, and/or consumer groups. Endorsement is a consensus-based process in which stakeholders evaluate a proposed measure based on established standards. Generally, stakeholders include health care professionals, consumers, payers, hospitals, health plans, and government agencies.

Evaluation of quality measures includes these important considerations:

- Are the necessary data fields available in a typical electronic health record (EHR) system?
- What is the data quality for those data fields?
- Can the measure be calculated reliably across different data sets or EHRs?
- Does the measure address one of the National Academy of Medicine quality properties? According to the academy, quality in the context of clinical care can be defined in terms of properties of effectiveness, equity, safety, efficiency, patient centeredness, and timeliness.[1]

FAST TRACK

Endorsement of quality measures is a consensus-based process in which stakeholders evaluate a proposed measure based on established standards

ACOG's role in developing quality measures

In October 2016, the Centers for Medicare and Medicaid Services released the final Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Under this rule, the Merit-based Incentive Payment System (MIPS) was created, which was intended to drive "value" rather than "volume" in payment incentives. Measures are critical to defining value-based care. However, the law has limited or no impact on providers who do not care for Medicare patients.

Clinicians eligible to participate in MACRA must bill more than $90,000 a year in Medicare Part B allowed charges and provide care for more than 200 Medicare patients per year.[6] This means that the MIPS largely overlooks ObGyns, as the bulk of our patients are insured either by private insurance or by Medicaid. However, maternity care spending is a significant part of both Medicaid and private insurers' outlay, and both payers are actively considering using value-based financial models that will need to be fed by quality metrics. ACOG wants to be at the forefront of measure development for quality metrics that affect members and has committed resources to formation of a measure development team.

ACOG wants providers to be in control of how their practices are evaluated. For this reason, ACOG is focusing on measures that are based on clinical data entered by providers into an EHR at the point of care. At the same time, ACOG is cognizant of not increasing the documentation burden for providers. Understanding the quality of the data, as opposed to the quality of care, will be a

TABLE Types of quality measures[4,5]

Type	Description	Example
Structure	Assesses the characteristics of care setting, including facilities, personnel, and/or policies related to care delivery	Does an intensive care unit have a critical care specialist on staff at all times?
Process	Determines if the services provided to patients are consistent with routine care delivery	Does a doctor ensure that his or her patients receive recommended cancer screenings?
Outcome	Evaluates patient health as a result of the care received	What is the survival rate for patients who experience heart attack?
Patient experience	Provides feedback on patients' experiences of care	Do patients report that their provider explains their treatment options in ways that are easy to understand?

fundamental task for the maternity care registry that ACOG is launching in 2018.

What can ObGyns do?

Quality measures are about more than just money. Public reporting of these measures on government and payer websites may influence public perception of a practice.[7] The focus on patient-centered care means that patients have a voice in their care, financially as well as literally, so expect to see increased scrutiny of provider performance by patients as well as payers. One way to measure patient experience of treatments, symptoms, and quality of life is through patient-reported outcome measures (PROMs). Assessing PROMs in routine care ensures that information only the patient can provide is collected and analyzed, thus further enhancing the delivery of care and evaluating how that care is impacting the lives of your patients.

The transition from fee-for-service to a value-based system will not happen overnight, but it will happen. This transition—from being paid for the quantity of documentation to the quality of documentation—will require some change management, rethinking of workflows, and better documentation tools (such as apps instead of EHR customization).

Many in the medical profession are actively exploring these changes and new developments. These changes are too important to leave to administrators, coders, scribes, app developers, and policy makers. Someone in your practice, hospital, or health system is working on these issues today. Tomorrow, you need to be at the table. The voices of practicing ObGyns are critical as we work to address the current challenging environment in which we spend more per capita than any other nation with far inferior results. Measures that matter to us and to our patients will help us provide better and more cost-effective care that payers and patients value.[8] ●

FAST TRACK

One way to measure patient experience of treatments, symptoms, and quality of life is through PROMs

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Dr. Kimberly Gregory and colleagues bring you part 3 of this series on value-based medicine next month, with "The role of patient-reported outcomes in women's health."

Postsurgical pain: Optimizing relief while minimizing use of opioids

Today, a 2-pronged strategy characterizes postoperative pain management: Offer analgesia with proven medical strategies, including multimodal approaches, and supported by patient education; and do this so that you curtail or avoid opioid analgesics

Mikio Nihira, MD, MPH, and Adam C. Steinberg, DO

IN THIS ARTICLE

CASE Managing pain associated with prolapse and SUI surgery

A 46-year-old woman (G4P4) described 3 years of worsening symptoms related to recurrent stage-3 palpable uterine prolapse. She had associated symptomatic stress urinary incontinence. She had been treated for uterine prolapse 5 years ago with vaginal hysterectomy, bilateral salpingectomy, and high uterosacral-ligament suspension.

After consultation, the patient elected to undergo laparoscopic sacral colpopexy, a mid-urethral sling, and possible anterior and posterior colporrhaphy. Appropriate discussion about the risks and benefits of mesh was provided preoperatively. The surgical team judged her to be highly motivated; she wanted same-day outpatient surgery so that she could go home and then return to work. She had excellent support at home.

How would you counsel this patient about expected postoperative pain? Which medications would you administer to her preoperatively and perioperatively? Which ones would you prescribe for her to manage pain postoperatively?

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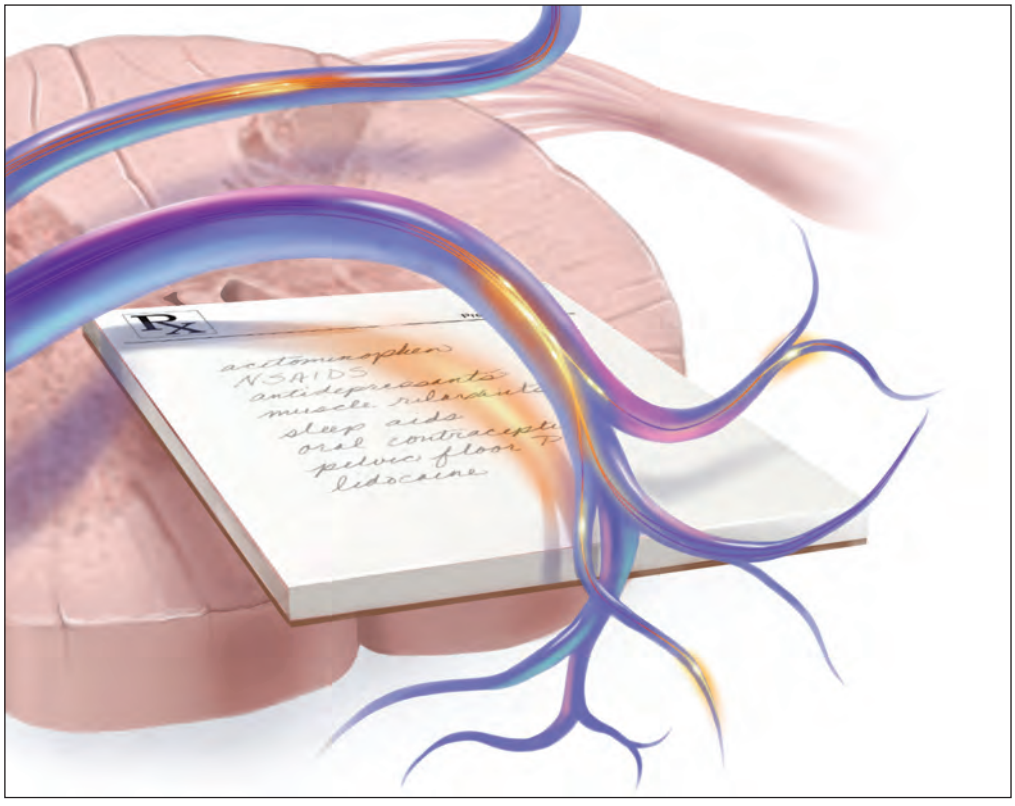
Dr. Nihira reports that he is a consultant to Pacira. Dr. Steinberg reports no financial relationships relevant to this article.

Adverse impact of prescription opioids in the United States

Although fewer than 5% of the world's population live in the United States, nearly 80% of the world's opioids are written for them.[1] In 2012, 259 million prescriptions were written for opioids in the United States—more than enough to give every American adult their own bottle of pills.[2] Sadly, drug overdose is now a leading cause of accidental death in the United States, with 52,404 lethal drug overdoses in 2015. A startling statistic is that prescription opioid abuse is driving this epidemic, with 20,101 overdose deaths related to prescription pain relievers and 12,990 overdose deaths related to heroin in 2015.[3]

It is likely that there are multiple reasons prescribing of opioids is epidemic. Surgical pain is a common indication for opioid prescriptions; fewer than half of patients who undergo surgery report adequate postoperative pain relief.[4] Recognition of these deficits



Although employed for several hundred years for pain management, opioids are highly addictive, have many adverse effects, and their use should be minimized or eliminated. All applicable categories of nonopioid alternatives for pain management and pain control strategies should be considered for surgical patients.

in pain management has inspired national campaigns to improve patients' experience with pain and aggressively address pain with drugs such as opioids.[5]

At the same time, marketing efforts by the pharmaceutical industry sought to reassure the medical community that patients would not become addicted to prescription opioid pain relievers if physical pain was the indication for such prescriptions. In response, health care providers began to prescribe opioids at a greater rate. As providers were encouraged to increase prescriptions, opioid medications began to be misused—and only then did it become clear that these medications are, in fact, highly addictive.[6] Opioid abuse and overdose rates began to increase; in 2015, more than 33,000 Americans died because of an opioid overdose, including prescription opioids and heroin[7] (**FIGURE**, page 36). In fact, although most people recognize the threat posed by illegal heroin, most of the 2 million who abused opioids in 2015 in the United States suffered from prescription abuse; only about a quarter, or about 600,000, abused heroin.[8] In addition, more than 80% of people who abuse heroin initially abused prescription opioids.[9]

Multimodal approach to pain management

The goals of postsurgical pain treatment are to relieve suffering, optimize bodily functioning after surgery, limit length of the stay, and optimize patient satisfaction. Pain-control regimens should consider the specific surgical procedure and the patient's medical, psychological, and physical conditions; age; level of fear or anxiety; personal preference; and response to previous treatments.[10]

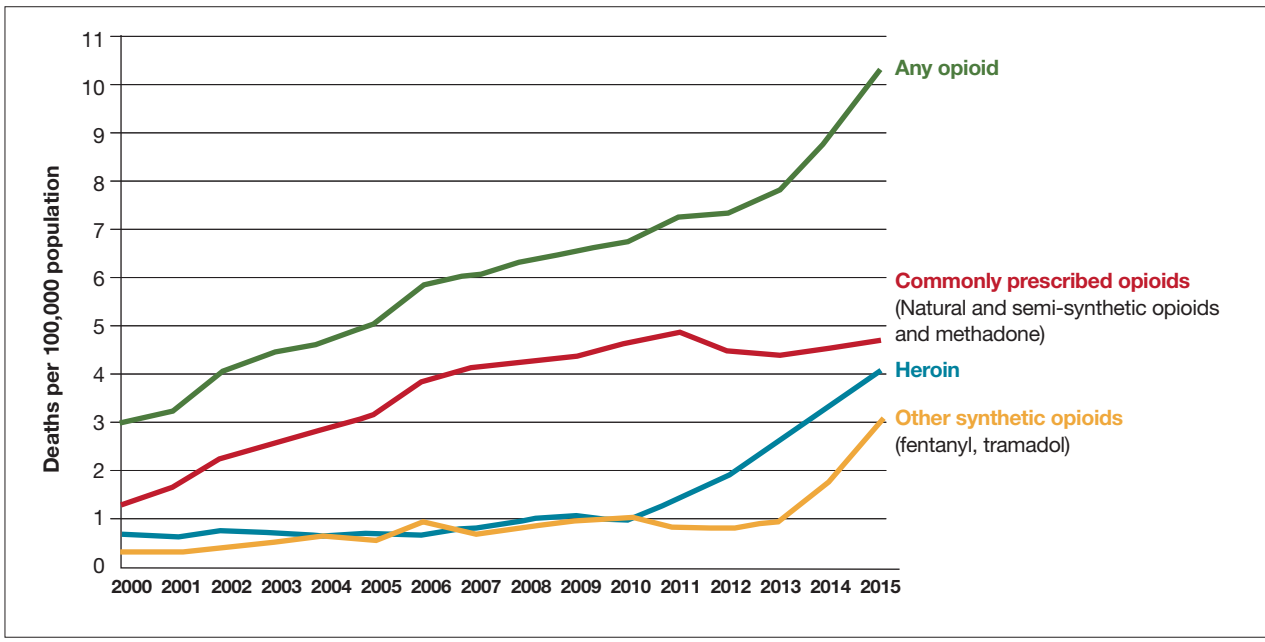
Optimally, postsurgical pain management

FAST TRACK

National campaigns to recognize inadequate postoperative pain relief and pharmaceutical company marketing practices led to increased opioid prescriptions and eventual misuse of opioid medications

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

FIGURE Overdose deaths involving opioids, United States, 2000–2015



Source: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. https://wonder.cdc.gov/.

starts well before the day of surgery. Employing such strategies as Enhanced Recovery after Surgery (ERAS) protocols does not necessarily mean providing the same care for every patient, every time. Rather, ERAS serves as a checklist to ensure that all applicable categories of pain medication and pain-control strategies are considered, selected, and dosed according to individual needs.[11] (See "Preoperative management of pain expectations.")

Opioids

Opioids have been employed to treat pain for 700 years.[12] They are powerful pain relievers because they target central mechanisms involved in the perception of pain. Regrettably, because of their central action, opioids have many adverse effects in addition to being highly addictive.

Nonopioid alternatives

Expert consensus, including recommendations of the World Health Organization,[11] favors using nonopioids as first-line medications to address surgical pain. Nonopioid analgesic options are acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjuvant medications. In addition, nonanalgesic medications such as sedatives, sleep aids, and muscle relaxants can relieve postsurgical pain. Optimal use of these nonopioid medications can significantly reduce or eliminate the need for opioid medications to treat pain. Goals are to 1) reserve opioids for the most severe pain and 2) minimize the number of doses/pills of opioids required to control postsurgical pain.

Acetaminophen. At dosages of 325 to 1,000 mg orally every 4 to 6 hours, to a maximum dosage of 4,000 mg/d, acetaminophen can be used to treat mild pain and, in combination with other medications, moderate-to-severe pain. The drug also can be administered intravenously (IV), although use of the IV route is limited in many hospitals because of its significantly higher expense compared to the oral form.

The mechanism of action of acetaminophen is unique among pain relievers; it can therefore be used in combination with other pain relievers to more effectively treat pain

with fewer concerns about medication-induced adverse effects or opioid overdose. However, keep in mind when considering combining analgesics, that acetaminophen is an active ingredient in hundreds of over-the-counter (OTC) and prescription formulations, and that a combination of more than one acetaminophen-containing product can create the risk of overdose.

Acetaminophen should be used with caution in patients with liver disease. That being said, multiple trials have documented safe use in normal body weight adults who do not have hepatic disease, at dosages as high as 4,000 mg over a 24-hour period.[13]

NSAIDs. A combination of an NSAID and acetaminophen has been documented to reduce the amount of opioid medications required to treat postsurgical pain. In most circumstances, especially for minor surgery, acetaminophen and NSAIDS can be administered just before surgery starts. This preoperative treatment, called "preventive analgesia" or "preemptive analgesia," has been demonstrated in multiple clinical trials to reduce postoperative pain.[14]

Adjuvant pain medications. Antidepressants, antiepileptic agents, and muscle relaxants—agents that have a primary indication for a condition (or conditions) other than pain and do not directly provide analgesia—have been used as adjuvant pain medications. When employed with traditional analgesics, they have been demonstrated to reduce postsurgical pain scores and the amount of opioids required. These medications need to be used cautiously because some are associated with serious sedation and vertigo (**TABLE,** page 38). Take caution when using adjuvant pain medications in patients older than 65 years; guidance on their use in older patients has been outlined by the American Geriatrics Society and other professional organizations.[15]

CASE Continued

The patient was given the expectation that the 11-mm left lower-quadrant port site would likely be the most bothersome site of pain—a rating of 4 or 5 on a visual analogue scale of 1 to 10, on postoperative day 1, while standing. The other 3 (5-mm) laparoscopic ports, she was told, would, typically, be less bothersome. The patient was educated regarding the role of analgesics and adjuvant medications and cautioned not to exceed 4,000 mg of acetaminophen in any 24-hour period. She was told that gabapentin may make her feel sedated or dizzy, or both; she was encouraged to hold this medication if she found these adverse effects bothersome or limiting.

The following multimodal pain management was established.

Preoperatively, the patient was given:

- Acetaminophen 1.5 g orally (as a liquid, 45 mL of a suspension of 500 mg/15 mL liquid), 2 to 3 hours preoperatively; the surgical suite did not stock IV acetaminophen.
- Gabapentin 600 mg orally, with a sip of water, the morning of surgery.
- Celecoxib 100 mg orally, with a sip of water, the morning of surgery.

Prescriptions for home postoperative pain management were provided preoperatively:

- OTC acetaminophen 1,000 mg (as 2 500-mg tablets) taken as a scheduled dose every 8 hours for the first 48 hours postoperatively.
- Meloxicam 15 mg daily as the NSAID, taken as a scheduled dose once per day for the first 48 hours postoperatively, then as needed.
- Gabapentin 300 mg (in addition to the preoperative dose, above), taken as a scheduled dose every 8 hours for the first 48 hours postoperatively, then as needed.
- Oxycodone 5 mg (without acetaminophen) for breakthrough pain.

Preoperative management of pain expectations

Ideally, before surgery, provide the patient with an opportunity to learn that:

- Her expectations about postsurgical pain should be realistic, and that freedom from pain is not realistic.
- Pain-reduction options should optimize her bodily function and mobility, reduce the degree to which pain interferes with activities, and relieve associated psychological stressors.
- Inherent in the pain management plan should be a goal of minimizing the risks of opioid misuse, abuse, and addiction—for the patient and for her family members and friends.

FAST TRACK

Acetaminophen, NSAIDs, antidepressants, antiepileptic agents, and muscle relaxants, or certain combinations of these drugs, can be used as alternatives to opioids for pre- and postoperative pain management

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TABLE Adjuvant analgesic drugs[a]

Medication	Uses	Starting dose	Dose range	Comments
Antidepressants (often use lower dosages to treat pain than to treat depression)				
Amitriptyline (Elavil) Nortriptyline (Pamelor) Desipramine (Norpramin)	Neuropathic pain	25 mg orally at bedtime (10 mg or less for elderly patients); titrate dose every few days to minimize side effects	75–150 mg orally at bedtime	Side effects include dry mouth, drowsiness, dizziness, constipation, orthostatic hypotension, urinary retention, confusion. Obtain baseline EKG for history of cardiac disease.
Selective serotonin and norepinephrine reuptake inhibitor (SSNRI) antidepressant				
Duloxetine (Cymbalta)	Diabetic peripheral neuropathy	30 mg	60 mg once daily sustained release	Should not use with MAOIs (Zyvox). Consider lower starting dose for patients for whom tolerability is a concern.
Antiepileptics				
Gabapentin (Neurontin)	Neuropathic pain	100–300 mg orally every 8 hours; increase by 100–300 mg every 3 days	300–3,600 mg/d	Adjust dose for renal dysfunction; can cause drowsiness
Pregabalin (Lyrica)	Diabetic peripheral neuropathy; postherpetic neuralgia; fibromyalgia	150 mg orally in 2–3 divided doses	150–600 mg/d (depending on indication)	Similar to gabapentin, often more rapid response than gabapentin; Schedule V controlled substance
Muscle relaxants				
Baclofen (Lioresal)	Muscle spasm	5 mg orally 3 times daily	80 mg orally in 24-hr divided doses	Caution in renal insufficiency
Tizanidine (Zanaflex)	Muscle spasm	4 mg daily–may be divided	36 mg/d	Gradually increase in 2–4 mg increments over 4 weeks; caution in elderly patients and those with renal insufficiency
Methocarbamol (Robaxin)	Muscle spasm	Up to 8 g daily in severe cases, decreasing as symptoms improve	4–4.5 g/d in 3–6 divided doses	Available IV 100 mg/mL or oral 750- or 500-mg tablets. IV should be given for maximum of 3 days only, but may be repeated 48 hours later.

[a]Most commonly used drugs. Consideration should be given to comorbidities, hepatic and renal insufficiency, and age.

Abbreviations: EKG; electrocardiogram; MAOIs, monoamine oxidase inhibitors.

Intraoperatively:

- Meticulous attention was paid to patient positioning, to reduce the possibility of back and upper- and lower-extremity injury postoperatively.
- A corticosteroid (dexamethasone 8 mg IV) was administered to minimize postoperative nausea and vomiting and as an adjuvant medication for postoperative pain control.
- Careful attention was paid to limit residual CO_2 gas and intraoperative intra-abdominal pressures.
- All laparoscopic port sites were injected with 30 mL of 0.25% bupivacaine with epinephrine, extending to subcutaneous, fascial, and peritoneal layers.

Why a multimodal plan to treat pain?

Pain following laparoscopy has been associated with many variables, including patient positioning, port size and placement, amount of port manipulation, and gas retention. After a laparoscopic surgical procedure,

patients report pain in the abdomen, back, and shoulders.

Postsurgical pain has 3 components:

- **Shoulder pain,** thought to result from phrenic nerve irritation caused by lingering CO_2 in the abdominal cavity.
- **Visceral pain,** occurring secondary to stretching of the abdominal cavity.
- **Somatic pain,** caused by the surgical incision; of the 3 components to pain, somatic pain can have the least impact because laparoscopic incisions are small.

For our patient, prior to the incisions being made, she received local anesthesia intraoperatively to the laparoscopic port sites to include the subcutaneous, fascial, and peritoneal layers. Involving these layers allows for more of a block. An ultrasonography-guided transversus abdominis plane (TAP) block, if available, is highly effective at decreasing postoperative pain, but its efficacy is dependent on the anatomy and the skill of the physician (whether anesthesiologist, gynecologist, or surgeon) who is placing it.[16]

We used dexamethasone 8 mg IV, intraoperatively because this single dose has been shown to decrease the perception of pain postoperatively. Dexamethasone also has been shown to decrease consumption of oxycodone during the 24 hours after laparoscopic gynecologic surgery.[17]

CO_2 used to insufflate the patient's abdomen can take as long as 2 days to fully resorb, resulting in increased pain. This discomfort has been described as delayed; the patient might not notice it until she goes home. In a study, 70% of patients had shoulder discomfort following laparoscopy 24 hours after their procedure.[18] For this reason, we employed several techniques to reduce this effect:

- We reduced the intra-abdominal pressure limit to 10 mm Hg (from 15 mm Hg) once dissection was complete.
- At the end of the procedure, careful attention was paid to removing as much intra-abdominal gas as possible, including placing the patient in the Trendelenburg position and having the anesthesiologist induce a Valsalva maneuver. This action has been shown to significantly improve pain control compared to placebo intervention.[19]
- We used humidified CO_2, which has been demonstrated to reduce pain in laparoscopic surgery.[20]

Preemptively, we provided this patient with acetaminophen, celecoxib, and gabapentin, which have been demonstrated to be effective in gynecologic patients to decrease the need for postoperative opioids.[21] Also, our patient received counseling, with specific expectations for what to expect following the surgical procedure.

CASE Resolved

Our patient did exceptionally well following surgery. She used only one of the oxycodone pills and did not require unplanned interventions. She took gabapentin, acetaminophen, and meloxicam at their scheduled doses for 2 days. She continued to use meloxicam for 4 more days for mild abdominal pain, then discontinued all medications.

A word about disposal of 'excess' opioids

The US Food and Drug Administration (FDA) recommends disposing of certain drugs through a take-back program or, if such a program is not readily available, by flushing them down a toilet or sink. In a recent study, investigators concluded that opioids on the FDA's so-called flush list include most opioids in clinical use—even if the entire supply prescribed is to be flushed down the drain. Conservative estimates of environmental degradation were employed in the study; the investigators' conclusion was that these drugs pose a "negligible" eco-toxicologic risk.[1]

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Online resources for pain management

- **Drug Disposal Information**
  (US Department of Justice Drug Enforcement Administration)
  https://www.deadiversion.usdoj.gov/drug_disposal/index.html
- **Surgical Pain Consortium**
  http://surgicalpainconsortium.org/

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She flushed her 9 unused oxycodone pills down the toilet. (See "A word about disposal of 'excess' opioids," page 39.[22]) The patient returned to her administrative duties at work 2 weeks after the procedure and reported that she was "very satisfied" with her surgical experience.

In conclusion

Postoperative pain is a complex entity that must be considered to require individualized strategies and, possibly, multiple interventions. Optimally, thorough education, including pain management options, is provided to the patient prior to surgery. Given the current state of opioid abuse in the United States, all gynecologic surgeons should be familiar with multimodal pain therapy and how to employ nonmedical techniques to reduce postsurgical pain without relying solely on opioids. (See "Online resources for pain management," page 39.) ●

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DON'T MISS: 3 cases of chronic pelvic pain managed with nonsurgical, nonopioid therapies . . . . . See page 41

3 cases of chronic pelvic pain managed with nonsurgical, nonopioid therapies

Chronic pain—different from acute injury or postsurgical pain—often arises from multiple organ systems. Three patient scenarios illustrate the importance of characterizing chronic pelvic pain and individualizing treatment to manage symptoms and improve quality of life.

Sara R. Till, MD, MPH, and Sawsan As-Sanie, MD, MPH

Chronic pelvic pain (CPP) is defined as noncyclic pain in the pelvis, anterior abdominal wall, back, or buttocks that has been present for at least 6 months and is severe enough to cause functional disability or require medical care.[1] CPP is very common, with an estimated prevalence of 15% to 20%. It accounts for 20% of gynecology visits and 15% of hysterectomies in the United States, and it is believed to account for $2.8 billion in direct health care spending annually.[2–5]

Caring for patients with CPP can be very challenging. They often arrive at your office frustrated, having seen multiple providers or having undergone multiple surgeries. They may come to you whether you are a general ObGyn or subspecialize in maternal-fetal medicine, oncology, reproductive endocrinology, urogynecology, or adolescent gynecology. From interactions with other providers or their own family members, these patients may have received the message—either subtly or overtly—that their pain is "all in their head." As such, some patients may resist any implication that their pain does not have an anatomic source. It is therefore critical to have appropriate tools for evaluating and managing the complex problem of CPP.

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Dr. Till reports no financial relationships relevant to this article.
Dr. As-Sanie reports that she is a consultant to AbbVie.

Perform a thorough and thoughtful assessment

Chronic pelvic pain often presents as a constellation of symptoms with contributions from multiple sources, as opposed to a single disease entity. Occasionally there is a single cause of pain, such as a large endometrioma or degenerating fibroid, where surgery can be curative. But more commonly the pain arises from multiple organ systems. In such cases, surgery may be unnecessary and, often, can worsen pain.

Thoughtful evaluation is critical in the CPP population. Take a thorough patient history to determine the characteristics of pain (cyclic or constant, widespread or localized), exacerbating factors, sleep disturbances,

IN THIS ARTICLE

fatigue, and current coping strategies. Focus a comprehensive physical examination on identifying the maneuvers that reproduce the patient's pain, and include an examination of the pelvic floor muscles.[6] In most cases, pelvic ultrasonography provides adequate evaluation for anatomic sources of pain.

Chronic pain does not behave like acute injury or postsurgical pain. Continuous peripheral pain signals for a prolonged period can lead to changes in how the brain processes pain; specifically, the brain can begin to amplify pain signals. This "central pain amplification" is characterized clinically by widespread pain, fatigue, sleep disturbances, memory difficulties, and somatic symptoms. Central pain amplification occurs in many chronic pain conditions, including fibromyalgia, interstitial cystitis, irritable bowel syndrome, low back pain, chronic headaches, and temporomandibular joint disorder.[7,8] Recent clinical and functional magnetic resonance imaging (MRI) studies demonstrate central pain amplification in many patients with CPP.[9–12] Notably, these findings are independent of the presence or severity of endometriosis.

In this article we discuss many therapies that have not been specifically studied in patients with CPP, and treatment efficacy is extrapolated from other conditions with chronic pain amplification, such as fibromyalgia or interstitial cystitis. Additionally, many treatments for conditions associated with central pain amplification are used off-label, that is, the US Food and Drug Administration (FDA) has not approved the medication for treatment of these specific conditions. This should be disclosed to patients during counseling.

FAST TRACK

Central pain amplification is characterized clinically by widespread pain, fatigue, sleep disturbances, memory difficulties, and somatic symptoms

Discuss treatment expectations with patients

Educating patients regarding the pathophysiology of chronic pain and setting reasonable expectations is the cornerstone of providing patient-centered care for this complex condition. We start most of our discussions about treatment options by telling patients that while we may not cure their pain, we will provide them with medical, surgical, and behavioral strategies that will reduce their pain, improve their function, and enhance their quality of life.

Surprisingly, most patients say that a cure is not their goal. They just want to feel better so they can return to work or activities, fully participate in family life, or not feel exhausted all the time. As such, a multimodal treatment plan is generally the best strategy for achieving a satisfactory improvement in symptoms.

CASE 1 Patient's pain continues after endometriosis excision

A 32-year-old woman (G1P1) reports having CPP for 8 years. She underwent excision of stage 1 endometriosis last year, which resulted in a modest improvement in pain for 6 months. Her pain is worse during menses, at the end of the day, and with vaginal intercourse (both during and lasting for 1 to 2 days after). On examination, you find diffuse pelvic floor tenderness but no adnexal masses or rectovaginal nodularity on palpation.

What treatment options would you consider for this patient?

Multimodal treatment often needed to manage CPP symptoms

The patient described in Case 1 may benefit from a combination of therapies that include analgesics, hormone suppression agents, and physical therapy (PT) (**TABLE**).

Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen and naproxen, work by inhibiting cyclooxygenase enzyme, which decreases assembly of peripheral prostaglandins and thromboxane. In a large Cochrane review, NSAIDs were associated with moderate or excellent pain relief for approximately 50% of patients with dysmenorrhea, and they have been shown to reduce menstrual flow due to decreased production of uterine prostaglandins.[13] There is little evidence for use of NSAIDs in chronic pain conditions.

TABLE Treatments used in the management of chronic pelvic pain

Treatment	Type of pain
Analgesics	Dysmenorrhea, cyclic pain exacerbation
NSAIDs	
Acetaminophen	
Hormonal suppression	Menstrual exacerbation of pain symptoms, endometriosis
Combined estrogen-progestin agents	
Progestin-only agents	
GnRH agonists	
Pelvic floor physical therapy	Myofascial pain (reproduced by palpation of pelvic floor, abdominal wall, or paraspinal-lumbar muscles)
Antidepressants	Widespread pain, fatigue, sleep disturbances
TCAs	
SNRIs	
Cyclobenzaprine	Myofascial pain, sleep disturbances, widespread pain
Calcium channel blockers	Widespread pain, fatigue, sleep disturbances
Gabapentin	
Pregabalin	
Anesthetic injections	Focal pain in a muscle or in distribution of an abdominal wall nerve
Lidocaine	
Bupivacaine	

Abbreviations: GnRH, gonadotropin-releasing hormone; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

Acetaminophen's mechanism of action is unclear, but the drug likely inhibits central prostaglandin synthesis, and it works synergistically with other analgesics.

Opioids act on μ and δ opioid receptors in the central and peripheral nervous systems as well as in the gastrointestinal system. No evidence supports opioid use in CPP or other chronic pain conditions. Long-term opioid use is associated with a multitude of adverse effects, risk for dependence, and the induction of opioid-induced hyperalgesia (in which patients develop greater sensitivity to pain stimuli).

Analgesics, specifically NSAIDs, can be considered for use in patients with dysmenorrhea, cyclic pain exacerbation, or a suspected inflammatory component of pain. Best practices include scheduling NSAID use before the onset of menses and continuing the drugs on a scheduled basis throughout. NSAIDs should be used for a brief period, and regular use on an empty stomach should be avoided.

Hormone suppression

Many types of hormone suppression therapy are available, including combined estrogen-progestin medications, progestin-only medications, and gonadotropin-releasing hormone (GnRH) agonists and antagonists.

Combined estrogen-progestin medications include oral contraceptive pills (OCPs), vaginal rings, and transdermal patches. Combined estrogen-progestin methods cause atrophy of eutopic and ectopic endometrium and suppress GnRH.

Progestin-only methods include oral formulations, the levonorgestrel intrauterine device, intramuscular and subcuticular injections, and subdermal implants. Progestin-only methods lead to atrophy of eutopic and ectopic endometrium.

A GnRH agonist, leuprolide depot works by downregulating luteinizing hormone and follicle stimulating hormone release from the pituitary, causing suppression of ovarian follicular development and ovulation, leading to a hypoestrogenic state.

FAST TRACK

No evidence supports opioid use in CPP or other chronic pain conditions. Long-term opioid use is associated with a multitude of adverse effects, risk for dependence, and the induction of opioid-induced hyperalgesia.

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Combined estrogen-progestin formulations and progestin-only options are often considered first-line therapy for dysmenorrhea and endometriosis.[13] Continuous administration, with the goal of inducing amenorrhea, is effective in the treatment of dysmenorrhea. Several randomized controlled trials have shown that different types of hormone suppression agents are, essentially, equally effective.[13–15] Treatment recommendations therefore should focus on adverse effects, cost, and patient preference. GnRH agonists and norethindrone are not FDA approved for the treatment of endometriosis.

It may be appropriate to consider use of hormone suppression therapy in patients with menstrual exacerbation of pain symptoms, including those with a history of endometriosis. We generally advise patients that the goal is amenorrhea and that achieving it often involves a process of trying different formulations to find the best fit. Remember that GnRH agonists are dependent on a functional hypothalamic-pituitary-ovarian axis, and they are unlikely to be effective in women with suspected residual endometriosis who have had a bilateral oophorectomy.

Physical therapy

For CPP, PT typically targets musculoskeletal dysfunction in the pelvic floor, abdominal wall, hips, and back. Interventions include muscle control, mobilization, and biofeedback. Pelvic PT has been shown to improve pain and dyspareunia in patients with CPP, coccydynia, and vestibulodynia.[16–18] One large study found a significant, patient-directed decrease in pain medication use after pelvic floor PT.[19] Pelvic PT for patients with interstitial cystitis and pelvic floor tenderness resulted in improved pain and bladder symptoms.[20]

Pelvic PT can be considered for patients with pain reproducible with palpation of the pelvic floor, abdominal wall, paraspinal-lumbar muscles, or sacroiliac joints. Best practices include referral to a therapist who has specialized training in CPP, including pelvic floor therapy. It is important to clearly list the indication for referral, as many of these therapists also treat stress urinary incontinence. The wrong exercises can result in increased hypercontractility of pelvic floor muscles, which can worsen pelvic pain.

It is also critical to clarify expectations with your patient at the time of PT referral. Specifically, advise patients that when beginning therapy, it is common to experience a temporary increase in discomfort of the pelvic muscles. Inform patients also to expect that their therapist will perform internal manipulation of the pelvic floor muscles through the vagina, as this can be surprising for some patients. Finally, counsel patients that their adherence to daily home exercises improves their chance of a durable, long-term successful response.[21]

FAST TRACK

Pelvic PT can be considered for patients with pain reproducible with palpation of the pelvic floor, abdominal wall, paraspinal lumbar muscles, or sacroiliac joints

CASE 1 Treatment recommendations

For treatment of this patient's CPP, consider scheduled naproxen therapy during menses, continuous OCPs, and referral for pelvic floor PT.

CASE 2 Patient with long-standing CPP, multiple diagnoses, and sleep problems

A 30-year-old woman (G2P2) reports having had CPP for 17 years. She is amenorrheic with continuous OCP treatment. She had experienced some improvement with pelvic PT. The patient reports that she has daily pain with intermittent pain flares and that she is exhausted and has poor sleep quality, which she attributes to pain. She has been diagnosed with interstitial cystitis, irritable bowel syndrome, and temporomandibular joint disorder. She has a history of depression, which she feels is well controlled with bupropion. Physical examination reveals that the patient has diffuse but mild pain in the pelvic floor and abdominal wall muscles.

What further pain management options can you offer for this patient?

Managing pain, sleep disturbance, and depression

This patient has been living with CPP for many years, and she has sleep difficulties that might be exacerbating pain or result from pain (or both). She is already on continuous OCPs and has had some relief with pelvic PT. Other options that may help with her multiple issues

include antidepressants, cyclobenzaprine, and calcium channel blockers.

Antidepressants

Several classes of antidepressants have been used in the treatment of chronic pain conditions, specifically, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Commonly used TCAs include amitriptyline, nortriptyline, desipramine, and doxepin. Commonly used SNRIs are duloxetine and milnacipran. Both TCAs and SNRIs increase the availability of norepinephrine and serotonin, which are thought to act on the descending pain inhibitory systems to decrease pain sensitivity. Of note, most selective serotonin reuptake inhibitors (SSRIs) at typical doses do not exert a significant enough impact on norepinephrine to be useful for chronic pain.[22]

Evidence is limited on the use of antidepressants for treating CPP. Amitriptyline is the most extensively studied antidepressant. Amitriptyline treatment resulted in modest pain improvement in patients with CPP and fibromyalgia.[23,24] Bothersome anticholinergic effects, including fatigue, dry mouth, and constipation, often are reported with TCAs. Adverse effects tend to be less with nortriptyline or desipramine compared with amitriptyline, but possibly at the expense of efficacy.

While SNRIs have not yet been studied in CPP, several investigations have shown that they improve pain and quality of life in fibromyalgia patients.[22,25]

Antidepressant therapy may be appropriate for patients with suspected central pain amplification, widespread pain, and sleep disturbances. Best practices include patient education and careful discussion of this option with your patient. We suggest that clinicians explain that antidepressant medications alter the function of neurotransmitters, which modulate pain signals. While neurotransmitters also are involved in mood modulation, this is not the therapeutic goal in this circumstance. In addition, the doses used for the effective treatment of chronic pain are significantly lower than those needed to treat depression effectively.

Patients often need to hear that you believe that their pain is real and is not a manifestation of depression or another mood disorder. If you suspect that the patient also has untreated depression, address this as its own issue and use medications that have greater efficacy for mood symptoms.

Because many antidepressants can cause sedation, they are best taken before bedtime. Also, slow dose titration over several weeks will reduce the chance of bothersome adverse effects. Counsel patients that efficacy is not generally seen until at goal dose for several weeks. Be aware of interactions with other medications that can cause serotonin syndrome.

Cyclobenzaprine

Cyclobenzaprine is a muscle relaxant that also has activity in the central nervous system. The drug's precise mechanism of action is not known, but it appears to potentiate norepinephrine and bind to serotonin receptors. Thus, it also likely has some TCA-like activity.

Cyclobenzaprine has not been studied in patients with CPP. In fibromyalgia patients, however, it produced significant improvements in pain, sleep, fatigue, and tenderness.[26,27] In our anecdotal experience with CPP patients, cyclobenzaprine has been one of the most impactful therapies. It hits the "chronic pain triad," meaning that it helps with myofascial pain, neuropathic pain, and sleep disturbances.

Cyclobenzaprine treatment may be considered for patients with myofascial pain, sleep disturbances, and clinical symptoms of central pain amplification. Best practices include starting with low (5 mg) scheduled doses at bedtime and slowly titrating the dose. Drowsiness is a very common side effect, so we try to use that to the patient's advantage to help with sleep quality.

Notably, sleep disturbances are highly prevalent in patients with chronic pain.[28] The relationship appears to be bidirectional, meaning that chronic pain negatively impacts sleep quality, and poor sleep quality causes amplified perception of pain.[28–30] Interventions that improve sleep quality have been

FAST TRACK

Cyclobenzaprine treatment may be considered for patients with myofacial pain, sleep disturbances, and clinical symptoms of central pain amplification

associated with improvements in pain, coping, mood, and functional status.[31] Helping a patient to improve her sleep generally requires a multifaceted approach. It always involves "sleep hygiene" or a behavioral component, and pharmacologic assistance may be considered when improved sleep hygiene does not provide adequately improved sleep quality.

Calcium channel blockers

Gabapentin and pregabalin are calcium channel blockers that inhibit the reuptake of glutamate, norepinephrine, and substance P, which helps to decrease pain sensitivity. They also act as membrane stabilizers, reducing hyperexcitability of peripheral and central nerves. Studies have shown that in patients with CPP, gabapentin resulted in improved pain and mood symptoms with few adverse effects.[23,32] Patients with fibromyalgia had improvements in pain, sleep, quality of life, fatigue, and anxiety with both gabapentin and pregabalin.[33]

FAST TRACK

It is appropriate to consider use of gabapentin or pregabalin in patients with central pain amplification and sleep disturbances

It is appropriate to consider use of gabapentin or pregabalin in patients with central pain amplification and sleep disturbances. Best practices include starting with a low dose at bedtime. Traditionally, gabapentin is given in 3 equal doses throughout the day. In our experience, patients report less daytime drowsiness and better sleep quality if two-thirds of the daily dose is given at night, with the remaining daily dose broken up into 2 smaller daytime doses. Slow titration over several weeks will reduce risk of bothersome adverse effects. Patients should be counseled that efficacy is not generally seen until treatment is at goal dose for several weeks.

CASE 2 Treatment recommendations

For this patient with daily pelvic pain, multiple diagnoses that have a pain component, and poor sleep quality, consider a treatment plan that includes scheduled cyclobenzaprine, improved sleep hygiene, and, if needed, gabapentin.

CASE 3 Cesarean delivery, hysterectomy, and continued pelvic pain

A 38-year-old woman (G2P2) has had CPP for the past 10 years. She developed persistent left lower-quadrant pain after cesarean delivery of her son. She had a hysterectomy 2 years ago for CPP, after which her pain worsened. She describes daily pain with intermittent flares. On examination, the patient has focal left lower-quadrant pain lateral to the left apex of her Pfannenstiel incision.

What treatment approach would be appropriate for this patient?

Focal pain requires a precisely targeted treatment

This patient with focal left lower-quadrant pain is a candidate for anesthetic trigger point injections in the affected area near her Pfannenstiel incision.

Anesthetic injections

Consider the presence of trigger points and peripheral neuropathy in patients with focal abdominal wall pain. Trigger points are focal, palpable nodules within muscles. They are markedly painful to palpation and are associated with referred pain, motor dysfunction, and occasionally autonomic symptoms. They frequently are seen in abdominal wall or pelvic floor muscles in patients with CPP and are caused by abnormal neuromuscular depolarization.

The ilioinguinal, iliohypogastric, and genitofemoral nerves are in close proximity to Pfannenstiel and laparoscopic port site incisions. These nerves may be injured directly during surgery, but they also may be compressed by postoperative scarring.

Anesthetics, such as lidocaine and bupivacaine, which act as sodium channel blockers, can be injected into this area, and improvement often substantially outlasts the anesthetic's duration of action. While these drugs' mechanism of action is not clear, theories include altered function of sodium channels on sensory nerves with repeated anesthetic exposure, dry needling that occurs during injection, hydrodissection of tight connective tissue bands surrounding neuromuscular bundles, or depletion of substance P and neuropeptides as a result of injection.[34,35]

In several studies, patients with CPP reported decreased pain with lidocaine injections in pelvic floor or abdominal wall trigger points.[36-38] Patients with fibromyalgia reported improvement in pain and a decreased need for NSAIDs with bupivacaine trigger point injections.[39] While abdominal wall nerve blocks have not been extensively studied in patients with chronic neuropathic pain following gynecologic surgery, they have been shown to substantially improve chronic neuropathic pain following inguinal hernia repair.[40]

Anesthetic injections appropriately may be considered in patients with focal pain in a muscle or in the distribution of abdominal wall nerves, palpation of which reproduces pain symptoms. Patients with diffuse pain are less likely to benefit from anesthetic injections. Best practices include careful examination with attention to areas of prior abdominal incisions.

Our practice is to inject each affected area with a mix of 9 mL of 1% lidocaine and 1 mL of sodium bicarbonate. If a patient reports at least 24 hours of improvement, we repeat the injection in 2 to 4 weeks. The goal is for the patient to experience a progressively longer duration of benefit with subsequent injections. We perform repeat injections shortly after pain begins to recur at that site. The patient should eventually graduate from receiving regular injections and may return for a remedial injection if pain recurs.

CASE 3 Treatment recommendations

For this patient with persistent focal left-lower quadrant pain and a defined trigger point near her Pfannenstiel incision, consider anesthetic injection in the left lower quadrant.

Work toward realistic symptom improvement

Remember that living with chronic pain is exhausting, and empathy with a patient-centered approach is the most important ingredient for patient improvement and satisfaction. Discuss realistic expectations with patients. Remind them that there is no magic bullet for the complex problem of CPP, and that chronic conditions generally do not improve overnight. Focus on improving the patient's function and quality of life, and applaud symptom improvement rather than focusing on complete pain resolution.

As these visits often require a good deal of patient education, budget more appointment time if feasible. We find that scheduling frequent return visits (approximately every 3 to 4 months) allows timely treatment follow-up so that changes may be made if needed. If you have maximized your available treatment options, referring the patient to a specialist with additional training in CPP is a sensible next step. ●

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Excessive cervical cancer screening, including frequent cotesting, could have minimal cancer prevention benefits while increasing the harms of screening. These data confirm guidance showing HPV testing alone is an effective cervical cancer screening strategy.

MARK H. EINSTEIN, MD, MS

Using multiple analyses, Schiffman and colleagues demonstrated the sensitivity advantage of HPV testing. They clearly showed that the cytology component to cotesting performance over many years is very limited for detecting precancers and early curable cancers. For example, prediagnostic HPV testing (76.7%) was more likely to be positive than cytology (59.1%; $P<.001$ for paired comparison); 82.6% of all prediagnostic cotests were positive by HPV and/or cytology; and only 5.9% of the cotests were positive by cytology alone (HPV negative.)

Primary HPV testing is recommended as a potential screening strategy by an interim guidance group led by the Society of Gynecologic Oncology and the American Society for Colposcopy and Cervical Pathology, and it is the primary cervical cancer screening recommendation of USPSTF draft guidelines.[1] There have been reports that reliance on primary HPV testing would encourage cervical cancer mortality; Schiffman and colleagues point out, however, that according to their study data, such reports are overstated.

Despite these data, practically speaking, shifting away from standard cotesting poses numerous challenges for clinicians and laboratories alike; however, these data clearly show the limited value of cytology and, due to the overtreatment of likely regressive cervical intraepithelial neoplasia grade 2, the possible increased risk of preterm birth and its subsequent harm as well.

Study strengths and weaknesses

The authors examined the long-term relative history of HPV testing and cytology prior to cancer diagnosis in a large, prospectively followed US cohort where hundreds of women in this cohort developed cancer. There will not be a validation study of this size and scale in the near future. Further, the authors showed that the relative value of cytology to cotesting is minimal. Multiple subsequent rounds of cotesting after negative results also can be questioned.

One weakness of the study is that the data were collected from only one health care system and therefore may not be representative of all populations. Additionally, cotesting was performed on 2 separately collected specimens, which may have reduced HPV testing performance. ●

FAST TRACK

HPV testing alone is an effective cervical cancer screening strategy

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The beginning of the end of the Pap?

It seems so. Investigators reviewed extended data from a large prospectively followed cohort of women within the Kaiser Permanente Northern California cohort to quantify the relative contributions of the cytology and human papillomavirus (HPV) test components of cotesting for detecting cervical precancer and cancer to help guide whether cotesting, with its costs and potential harms, should be recommended. Although bringing an end to standard cotesting presents challenges for clinicians and laboratories alike, the researchers found that cytology had limited value.

FAST TRACK

While the addition of cytology to HPV testing can add performance, it also can add further costs and the potential for unnecessary colposcopies

Schiffman M, Kinney WK, Cheung LC, et al. Relative performance of HPV and cytology components of cotesting in cervical screening [published online ahead of print November 14, 2017]. Natl Cancer Inst. doi: 10.1093/jnci/djx225.

EXPERT COMMENTARY
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Realistic prospective performance data are needed to quantify the additional benefit of the cytology component of cotesting on top of what is already known to be highly sensitive molecular HPV testing. While the addition of cytology to HPV testing can add performance, it also can add further costs and the potential for unnecessary colposcopies for what are merely cytomorphologic manifestations of an active HPV infection. Frequent invasive procedures such as colposcopy, which can be costly and lead to anxiety and distress in generally young women and the potential for overtreatment of likely regressive lesions, has been defined as a harm of screening by the US Preventive Services Task Force (USPSTF).

Dr. Einstein has advised, but does not receive an honorarium from any companies. In specific cases his employer has received payment for his consultation from Cynvec, Altum Pharmaceuticals, Photocure, Papivax, PDS Biotechnologies, and Natera. If travel is required for meetings with any industry, the company pays for Dr. Einstein's travel-related expenses. Also, his employers have received grant funding for research-related costs of clinical trials that Dr. Einstein has been the overall principal investigator or local principal investigator for the past 12 months from Johnson & Johnson, Pfizer, Inovio, PDS Biotechnologies, and Becton-Dickinson.

Details of the study

In a cohort from Kaiser Permanente Northern California, 1,208,710 women aged 30 years or older were screened with cotesting from 2003 to 2015. Those who cotested HPV negative and cytology negative were offered triennial screening. Positive cotest results were managed according to Kaiser protocol. Women with cytologic abnormalities were referred for colposcopy. Those with HPV positive/cytology negative results or HPV negative/cytology equivocal results underwent accelerated testing at 1 year. A total of 623 cervical cancers were identified and included in the analyses.

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

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

WARNINGS

1. Intrauterine Pregnancy

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

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

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

2. Ectopic Pregnancy

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

3. Pelvic Infection

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

PID can have serious consequences, such as tubal damage (leading to ectopic pregnancy or infertility), hysterectomy, sepsis, and, rarely, death. It is therefore important to promptly assess and treat any woman who develops signs or symptoms of PID.

Guidelines for treatment of PID are available from the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia at www.cdc.gov or 1-800-311-3435. Antibiotics are the mainstay of therapy. Most healthcare professionals also remove the IUD.

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

4. Immunocompromise

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

5. Embedment

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

6. Perforation

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

7. Expulsion

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

8. Wilson's Disease

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

PRECAUTIONS

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

1. Information for patients

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

2. Insertion precautions, continuing care, and removal.

3. Vaginal bleeding

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

4. Vasovagal reactions, including fainting

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

5. Expulsion following placement after a birth or abortion

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

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

6. Magnetic resonance imaging (MRI)

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

7. Medical diathermy

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

8. Pregnancy

ParaGard® is contraindicated during pregnancy.

9. Nursing mothers

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

10. Pediatric use

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

ADVERSE REACTIONS

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

Intrauterine pregnancy	Pelvic infection
Septic abortion	Perforation
Ectopic pregnancy	Embedment

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

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

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

PAR-41287 01/18

ASK HER IF SHE WANTS A birth control that's HORMONE FREE

PARAGARD®
(intrauterine copper contraceptive)—
the only highly effective, reversible birth control that is *completely hormone free*[1]

- **100% hormone free**
- **94% patient satisfaction*[2]**
- **Removable whenever she decides†**
- **>99% effective for up to 10 years**

56% of women reported that they had **concerns with hormones** in their birth control‡[3]

Tell her she has a hormone-free choice—tell her about PARAGARD.

INDICATION

PARAGARD is indicated for intrauterine contraception for up to 10 years.

IMPORTANT SAFETY INFORMATION

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

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

*Data are from the Contraceptive CHOICE Project. The study evaluated 3- and 6-month self-reported bleeding and cramping patterns in 5011 long-acting reversible contraceptive (LARC) users (n=826, PARAGARD), and the association of these symptoms with method satisfaction. Study participants rated satisfaction with their LARC method as "very satisfied," "somewhat satisfied," or "not satisfied." For the data analyses, "satisfied" and "very satisfied" were grouped together as "satisfied."[2]

†PARAGARD must be removed by a healthcare professional.

‡Based on a September 2017 web-based survey of US women aged 18-45 years (N=300), where participants were asked about their attitudes about birth control that contains hormones. Respondents were required to be currently using birth control or have plans to use birth control in the next year. Repeat respondents within the previous 6 months were not permitted.

References: 1. Kaneshiro B, Aeby T. Long-term safety, efficacy, and patient acceptability of the intrauterine Copper T-380A contraceptive device. *Int J Womens Health*. 2010;2:211-220. **2.** Diedrich JT, Desai S, Zhao Q, Secura G, Madden T, Peipert JF. Association of short-term bleeding and cramping patterns with long-acting reversible contraceptive method satisfaction. *Am J Obstet Gynecol*. 2015;212(1):50.e1- 50.e8. **3.** Data on File. CooperSurgical, Inc., September 2017.

PARAGARD® T380A
intrauterine copper contraceptive
Life on *Her* Terms.

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