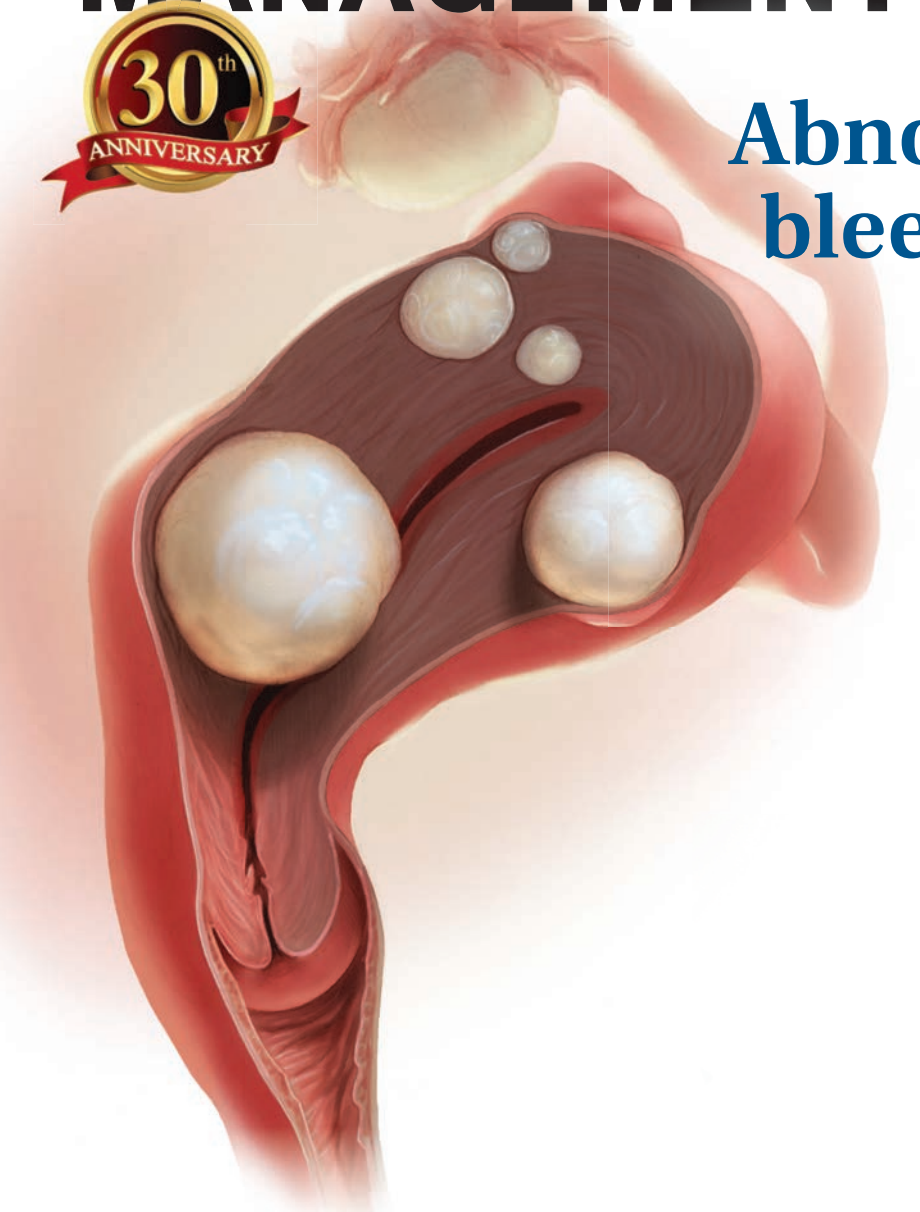
MDEDGE.COM/OBGMANAGEMENT | VOL 30, NO 8 | AUGUST 2018

OBG MANAGEMENT

30th ANNIVERSARY



Abnormal uterine bleeding updates

Howard T. Sharp, MD
and Marisa R. Adelman, MD

Makena®
hydroxyprogesterone
caproate injection

Now Approved!

FOR YOUR PATIENTS AT RISK FOR ANOTHER SINGLETON SPONTANEOUS PRETERM BIRTH (<37 WEEKS)

THE NEXT GENERATION OF MAKENA: ANOTHER WAY TO GET CLOSER TO TERM

Actual size

See how to use the auto-injector at **MakenaAutoInjector.com**

Makena helps give baby more time to develop[1]

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.**

Important Safety Information for Makena® (hydroxyprogesterone caproate injection)

- Do not use Makena in women with any of the following conditions:
  - Current or history of thrombosis or thromboembolic disorders
  - Known or suspected breast cancer, other hormone-sensitive cancer or history of these conditions
  - Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
  - Cholestatic jaundice of pregnancy
  - Liver tumors, benign or malignant, or active liver disease
  - Uncontrolled hypertension
- Makena should be discontinued if thrombosis or thromboembolism occurs
- Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil

Same Makena. Innovative Delivery Device.[1]

EFFICIENT

- Pre-filled auto-injector that is ready to use out of the box
- Administered in ~15 seconds

DISCREET

- Shorter, thinner, nonvisible needle
- Administered in the back of the upper arm—no need for patients to disrobe

ADMINISTRATION FRIENDLY

- Protective needle guard to help minimize accidental needle-sticks
- Appointment flexibility—no need for private exam rooms

Personalized patient support. Healthcare professional resources. More than Makena.

Makena Care Connection®

- Women receiving Makena should be monitored if they:
  - Are prediabetic or diabetic
  - Have conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction
  - Have a history of clinical depression; Makena should be discontinued if depression recurs
  - Develop jaundice; consider whether benefit of use warrants continuation
  - Develop hypertension
- Certain pregnancy-related fetal and maternal complications or events were numerically increased in Makena-treated subjects as compared to placebo subjects, including miscarriage (2.4% vs. 0%) and stillbirth (2% vs. 1.3%), admission for preterm labor (16% vs. 13.8%), preeclampsia or gestational hypertension (8.8% vs. 4.6%), gestational diabetes (5.6% vs. 4.6%), and oligohydramnios (3.6% vs. 1.3%)
- In a study where the Makena intramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in ≥2% of subjects and higher than in the control group) were: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%)
- In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena Auto-Injector use (and higher than with Makena intramuscular injection) was injection site pain (10% in one study and 34% in another)

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

Reference: 1. Makena® (hydroxyprogesterone caproate injection) prescribing information, AMAG Pharmaceuticals, 2018.

Makena®
hydroxyprogesterone caproate injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please consult full prescribing information.

INDICATIONS AND USAGE

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.
Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.**

CONTRAINDICATIONS

Do not use Makena in women with any of the following conditions:
- Current or history of thrombosis or thromboembolic disorders
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- Uncontrolled hypertension

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders

Discontinue Makena if an arterial or deep venous thrombotic or thromboembolic event occurs.

Allergic Reactions

Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

Decrease in Glucose Tolerance

A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Makena.

Fluid Retention

Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).

Depression

Monitor women who have a history of clinical depression and discontinue Makena if clinical depression recurs.

Jaundice

Carefully monitor women who develop jaundice while receiving Makena and consider whether the benefit of use warrants continuation.

Hypertension

Carefully monitor women who develop hypertension while receiving Makena and consider whether the benefit of use warrants continuation.

ADVERSE REACTIONS

For the most serious adverse reactions to the use of progestins, see *Warnings and Precautions.*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In a vehicle (placebo)-controlled clinical trial of 463 pregnant women at risk for spontaneous preterm delivery based on obstetrical history, 310 received 250 mg of Makena and 153 received a vehicle formulation containing no drug by a weekly intramuscular injection beginning at 16 to 20 weeks of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first. Certain pregnancy-related fetal and maternal complications or events were numerically increased in the Makena-treated subjects as compared to control subjects, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Tables 1 and 2).

Table 1 Selected Fetal Complications

Pregnancy Complication	Makena n/N	Control n/N
Miscarriage (<20 weeks)[1]	5/209	0/107
Stillbirth (≥20 weeks)[2]	6/305	2/153

[1]N = Total number of subjects enrolled prior to 20 weeks 0 days
[2]N = Total number of subjects at risk ≥20 weeks

Table 2 Selected Maternal Complications

Pregnancy Complication	Makena N=310 %	Control N=153 %
Admission for preterm labor[1]	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

[1]Other than delivery admission

Common Adverse Reactions:
The most common adverse reaction with intramuscular injection was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥2% of subjects and at a higher rate in the Makena group than in the control group.

Table 3 Adverse Reactions Occurring in ≥2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects

Preferred Term	Makena N=310 %	Control N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0
Diarrhea	2.3	0.7

In the clinical trial using intramuscular injection, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

Pulmonary embolus in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

Two clinical studies were conducted in healthy post-menopausal women, comparing Makena administered via subcutaneous auto-injector to Makena administered as an intramuscular injection. In the first study, injection site pain occurred in 3/30 (10%) of subjects who used the subcutaneous auto-injector vs. 2/30 (7%) of subjects receiving intramuscular injection. In the second study, injection site pain occurred in 20/59 (34%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Makena. 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.
- *Body as a whole*: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth); fatigue; fever; hot flashes/flushes
- *Digestive disorders*: Vomiting
- *Infections*: Urinary tract infection
- *Nervous system disorders*: Headache, dizziness
- *Pregnancy, puerperium and perinatal conditions*: Cervical incompetence, premature rupture of membranes
- *Reproductive system and breast disorders*: Cervical dilation, shortened cervix
- *Respiratory disorders*: Dyspnea, chest discomfort
- *Skin*: Rash

DRUG INTERACTIONS

In vitro drug-drug interaction studies were conducted with Makena. Hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. *In vitro* data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. No *in vivo* drug-drug interaction studies were conducted with Makena.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Fetal, neonatal, and maternal risks are discussed throughout labeling. Data from the placebo-controlled clinical trial and the infant follow-up safety study did not show a difference in adverse developmental outcomes between children of Makena-treated women and children of control subjects. However, these data are insufficient to determine a drug-associated risk of adverse developmental outcomes as none of the Makena-treated women received the drug during the first trimester of pregnancy. In animal reproduction studies, intramuscular administration of hydroxyprogesterone caproate to pregnant rats during gestation at doses 5 times the human dose equivalent based on a 60-kg human was not associated with adverse developmental outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Data: *Animal Data* Reproduction studies of hydroxyprogesterone caproate administered to various animal species have been reported in the literature. In nonhuman primates, embryolethality was reported in rhesus monkeys administered hydroxyprogesterone caproate up to 2.4 and 24 times the human dose equivalent, but not in cynomolgus monkeys administered hydroxyprogesterone caproate at doses up to 2.4 times the human dose equivalent, every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either strain of monkey.
Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to hydroxyprogesterone caproate.

Lactation

Risk Summary: Low levels of progestins are present in human milk with the use of progestin-containing products, including hydroxyprogesterone caproate. Published studies have reported no adverse effects of progestins on the breastfed child or on milk production.

Pediatric Use

Makena is not indicated for use in women under 16 years of age. Safety and effectiveness in patients less than 16 years of age have not been established. A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older.

Hepatic Impairment

No studies have been conducted to examine the pharmacokinetics of Makena in patients with hepatic impairment. Makena is extensively metabolized and hepatic impairment may reduce the elimination of Makena.

#1 IN READERSHIP!*

OBG MANAGEMENT
mdedge.com/obgmanagement

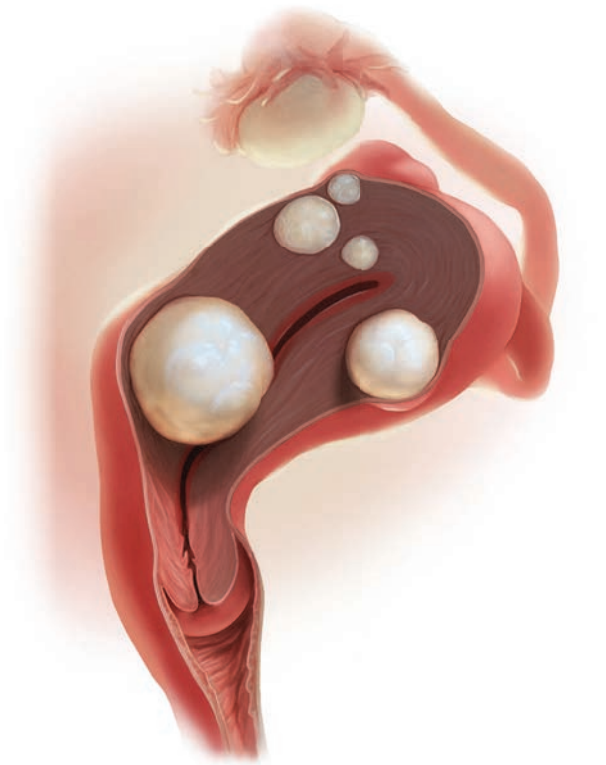
Enhancing the quality of women's health care and the professional development of ObGyns and all women's health care clinicians

*Source: Kantar Media, Medical Surgical Study June 2018, Obstetrics/Gynecology Combined Office & Hospital Readers.

AUGUST 2018 | VOL 30, NO 8

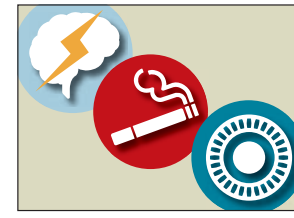
OBG MANAGEMENT

Follow us on Facebook and on Twitter @MDedgeObGyn



See what's ON THE WEB! page 6

Maintenance of certification **26**



Migraine and stroke **33**

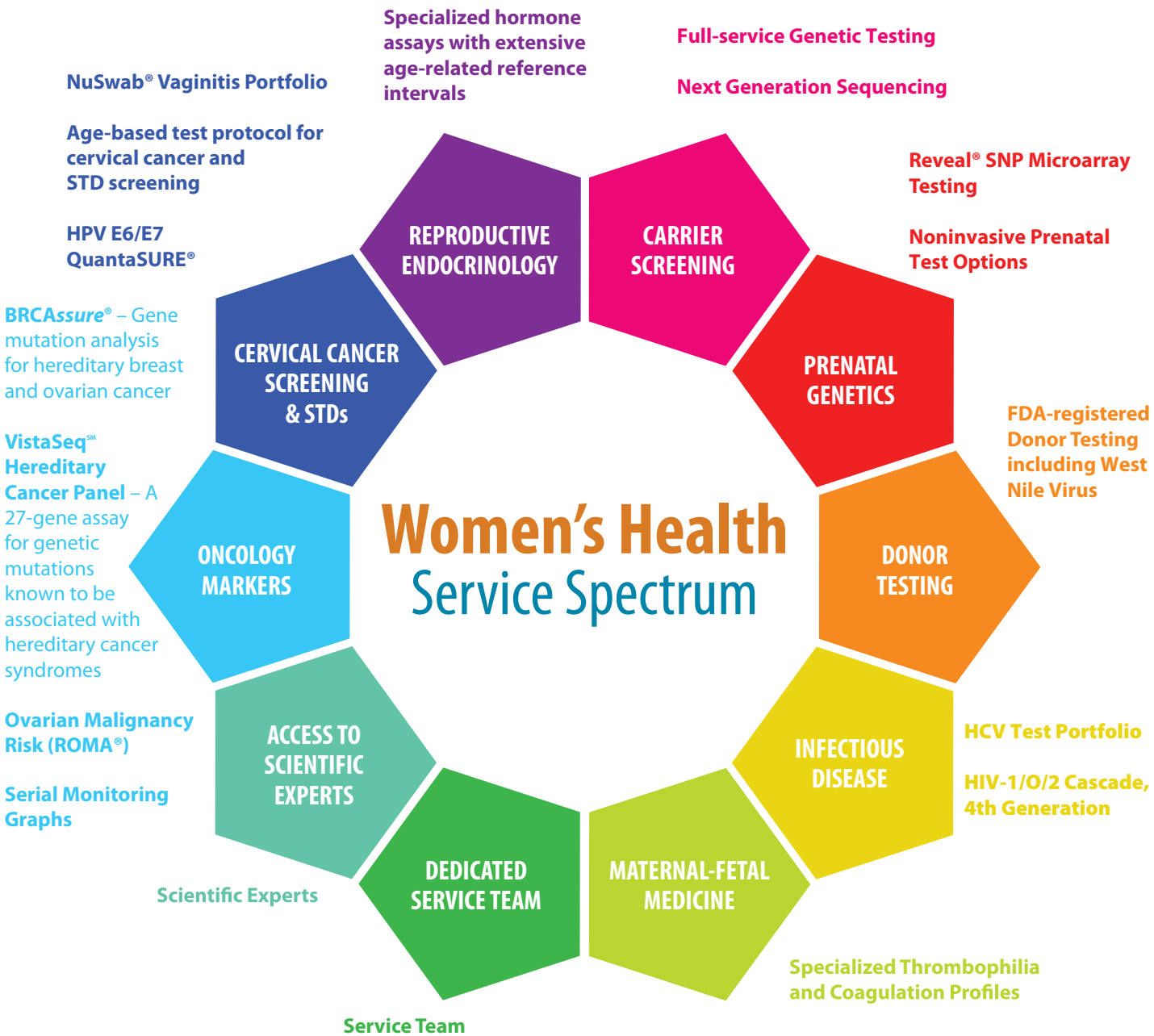
FAST TRACK is a system to enable you as a reader to move quickly through each issue of **OBG MANAGEMENT**, identifying articles or sections of articles to read in depth.

OBG MANAGEMENT (ISSN 1044-307x) is published monthly by Frontline Medical Communications Inc, 7 Century Drive, Suite 302, Parsippany, New Jersey 07054. 2018 subscription rates (includes full-text access to mdedge.com/obgmanagement): United States: $158.00; elsewhere: $205.00. Single copy orders must be prepaid: United States: $27.00; Canada/Mexico: $33.00; other: $38.00. Periodicals postage paid at Parsippany, NJ, and additional mailing offices. Orders and Claims: OBG Management, Subscription Service, P.O. Box 3000, Denville, NJ 07834-3000, phone (833) 836-2705, or e-mail custsvc.obgm@fulcoinc.com. POSTMASTER: Please send address changes to OBG Management Subscription Service, 10255 W. Higgins Road, Suite 280, Rosemont, IL 60018-9914.

COVER IMAGE: KIMBERLY MARTENS

Everything **she** needs

with the services **you** expect.



LabCorp

For more information about LabCorp tests and services, visit www.labcorp.com.

ON THE WEB at obgmanagement.com

FROM ENDOMETRIOSIS JOURNEY

What pain mechanisms are involved with endometriosis-caused pelvic pain?

Managing genitourinary endometriosis

Visit the Endometriosis Journey online at endometriosisjourney.com

WEB EXCLUSIVE

Title X and proposed changes: Take action now

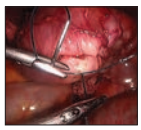
EMILY L. KELLOGG, MD, AND MEGAN L. EVANS, MD, MPH

Visit us online for daily news

VIDEO LIBRARY

Does hypertensive disease of pregnancy increase future risk of CVD?

JOHN T. REPKE, MD

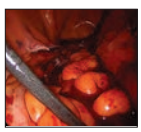


Surgical management of cornual, cervical, and cesarean scar pregnancies

J.K. ROBINSON, MD, MS; W.A. BARNES, MD; N. HAZEN, MD; P. ALAM, MD; AND S. BRADLEY, MD

Brought to you by the Society of Gynecologic Surgeons

See page 32 for QR code



Size can matter: Laparoscopic hysterectomy for the very large uterus

DEIRDRE LUM, MD

Brought to you by the Society of Gynecologic Surgeons

Watch these, and more, expert surgical technique and commentary videos in the EXPLORE: Multimedia section online

MDedge | FRONTLINE MEDICAL COMMUNICATIONS
7 Century Drive, Suite 302
Parsippany, NJ 07054-4609
www.mdedge.com

BPA WORLDWIDE | AMM Association of Medical Media

Reader services. Address correspondence to OBG MANAGEMENT®, 7 Century Drive, Suite 302, Parsippany, NJ 07054.

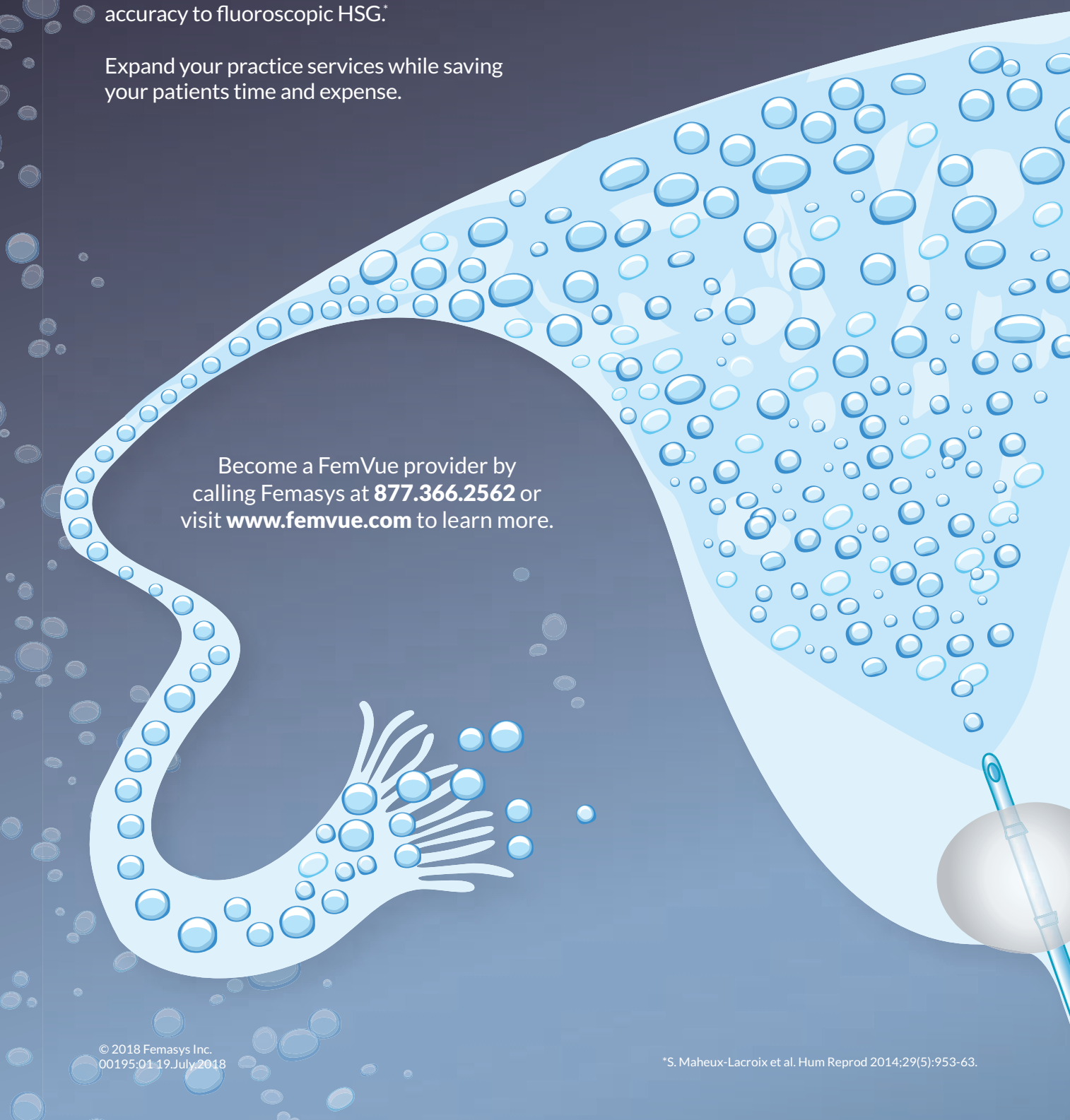
femVue®

In-office **tubal patency** diagnostic test

Sono HSG with FemVue allows you to provide your patients with a convenient, ultrasound-based tubal patency evaluation.

Clinical studies have shown Sono HSG has concordant diagnostic accuracy to fluoroscopic HSG.*

Expand your practice services while saving your patients time and expense.



Become a FemVue provider by calling Femasys at **877.366.2562** or visit **www.femvue.com** to learn more.

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

EDITORIAL

Optimize the medical treatment of endometriosis—Use all available medications

In my referral practice, the most common problem I see in the medical management of endometriosis is a reluctance to prescribe approved hormonal medications from all available drug classes

Robert L. Barbieri, MD
Editor in Chief, OBG Management
Chair, Obstetrics and Gynecology
Brigham and Women's Hospital, Boston, Massachusetts
Kate Macy Ladd Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School, Boston

CASE Endometriosis pain increases despite hormonal treatment

A 25-year-old woman (G0) with severe dysmenorrhea had a laparoscopy showing endometriosis in the cul-de-sac and a peritoneal window near the left uterosacral ligament. Biopsy of a cul-de-sac lesion showed endometriosis on histopathology. The patient was treated with a continuous low-dose estrogen-progestin contraceptive. Initially, the treatment helped relieve her pain symptoms. Over the next year, while on that treatment, her pain gradually increased in severity until it was disabling. At an office visit, the primary clinician renewed the estrogen-progestin contraceptive for another year, even though it was not relieving the patient's pain. The patient sought a second opinion.

We are the experts in the management of pelvic pain caused by endometriosis

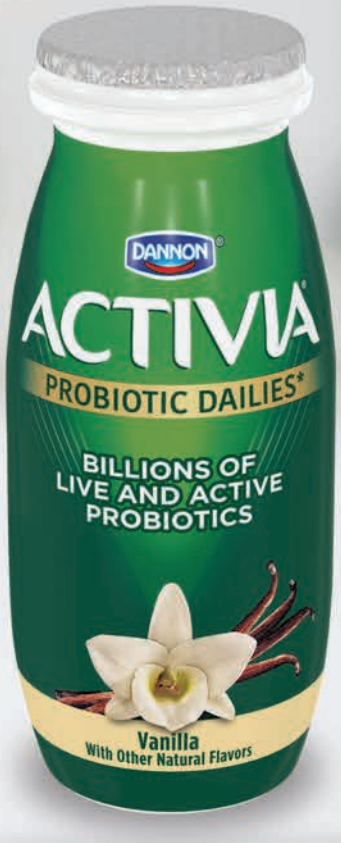
Women's health clinicians are the specialists best trained to care for patients with severe pain caused by endometriosis. Low-dose continuous estrogen-progestin contraceptives are commonly prescribed as a first-line hormonal treatment for pain caused by endometriosis. My observation is that estrogen-progestin contraceptives are often effective when initially prescribed, but with continued use over years, pain often recurs. Estrogen is known to stimulate endometriosis disease activity. Progestins at high doses suppress endometriosis disease activity. However, endometriosis implants often manifest decreased responsiveness to progestins, permitting the estrogen in the combination contraceptive to exert its disease-stimulating effect.[1,2] I frequently see women with pelvic pain caused by endometriosis, who initially had a significant decrease in pain with continuous estrogen-progestin contraceptive treatment but who develop increasing pain with continued use of the medication. In this clinical situation, it is useful to consider stopping the estrogen-progestin therapy and to prescribe a hormone with a different mechanism of action (**TABLE,** page 10).

Progestin-only medications

Progestin-only medications are often effective in the treatment of pain caused by endometriosis. High-dose progestin-only medications suppress pituitary secretion of luteinizing hormone (LH) and follicle-stimulating

CONTINUED ON PAGE 10

Make ACTIVIA® your probiotic choice.

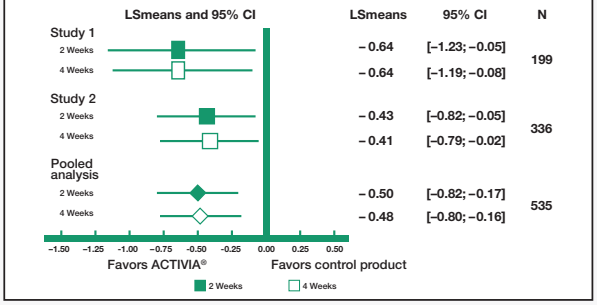


Consume twice a day.

There are several reasons why your clients should get probiotics from food:

- Probiotic foods can buffer stomach acids and increase the chance that the probiotics survive and make it to the intestine.
- Probiotic supplements in the form of pills don't usually provide nutrients that some cultures produce during fermentation.
- Fermented dairy products, like yogurt, are a source of nutrients such as calcium, protein, and potassium.
- Some individuals have trouble swallowing, or just don't like pills; but yogurt is easy and enjoyable to consume.

Forest plot of composite score of the frequency of minor digestive issues. LSmeans = least squares means; CI = confidence interval; N = number of subjects that completed the study; test for heterogeneity $P > 0.10$; test for overall effect $P = 0.003$.



ACTIVIA may help reduce the frequency of minor digestive discomfort.*

Two double-blind, randomized, placebo-controlled studies, and a pooled analysis of these studies, show that ACTIVIA may help reduce the frequency of minor digestive discomfort like bloating, gas, abdominal discomfort, and rumbling.[1,2]*

Both studies were designed to investigate the effect of ACTIVIA on different gastrointestinal (GI) outcomes, including GI well-being and frequency of minor digestive discomfort, in healthy women.

In both studies, and in the pooled analysis, the composite score of the frequency of minor digestive issues over the two-[3] and four-week[1,2] test periods in the ACTIVIA group was significantly lower ($P<0.05$) than that in the control group.

*Consume twice a day for two weeks as part of a balanced diet and healthy lifestyle. Minor digestive discomfort includes bloating, gas, abdominal discomfort, and rumbling.

1. Guyonnet et al. *Br J Nutr.* 2009;102(11):1654-62. **2.** Marteau et al. *Neurogastroenterol Motil.* 2013;25(4):331-e252. **3.** Data on file.

Recommend ACTIVIA. Visit **www.activiareferralpad.com**
to order your referral pad today. Offer available to healthcare professionals only.

CONTINUED FROM PAGE 8

TABLE Hormone medication options currently available to treat pelvic pain caused by endometriosis

Medication[a]	Route of administration	Dose	Relative cost[b]
Progestins			
Norethindrone acetate	Oral	5 mg daily	$
Medroxyprogesterone acetate	Oral	20 to 40 mg daily	$
Depot-medroxyprogesterone acetate	Intramuscular	150 mg every 3 months	$
Depot-medroxyprogesterone acetate	Subcutaneous	104 mg every 3 months	$$
Levonorgestrel (LNG) intrauterine device	Intrauterine device	52-mg device releasing about 20 µg of LNG daily	Cost depends on number of months of use
GnRH analogues			
Nafarelin acetate	Intranasal	One spray twice daily	$$$$$
Depot-leuprolide acetate	Intramuscular	3.75 mg monthly	$$$$$
Goserelin	Subcutaneous implant	3.6 mg monthly	$$$$
Elagolix	Oral	150 mg daily or 200 mg twice daily	$$$$
Androgen			
Danazol	Oral	200 mg twice daily	$$$

[a]Italicized medications are US Food and Drug Administration approved to treat endometriosis.

[b]Relative cost: $ = < $50 per month; $$ = $50 to $150 per month; $$$ = > $150 and < $250 per month; $$$$ = ≥ 250 and < 1,000 per month; $$$$$ = > $1,000 per month.

hormone (FSH), thereby suppressing ovarian synthesis of estrogen, resulting in low circulating levels of estrogen. This removes the estrogen stimulus that exacerbates endometriosis disease activity. High-dose progestins also directly suppress cellular activity in endometriosis implants. High-dose progestins often overcome the relative resistance of endometriosis lesions to progestin suppression of disease activity. Hence, high-dose progestin-only medications have two mechanisms of action: suppression of estrogen synthesis through pituitary suppression of LH and FSH, and direct inhibition of cellular activity in the endometriosis lesions. High-dose progestin-only treatments include:

- oral norethindrone acetate 5 mg daily
- oral medroxyprogesterone acetate (MPA) 20 to 40 mg daily
- subcutaneous, or depot MPA
- levonorgestrel-releasing intrauterine device (LNG-IUD).

In my practice, I frequently use oral norethindrone acetate 5 mg daily to treat pelvic pain caused by endometriosis. In one randomized trial, 90 women with pelvic pain and rectovaginal endometriosis were randomly assigned to treatment with norethindrone acetate 2.5 mg daily or an estrogen-progestin contraceptive. After 12 months of treatment, satisfaction with treatment was reported by 73% and 62% of the women in the norethindrone acetate and estrogen-progestin groups, respectively.[3] The most common adverse effects reported by women taking norethindrone acetate were weight gain (27%) and decreased libido (9%).

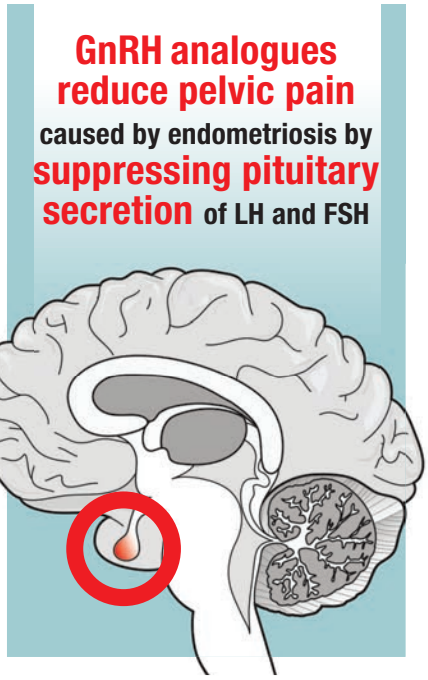
Oral MPA at doses of 30 mg to 100 mg daily has been reported to be effective for the treatment of pelvic pain caused by endometriosis. MPA treatment can induce atrophy and pseudodecidualization in endometrium and endometriosis implants. In my practice I typically prescribe doses in the range of 20 mg to 40 mg daily. With oral MPA treatment, continued uterine bleeding may occur in up to 30% of women, somewhat limiting its efficacy.[4–7]

Subcutaneous and depot MPA have been reported to be effective in the treatment of pelvic pain caused by endometriosis.[4,8] In some resource-limited countries, depot MPA may be the most available progestin for the treatment of pelvic pain caused by endometriosis.

The LNG-IUD, inserted after surgery for endometriosis, has been reported to result in decreased pelvic pain in studies with a modest number of participants.[9–11]

CONTINUED ON PAGE 12

CONTINUED FROM PAGE 10



GnRH analogue medications

Gonadotropin-releasing hormone (GnRH) analogues, including both GnRH agonists (nafarelin, leuprolide, and goserelin) and GnRH antagonists (elagolix) reduce pelvic pain caused by endometriosis by suppressing pituitary secretion of LH and FSH, thereby reducing ovarian synthesis of estradiol. In the absence of estradiol stimulation, cellular activity in endometriosis lesions decreases and pain symptoms improve. In my practice, I frequently use either nafarelin[12] or leuprolide acetate depot plus norethindrone add-back.[13] I generally avoid the use of leuprolide depot monotherapy because in many women it causes severe vasomotor symptoms.

At standard doses, nafarelin therapy generally results in serum estradiol levels in the range of 20 to 30 pg/mL, a "sweet spot" associated with modest vasomotor symptoms and reduced cellular activity in endometriosis implants.[12,14] In many women who become amenorrheic on nafarelin two sprays daily, the dose can be reduced with maintenance of pain control and ovarian suppression.[15] Leuprolide acetate depot monotherapy results in serum estradiol levels in the range of 5 to 10 pg/mL, causing severe vasomotor symptoms and reduction in cellular activity in endometriosis lesions. To reduce the adverse effects of leuprolide acetate depot monotherapy, I generally initiate concomitant add-back therapy with norethindrone acetate.[13] A little recognized pharmacokinetic observation is that a very small amount of norethindrone acetate, generally less than 1%, is metabolized to ethinyl estradiol.[16]

The oral GnRH antagonist, elagolix, 150 mg daily for up to 24 months or 200 mg twice daily for 6 months, was approved by the US Food and Drug Administration (FDA) in July 2018. It is now available in pharmacies. Elagolix treatment results in significant reduction in pain caused by endometriosis, but only moderately bothersome vasomotor symptoms.[17,18] Elagolix likely will become a widely used medication because of the simplicity of oral administration, efficacy against endometriosis, and acceptable adverse-effect profile. A major disadvantage of the GnRH analogue-class of medications is that they are more expensive than the progestin medications mentioned above. Among the GnRH analogue class of medications, elagolix and goserelin are the least expensive.

Androgens

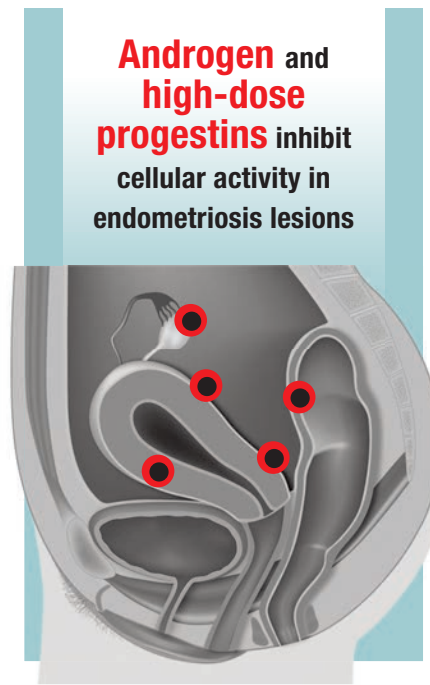
Estrogen stimulates cellular activity in endometriosis lesions. Androgen and high-dose progestins inhibit cellular activity in endometriosis lesions. Danazol, an attenuated androgen and a progestin is effective in treating pelvic pain caused by endometriosis.[19,20] However, many women decline to use danazol because it is often associated with weight gain. As an androgen, danazol can permanently change a woman's voice pitch and should not be used by professional singers or speech therapists.

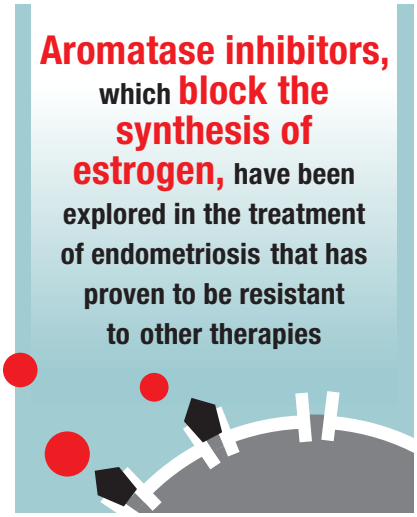
Aromatase Inhibitors

Estrogen is a critically important stimulus of cell activity in endometriosis lesions. Aromatase inhibitors, which block the synthesis of estrogen, have been explored in the treatment of endometriosis that has proven to be resistant to other therapies. Although the combination of an aromatase inhibitor plus a high-dose progestin or GnRH analogue may be effective, more data are needed before widely using the aromatase inhibitors in clinical practice.[21]

Don't get stuck in a rut

When treating pelvic pain caused by endometriosis, if the patient's





hormone regimen is not working, prescribe a medication from another class of hormones. In the case presented above, a woman with pelvic pain and surgically proven endometriosis reported inadequate control of her pain symptoms with a continuous estrogen-progestin medication. Her physician prescribed another year of the same estrogen-progestin medication. Instead of renewing the medication, the physician could have offered the patient a hormone medication from another drug class: 1) progestin only, 2) GnRH analogue, or 3) danazol. By using every available hormonal agent, physicians will improve the treatment of pelvic pain caused by endometriosis. Millions of women in our country have pelvic pain caused by endometriosis. They are counting on us, women's health specialists, to effectively treat their disease. ●

RBARBIERI@MDEDGE.COM

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

References

1. Patel BG, Rudnicki M, Yu J, Shu Y, Taylor RN. Progesterone resistance in endometriosis: origins, consequences and interventions. Acta Obstet Gynecol Scand. 2017;96(6):623–632.
2. Bulun SE, Cheng YH, Pavone ME, et al. Estrogen receptor-beta, estrogen receptor-alpha, and progesterone resistance in endometriosis. Semin Reprod Med. 2010;28(1):36–43.
3. Vercellini P, Pietropaolo G, De Giorgi O, Pasin R, Chiodini A, Crosignani PG. Treatment of symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low-dose norethindrone acetate. Fertil Steril. 2005;84(5):1375-1387.
4. Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database of Syst Rev. 2012;(3):CD002122.
5. Moghissi KS, Boyce CR. Management of endometriosis with oral medroxyprogesterone acetate. Obstet Gynecol. 1976;47(3):265–267.
6. Telimaa S, Puolakka J, Rönnberg L, Kauppila A. Placebo-controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis. Gynecol Endocrinol. 1987;1(1):13–23.
7. Luciano AA, Turksoy RN, Carleo J. Evaluation of oral medroxyprogesterone acetate in the treatment of endometriosis. Obstet Gynecol. 1988;72(3 pt 1):323–327.
8. Schlaff WD, Carson SA, Luciano A, Ross D, Bergqvist A. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. Fertil Steril. 2006;85(2):314–325.
9. Abou-Setta AM, Houston B, Al-Inany HG, Farquhar C. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Cochrane Database of Syst Rev. 2013;(1):CD005072.
10. Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Indhavivadhana S, Leerasiri P. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-pain: a randomized controlled trial. Obstet Gynecol. 2012;119(3):519–526.
11. Wong AY, Tang LC, Chin RK. Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomised controlled trial. Aust N Z J Obstet Gynaecol. 2010;50(3):273–279.
12. Henzl MR, Corson SL, Moghissi K, Buttram VC, Berqvist C, Jacobsen J. Administration of nasal nafarelin as compared with oral danazol for endometriosis. A multicenter double-blind comparative clinical trial. N Engl J Med. 1988;318(8):485–489.
13. Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. Lupron Add-Back Study Group. Obstet Gynecol. 1998;91(1):16–24.
14. Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol. 1992;166(2):740–745.
15. Hull ME, Barbieri RL. Nafarelin in the treatment of endometriosis. Dose management. Gynecol Obstet Invest. 1994;37(4):263–264.
16. Barbieri RL, Petro Z, Canick JA, Ryan KJ. Aromatization of norethindrone to ethinyl estradiol by human placental microsomes. J Clin Endocrinol Metab. 1983;57(2):299–303.
17. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med. 2017;377(1):28–40.
18. Surrey E, Taylor HS, Giudice L, et al. Long-term outcomes of elagolix in women with endometriosis: results from two extension studies. Obstet Gynecol. 2018;132(1):147–160.
19. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst Rev. 2007;(4):CD000068.
20. Barbieri RL, Ryan KJ. Danazol: endocrine pharmacology and therapeutic applications. Am J Obstet Gynecol. 1981;141(4):453–463.
21. Dunselman GA, Vermeulen N, Becker C, et al; European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29(3):400–412.

Watch for next month's guest editorial:

›› An oath to save lives against a backdrop of growing disparities
Laurie Green, MD

2018 UPDATE ON CERVICAL DISEASE
MARK H. EINSTEIN, MD, MS
(MAY 2018)

Cervical screening recommendations do not cover all circumstances

Starting cervical cancer screening at age 21 does not necessarily take into account the fact that we are seeing youngsters initiating sexual activity as young as age 9. We obviously see pregnancies early as well. Waiting to screen until age 21, therefore, may cause us to miss the development of high-grade lesions and cervical cancer. As you know, cases in the literature report instances of invasive cancer with first Pap test at age 21. Also, human papillomavirus (HPV) is spread by sexual activity, with the squamous columnar junction more susceptible to infection at a young age.

Recommendations regarding cervical cancer screening for older women also should take into account new sexual partners. Currently, both men and women are living longer and are remarrying or are sexually active with multiple partners. The fact that older women are desiring hormone replacement for vaginal lubrication and dyspareunia shows that they are sexually active even in their late 70s. I believe that the incidence of HPV infection to cervical, vaginal, and vulvar tissue will be increasing as a result.

In an age in which primary care physicians do not have time to perform Pap tests or vaginal, cervical, and vulvar exams because they are overwhelmed with keeping up with patients' major medical issues is a misunderstanding regarding current recommendations for Pap test screening.

Elizabeth Reinoehl-McClaskey, MD
Onley, Virginia

MAY 2018

Dr. Einstein responds

Sexual behavior can start early, but this does not lead to cancer. When we screen, we are looking for cancer, not HPV infection, which is quite common in women and men younger than age 21. Also, one might question whether current screening techniques pick up early-onset tumors. Regarding older women, sexual activity and the rate of older women getting cervical cancer should be considered in future guidelines.

TACTICS FOR REDUCING THE RATE OF SURGICAL SITE INFECTION FOLLOWING CESAREAN DELIVERY
ROBERT L. BARBIERI, MD
(EDITORIAL; APRIL 2018)

Midwife-physician alliance benefits women

I want to thank Dr. Barbieri for the introduction to his April editorial in which he states that the "trusted nurse midwife asks you to consult on her patient." Where I practice (in a large suburb of Kansas with a hospital where more than 5,000 babies are delivered yearly), there is a serious lack of midwives and an even greater lack of physicians to support them.

As the co-owner of an independently owned nurse-midwife practice, after losing our collaborating physician, we were unable to secure collaboration from any other group, despite our cesarean delivery rate of 5%, vaginal birth after cesarean success rate of 87%, and chorioamnionitis rate of 0%. Please continue to educate your readers on the benefit to women when all obstetric providers work together.

Julie Gorenc, CNM
Lenexa, Kansas

Dr. Barbieri responds

I thank Ms. Gorenc for her support of OBG MANAGEMENT and share her concern about optimizing obstetric care. Given the pending shortage of clinicians, we will need all experienced clinicians to work together to ensure access to high-quality obstetric care. My observation is that many obstetricians are concerned about liability issues that can be associated with coverage of other clinicians, including nurse midwives. The quality of obstetric care and collaboration would be enhanced if our medical tort system could evolve to a "just culture," ending the "blame and shame" associated with tort litigation.

2018 UPDATE ON GYNECOLOGIC CANCER
JASON D. WRIGHT, MD
(MARCH 2018)

Diagnostics company asserts medical and pathology groups prefer cotesting for cervical cancer screening

We are concerned about Dr. Wright's March 2018 gynecologic cancer coverage of US Preventive Services Task Force (USPSTF) screening guidelines for cervical cancer.

CONTINUED ON PAGE 17

Balcoltra™

(levonorgestrel and ethinyl estradiol tablets, USP, and ferrous bisglycinate tablets)
0.1mg/0.02mg and 36.5mg

A new choice for balanced control

Balcoltra™ offers a balance of high efficacy and low dose[1]

- **Low-dose levonorgestrel/ethinyl estradiol combination oral contraceptive (COC)[1]**
- **Familiar 21/7 dosing[1]**
- **Cycle control with 4% breakthrough bleeding and 1 unintended pregnancy per 100 woman-years[1]**

Visit balcoltra.com to learn more about how Balcoltra may help your patients.

*Most eligible patients will pay no more than $21 per co-pay. Patients should present this coupon with their prescription to their participating pharmacy. For each Balcoltra prescription, patients pay the first $21 of their out-of-pocket expense and Avion will cover up to $100 of their remaining expense. They could have additional responsibility depending on their insurance plan or remaining expense. This offer is good for 21 uses. Cardholders with questions, please call 1-877-838-3846 (8:30 AM -5:30 PM ET, Monday-Friday).

INDICATIONS AND USAGE

Balcoltra is a progestin/estrogen combination oral contraceptive (COC) indicated for use by females of reproductive potential to prevent pregnancy.

IMPORTANT SAFETY INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke.

CONTRAINDICATIONS

Balcoltra is contraindicated in women with a high risk of arterial or venous thrombotic diseases, liver tumors (benign or malignant) or liver disease, undiagnosed abnormal uterine bleeding, during pregnancy, with breast cancer or other estrogen- or progestin-sensitive cancer (now or in the past), hypersensitivity to any of the components, or in women who are currently taking Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir (with or without dasabuvir).

WARNINGS AND PRECAUTIONS

- Discontinue Balcoltra if an arterial thrombotic event or venous thromboembolic event (VTE) occurs, and at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during prolonged immobilization. Balcoltra should not be started any earlier than 4 weeks after delivery, in women who are not breastfeeding. The use of COCs increases the risk of VTE. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions. Use COCs with caution in women with cardiovascular disease risk factors.
- If jaundice occurs, treatment should be discontinued.
- Balcoltra should not be prescribed for women with uncontrolled hypertension or hypertension with vascular disease. An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. If Balcoltra is used in women with well-controlled hypertension, monitor blood pressure and stop treatment if blood pressure rises significantly.
- Women who are prediabetic or diabetic should be monitored while using Balcoltra. Alternate contraceptive methods should be considered for women with uncontrolled dyslipidemia.
- Patients using Balcoltra who have a significant change in headaches or who develop new headaches that are recurrent, persistent, or severe should be evaluated, and Balcoltra should be discontinued if indicated.
- Irregular bleeding and spotting sometimes occurs in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles on Balcoltra, check for causes such as pregnancy or malignancy.
- This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Sensitivity to tartrazine is frequently seen in patients who have aspirin hypersensitivity.

ADVERSE REACTIONS

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg, the most common adverse reactions (incidence ≥ 2%) were headache (14%), metrorrhagia (8%), dysmenorrhea (7%), nausea (7%), abdominal pain (4%), breast pain (4%), emotional lability (3%), acne (3%), depression (2%), amenorrhea (2%), and vaginal moniliasis (2%).

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding.

Patients should be counseled that COCs do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Please see full Prescribing Information, including BOXED WARNING, for Balcoltra.

References: 1. Balcoltra [package insert]. Alpharetta, GA: Avion Pharmaceuticals LLC; 2018.

Avion PHARMACEUTICALS
1-888-612-8466
Alpharetta, GA 30005

Balcoltra™ (levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets and ferrous bisglycinate 36.5 mg tablets) for oral administration

Brief Summary of Prescribing Information

For additional information, refer to the full Prescribing Information.

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke.

INDICATIONS AND USAGE

Balcoltra is indicated for use by females of reproductive potential to prevent pregnancy.

DOSAGE AND ADMINISTRATION

Patients should take one tablet by mouth at the same time every day in the order directed on the blister pack.

CONTRAINDICATIONS

Balcoltra is contraindicated in individuals with:

- A high risk of arterial or venous thrombotic diseases, including in women who:
  - -Smoke, if over age 35
  - -Have deep vein thrombosis or pulmonary embolism, now or in the past
  - -Have inherited or acquired hypercoagulopathies
  - -Have cerebrovascular disease
  - -Have coronary artery disease
  - -Have thrombogenic valvular or rhythm diseases of the heart
  - -Have uncontrolled hypertension
  - -Have diabetes mellitus with vascular disease
  - -Have headaches with focal neurological symptoms or have migraine headaches with aura
- Women over age 35 with any migraine headaches
- Liver tumors or liver disease
- Undiagnosed abnormal uterine bleeding
- Pregnancy
- Breast cancer or other estrogen- or progestin-sensitive cancer or history of these cancers
- Hypersensitivity of any of the components
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir

WARNINGS AND PRECAUTIONS

Thrombotic Disorders and Other Vascular Problems

Stop Balcoltra if an arterial thrombotic event or venous thromboembolic (VTE) event occurs, or if unexplained visual loss, proptosis, diplopia, papilledema or retinal vascular lesions occur. If possible, stop at least 4 weeks before through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during the following prolonged immobilization. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding.

The use of COCs increases the risk of VTE; however, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke. Use COCs with caution in women with cardiovascular disease risk factors.

Liver Disease

Do not use Balcoltra in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Balcoltra if jaundice develops. Balcoltra is contraindicated in women with benign and malignant liver tumors. Hepatic adenomas are associated with COC use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue Balcoltra prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. Balcoltra can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

High Blood Pressure

Balcoltra is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease.

If used in women with well-controlled hypertension, monitor blood pressure and stop Balcoltra if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. COCs may worsen existing gallbladder disease. A history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

Carbohydrate and Lipid Metabolic Effects

Monitor prediabetic and diabetic women taking Balcoltra, as COCs may decrease glucose tolerance. Consider an alternative contraceptive method for women with uncontrolled dyslipidemia. Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

Headache

If a woman taking Balcoltra develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Balcoltra if indicated. Consider discontinuation of Balcoltra in the case of increased frequency or severity of migraine during COC use.

Bleeding Irregularities and Amenorrhea

Evaluate irregular bleeding or amenorrhea.

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different contraceptive product.

Women who use Balcoltra may experience amenorrhea. In the clinical trial, 2.6% of the evaluable cycles were amenorrheic. Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was preexistent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

FD&C Yellow No. 5 Allergic-type Reaction

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Depression

Carefully observe women with a history of depression and discontinue Balcoltra if depression recurs to a serious degree.

Carcinoma of the Breast and Cervix

Balcoltra is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive.

Effect on Binding Globulins

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

Monitoring

A woman who is taking COCs should have her blood pressure checked periodically with her healthcare provider.

Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Balcoltra.

ADVERSE REACTIONS

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets, a total of 1477 healthy women of child-bearing potential were enrolled and had 7870 cycles of exposure. Of these, 792 subjects had completed 6 cycles of treatment. The women ranged in age from 17 to 49 years and 87% were Caucasian.

Common Adverse Reactions (≥ 2% of women):

Headache (14%), metrorrhagia (8%), dysmenorrhea (7%), nausea (7%), abdominal pain (4%), breast pain (4%), emotional lability (3%), acne (3%), depression (2%), amenorrhea (2%), and vaginal moniliasis (2%).

At the time of the report, 133 (9%) subjects had withdrawn from the study due to adverse events. The most frequent were due to headache and metrorrhagia (1% each). Other adverse events occurring in < 1% of those who discontinued included amenorrhea, depression, emotional lability, hypertension, acne, menorrhagia, nausea, hypercholesterolemia, weight gain, dysmenorrhea, and flatulence. All other reasons for discontinuation were reported by 3 or fewer subjects. These are not all of the possible adverse reactions of Balcoltra.

DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain more information about interactions with hormonal contraceptives. Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of ethinyl estradiol (EE). The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors, such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, tipranavir/ritonavir, boceprevir, telaprevir, nevirapine and efavirenz] or increase [e.g., indinavir, atazanavir/ritonavir and etravirine]).

Combined oral contraceptives containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. Combined oral contraceptives have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs.

Do not co-administer Balcoltra with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations.

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

USE IN SPECIFIC POPULATIONS

Pregnant Women

Balcoltra is contraindicated in pregnancy because there is no reason to use combined hormonal contraceptives (CHCs) in pregnancy. Discontinue Balcoltra if pregnancy occurs. Based on epidemiologic studies and meta-analyses, there is little or no increased risk of birth defects in the children of females who inadvertently use COCs during early pregnancy.

Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to COCs before conception or during early pregnancy.

Nursing Mothers

Combined hormonal contraceptives (CHCs) and/or metabolites are present in human milk and in breast-fed infants. CHCs, including Balcoltra, can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Balcoltra and any potential adverse effects on the breast-fed child from Balcoltra or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of Balcoltra have been established in women of reproductive age. Efficacy is expected to be the same in post-pubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

Geriatric Use

Balcoltra has not been studied in postmenopausal women and is not indicated in this population.

Hepatic Impairment

The pharmacokinetics of Balcoltra has not been studied in women with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

OVERDOSAGE

There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

The FDA-approved product labeling can be found at www.balcoltra.com, or call 1-888-612-8466.

Distributed by:
Avion Pharmaceuticals, LLC,
Alpharetta, GA 30005

1-888-61-AVION (1-888-612-8466)
Rev. 0002 AV-624

Avion PHARMACEUTICALS

CONTINUED FROM PAGE 14

The article suggests that draft USPSTF cervical cancer guidelines issued in September 2017 are final when in fact that is not the case. The USPSTF issued draft guidelines in late 2017, but final publication is pending USPSTF revisions in response to submitted public comments. This means that, for now, existing USPSTF guidelines remain in place, and these guidelines clearly recommend cotesting (high-risk HPV and cytology/Pap) in women 30 to 65 years of age every 5 years as an appropriate screening modality, in alignment with the American College of Obstetricians and Gynecologists, the American Society for Colposcopy and Cervical Pathology, and the American Cancer Society, among others.

It is also notable that the proposed USPSTF guidelines have been met with sharp resistance. ACOG, as well as several organizations, including the American Society of Clinical Pathology, American Society of Cytopathology, the American Society for Cytotechnology, the College of American Pathologists, the International Academy of Cytology, and the Papanicolaou Society of Cytopathology, cite concerns with the proposed USPSTF guidelines and continue to argue in favor of cotesting in women 30 to 65 years of age.[1,2]

We also fear that Dr. Wright may have provided data out of context. For instance, he notes that the USPSTF, in its draft guidelines, found that cotesting increased the number of follow-up tests but did not increase detection of CIN3+ in a decision model. Yet, the USPSTF analysis overrelied on research from European populations (not representative of the US cervical cancer experience) and excluded peer-reviewed data of women in the United States, which clearly shows that HPV-Pap together catches more cervical cancers than either Pap or HPV alone.[3]

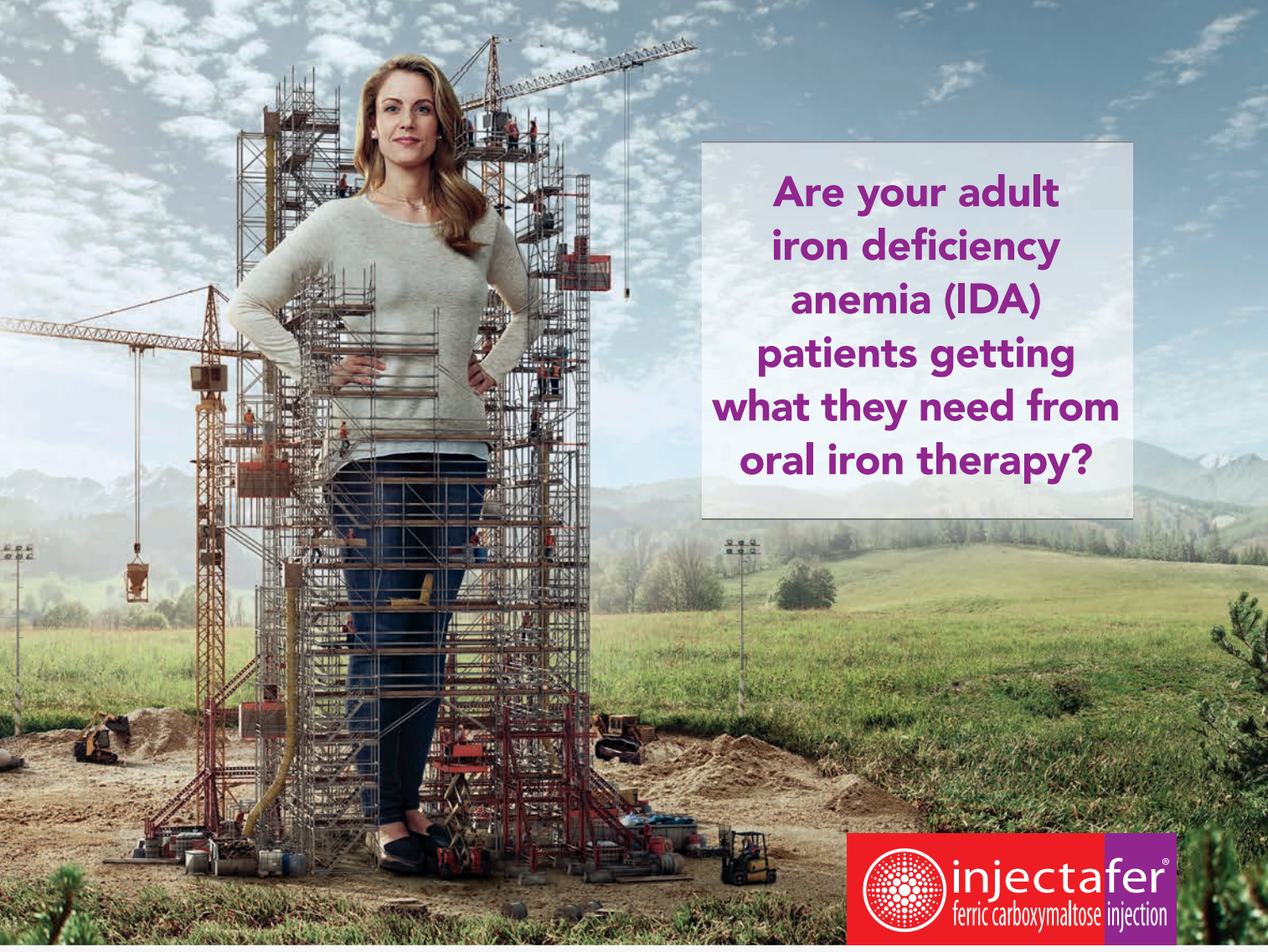
D.P. Alagia, MD, and
Harvey W. Kaufman, MD, MBA
Quest Diagnostics
Madison, New Jersey

References

1. American College of Obstetricians and Gynecologists. Leading women's health care groups issue joint statement on USPSTF draft cervical cancer screening recommendations. September 13, 2017. https://www.acog.org/About-ACOG/News-Room/Statements/2017/Leading-Womens-Health-Care-Groups-Issue-Joint-Statement-on-USPSTF. Accessed July 5, 2018.
2. Cytopathology Education and Technology Consortium. Response to new USPSTF guidelines for cervical cancer screening. October 2, 2017. https://s3.amazonaws.com/ascpcdn/static/ONELab/pdf/2017/CETC+-USPSTF+Letter+10-2-17.PDF. Accessed July 5, 2018.
3. Blatt AJ, Kennedy R, Luff RD, Austin RM, Rabin DS. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. Cancer Cytopathol. 2015;123:282–288.

Dr. Wright responds

I thank Drs. Alagia and Kaufman for their interest in the work and their comments regarding the USPSTF cervical cancer guidelines. As stated in the article, the USPSTF recommendations are currently in draft form and subject to revision based on public comment. The guidelines are a synthesis of best available evidence and are meant to weigh the benefits and harms of various cervical cancer screening strategies. The recommendations are based in part on simulation modeling that incorporates available evidence and projects the long-term effects of multiple rounds of screening. While the decision models incorporated a large amount of data and were robust in a variety of sensitivity analyses, as with all decision analyses, they are limited by the underlying assumptions utilized in the model. Over the last 2 decades, screening practices for cervical cancer have dramatically shifted. Highlighting the USPSTF draft guidelines was meant to raise awareness among clinicians and policy makers of the evolving role of high-risk HPV testing, either alone or in combination with cytology, as a screening modality for cervical cancer.



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.[1]

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

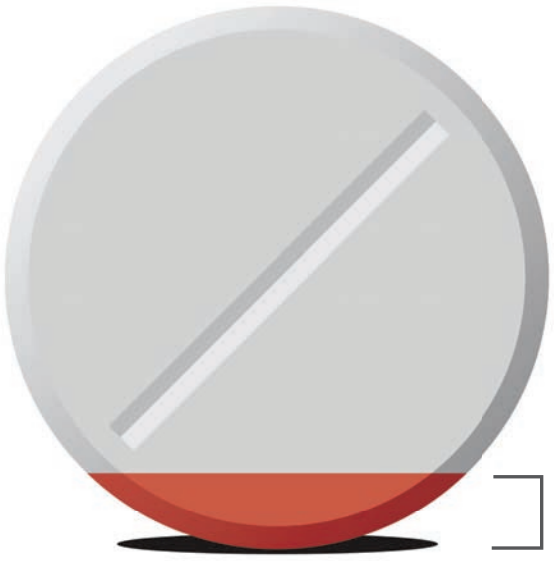
In two randomized clinical studies, a total of 1775 patients were exposed to Injectafer, 15 mg/kg of body weight, up to a single maximum dose of 750 mg of iron on two occasions, separated by at least 7 days, up to a cumulative dose of 1500 mg of iron. Adverse reactions reported by ≥2% of Injectafer-treated 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.

Patients with IDA may fail oral iron



LESS THAN 10% OF ORAL IRON IS ABSORBED[2]

Monitor your patients. When oral iron fails, it's time to consider Injectafer—the fastest-growing IV iron in the US.†

Injectafer provides up to 1500 mg of iron in just 2 administrations separated by at least 7 days[1]

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

*American Regent® is a registered trademark of Luitpold Pharmaceuticals, Inc., a member of the Daiichi Sankyo group.

†Based on Symphony Health PHAST Non-Retail Mg Administration Volume Data (January 2017-December 2017).

References: 1. Injectafer [package insert]. Shirley, NY: American Regent, Inc.; 2018. **2.** Zhu A, Kaneshiro M, Kaunitz JD. Evaluation and treatment of iron deficiency anemia: a gastroenterological perspective. *Dig Dis Sci.* 2010;55(3):548-559.

Daiichi-Sankyo

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

injectafer® ferric carboxymaltose injection

INJECTAFER® (ferric carboxymaltose injection), for intravenous use
Initial U.S. Approval: 2013

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

Injectafer is 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.

2 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-dose 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.

3 DOSAGE FORMS AND STRENGTHS

Injection: 750 mg iron / 15 mL single-dose vial

4 CONTRAINDICATIONS

Hypersensitivity to Injectafer or any of its components [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 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. *[see Adverse Reactions (6.1, 6.2)]*. 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.

5.2 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 [*see Dosage and Administration (2)*].

5.3 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*
- Laboratory Test Alterations *[see Warnings and Precautions (5.3)]*

6.1 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 (14)*], 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.

6.2 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published studies on the use of ferric carboxymaltose in pregnant women have not reported an association with ferric carboxymaltose and adverse developmental outcomes. However, these studies cannot establish or exclude the absence of any drug-related risk during pregnancy because the studies were not designed to assess for the risk of major birth defects (*see Data*). There are risks to the mother and fetus associated with untreated iron deficiency anemia (IDA) in pregnancy (*see Clinical Considerations*).

In animal reproduction studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused adverse developmental outcomes including 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 estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Untreated iron deficiency anemia (IDA) in pregnancy is associated with adverse maternal outcomes such as post-partum anemia. Adverse pregnancy outcomes associated with IDA include increased risk for preterm delivery and low birth weight.

Data

Human Data

Published data from randomized controlled studies, prospective observational studies and retrospective studies on the use of ferric carboxymaltose in pregnant women have not reported an association with ferric carboxymaltose and adverse developmental outcomes. However, these studies cannot establish or exclude the absence of any drug-related risk during pregnancy because of methodological limitations, including that the studies were not primarily designed to capture safety data nor designed to assess the risk of major birth defects. Maternal adverse events reported in these studies are similar to those reported during clinical trials in adult males and non-pregnant females *[see Adverse Reactions (6.1)]*.

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 embryonic or fetal 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 embryonic or fetal 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.

8.2 Lactation

Risk Summary

The available published data on the use of ferric carboxymaltose in lactating women demonstrate that iron is present in breast milk. However, the data do not inform the full potential exposure of iron for the breastfed infant. Among the breastfed infants, there were no adverse events reported that were considered related to ferric carboxymaltose exposure through breastmilk. There is no information on the effects of ferric carboxymaltose on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Injectafer in addition to any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Clinical Considerations

Monitor breastfed infants for gastrointestinal toxicity (constipation, diarrhea).

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 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.

10 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. [*see Adverse Reactions (6.2)*].

11 DESCRIPTION

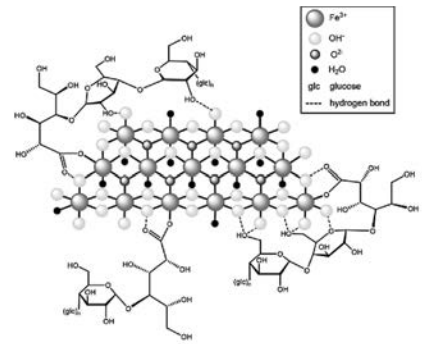
Ferric carboxymaltose, an iron replacement product, is an iron carbohydrate complex with the chemical name of polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Da corresponding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

The chemical structure is presented below:



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-dose 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 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% at 24 days after Injectafer dose.

12.3 Pharmacokinetics

After administration of a single dose of Injectafer of 100 to 1000 mg of iron in iron deficient patients, maximum iron concentration 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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

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

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: A Multi-center, Randomized, Active Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose (FCM) in Patients with Iron Deficiency Anemia (IDA), (NCT00982007) 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)

Hemoglobin (g/dL) Mean (SD)	Cohort 1		Cohort 2	
	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.

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

Trial 2: REPAIR-IDA, Randomized Evaluation of efficacy and safety of Ferric carboxymaltose in Patients with iron deficiency Anemia and Impaired Renal function, (NCT00981045) 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 101); 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 prior to Day 56 in Injectafer-treated patients.

17 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 [*see Warnings and Precautions (5)*].

Injectafer is manufactured under license from Vifor (International) Inc, Switzerland.

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

IN0650
RQ1052-B Revised: 04/2018

What works best for genitourinary syndrome of menopause: vaginal estrogen, vaginal laser, or combined laser and estrogen therapy?

There are not enough data to recommend laser therapy over the gold standard, transvaginal estrogen, for treating symptoms of the genitourinary syndrome of menopause (GSM). This study's findings are preliminary, slightly contradictory, and raise more questions. At short-term follow-up (20 weeks), all 3 treatment options—fractionated carbon dioxide (CO2) laser alone, laser combined with local vaginal estriol, and vaginal estriol alone—were effective in treating vaginal dryness. Laser therapy alone and laser combined with vaginal estriol were more effective than estriol alone for dyspareunia and burning; however, both laser alone and laser combined with vaginal estriol appear to worsen vaginal pain (based on the Female Sexual Function Index [FSFI] at 20 weeks).

FAST TRACK

The study raises important questions related to optimizing therapy for vaginal atrophy and the need for more research and clinical care protocols involving vaginal laser therapy for GSM

EXPERT COMMENTARY

Cheryl B. Iglesia, MD, is Professor, Departments of Obstetrics and Gynecology and Urology, Georgetown University School of Medicine, Washington, DC, and Director, Section of Female Pelvic Medicine and Reconstructive Surgery, MedStar Washington Hospital Center. Dr. Iglesia serves on the OBG MANAGEMENT Board of Editors.

Cruz VL, Steiner ML, Pompei LM, et al. Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO_2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. Menopause. 2018;25(1)21–28.

The author reports receiving grant or research support from the Foundation for Female Health Awareness (paid to MedStar Research Institute) and the National Vulvodynia Association.

GSM encompasses a constellation of symptoms involving the vulva, vagina, urethra, and bladder, and it can affect quality of life in more than half of women by 3 years past menopause.[1,2] Local estrogen creams, tablets, and rings are considered the gold standard treatment for GSM.[3] The rising cost of many of these pharmacologic treatments has created headlines and concerns over price gouging for drugs used to treat female sexual dysfunction.[4] Recent alternatives to local estrogens include vaginal moisturizers and lubricants, vaginal dehydroepiandrosterone (DHEA) suppositories, oral ospemifene, and vaginal laser therapy.

Laser treatment (with fractionated CO2, erbium, and hybrid lasers) activates heat shock proteins and tissue growth factors to stimulate

FDA issues warning to energy-based device companies advertising vaginal "rejuvenation"

On July 30, 2018, the US Food and Drug Administration (FDA) issued a safety warning against the use of energy-based devices for vaginal "rejuvenation"[1] and sent warning letters to 7 companies—Alma Lasers; BTL Aesthetics; BTL Industries, Inc; Cynosure, Inc; InMode MD; Sciton, Inc; and Thermigen, Inc.[2] The concern relates to marketing claims made on many of these companies' websites on the use of radiofrequency and laser technology for such specific conditions as vaginal laxity, vaginal dryness, urinary incontinence, and sexual function and response. These devices are neither cleared nor approved by the FDA for these specific indications; they are rather approved for general gynecologic conditions, such as the treatment of genital warts and precancerous conditions.

The FDA sent the safety warning related to energy-based vaginal therapies to patients and providers and have encouraged them to submit any adverse events to MedWatch, the FDA Safety Information and Adverse Event Reporting system.[1] The "It has come to our attention letters" issued by the FDA to the above manufacturers request additional information and FDA clearance or approval numbers for claims made on their websites—specifically, referenced benefits of energy-based devices for vaginal, vulvar, and sexual health.[2] This information is requested from manufacturers in writing by August 30, 2018 (30 days).

References

1. FDA warns against use of energy-based devices to perform vaginal 'rejuvenation' or vaginal cosmetic procedures: FDA safety communication. US Food and Drug Administration website. https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm615013.htm. Updated July 30, 2018. Accessed July 30, 2018.
2. Letters to industry. US Food and Drug Administration website. https://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm111104.htm. Updated July 30, 2018. Accessed July 30, 2018.

FAST TRACK

Women in the laser treatment arms showed significant improvement in dyspareunia and burning versus those treated with estriol alone; however, at 20 weeks women in both laser arms had more pain compared with the estriol-alone group

neocollagenesis and neovascularization within the vaginal epithelium, but it is expensive and not covered by insurance because it is considered a cosmetic procedure.[5]

Most evidence on laser therapy for GSM comes from prospective case series with small numbers and short-term follow-up with no comparison arms.[6,7] A recent trial by Cruz and colleagues, however, is notable because it is one of the first published studies that compared vaginal laser with vaginal estrogen alone and with a combination laser plus estrogen arm. We need level 1 comparative data from studies such as this to help us counsel the millions of US women with GSM.

Details of the study

In this single-site randomized, double-blind, placebo-controlled trial conducted in Brazil, postmenopausal women were assigned to 1 of 3 treatment groups (15 per group):

- CO2 laser (MonaLisa Touch, SmartXide 2 system; DEKA Laser; Florence, Italy): 2 treatments total, 1 month apart, plus placebo cream (laser arm)
- estriol cream (1 mg estriol 3 times per week for 20 weeks) plus sham laser (estriol arm)
- CO2 laser plus estriol cream 3 times per week (laser plus estriol combination arm).

The primary outcome included a change in visual analog scale (VAS) score for symptoms related to vulvovaginal atrophy (VVA), including dyspareunia, dryness, and burning (0–10 scale with 0 = no symptoms and 10 = most severe symptoms), and change in the objective Vaginal Health Index (VHI). Assessments were made at baseline and at 8 and 20 weeks. Participants were included if they were menopausal for at least 2 years and had at least 1 moderately bothersome VVA symptom (based on a VAS score of 4 or greater).

Secondary outcomes included the objective FSFI questionnaire evaluating desire, arousal, lubrication, orgasm, satisfaction, and pain. FSFI scores can range from 2 (severe dysfunction) to 36 (no dysfunction). A total FSFI score less than 26 was deemed equivalent to dysfunction. Cytologic smear evaluation using a vaginal maturation index was included in all 3 treatment arms. Sample size calculation of 45 patients (15 per arm) for this trial was based on a 3-point difference in the VHI.

The baseline characteristics for participants in each treatment arm were similar, except that participants in the vaginal estriol group were less symptomatic at baseline.

TABLE Comparison of VAS and FSFI scores by treatment group in a randomized trial (45 participants) by Cruz and colleagues

VAS scores[a]				
	Laser	Estriol	Laser plus estriol	*P*[c]
Dyspareunia				
Baseline	4.9 (3.7)	3.2 (3.4)	6.5 (3.9)	.09
Week 20	0.7 (1.5)	0.2 (0.6)	0.9 (1.8)	.95
Dryness				
Baseline	8.0 (2.6)	5.6 (2.9)	7.9 (3.0)	.07
Week 20	1.4 (2.0)	0.5 (1.4)	0.3 (.07)	.35
Burning				
Baseline	3.9 (4.5)	0.9 (1.6)	4.9 (3.8)	.017[d]
Week 20	0.5 (1.5)	0.1 (0.3)	0.4 (1.1)	.95
Total FSFI scores[b]				
Baseline	18.6 [16.4; 24.6]	23.6 [17.5; 29.8]	18.7 [7.2; 22.6]	.21
Week 20	14.4 [7.8; 22.4]	25.4 [16.8; 29.3]	23.6 [14.9; 28.6]	.10

[a]Items listed as mean (SD).

[b]Items listed as median [interquartile range].

[c]*P* values of .05 were considered statistically significant.

[d]*P*<.05.

Abbreviations: FSFI, Female Sexual Function Index; VAS, visual analog scale.

This group had less burning at baseline based on the FSFI and less dyspareunia based on the VAS.

Laser treatment improved dryness, burning, and dyspareunia but caused more pain

All 3 treatment groups showed statistically significant improvement in vaginal dryness at 20 weeks, but only the laser-alone arm and the laser plus estriol arms showed improvement in dyspareunia and burning. The total FSFI scores improved significantly only in the laser plus estriol arm (**TABLE**). No difference in the vaginal maturation index was noted between groups; however, improved numbers of parabasal cells were found in participants in the laser treatment arms.

While participants in the laser treatment arms (alone and in combination with estriol) showed significant improvement in the VAS domains of dyspareunia and burning compared with those treated with estriol alone, there was a contradictory finding of more pain in both laser arms at 20 weeks compared with the estriol-alone group, based on the FSFI. The FSFI is a validated, objective quality-of-life questionnaire, and the finding of more pain with laser treatment is a concern.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Exercise caution when interpreting these study findings. While this preliminary study showed that fractionated CO2 laser treatment had favorable outcomes for dyspareunia, dryness, and burning, the propensity for increased vaginal pain with this treatment is a concern. This study was not adequately powered to analyze multiple comparisons in postmenopausal women with GSM symptoms. There were significant baseline differences, with less bothersome burning and sexual complaints based on the FSFI and VAS, in the vaginal estriol arm. The finding of more pain in the laser treatment arms at 20 weeks compared with that in the vaginal estriol arm is of concern and warrants further investigation.

CHERYL B. IGLESIA, MD

CONTINUED ON PAGE 40

MOC: ACOG's role in developing a solution to the heated controversy

ObGyn leaders are working with the ABMS to rebuild the process of continuing board certification, formerly known as MOC

Lucia DiVenere, MA

IN THIS ARTICLE

The American Board of Medical Specialties (ABMS) has decided to trade the phrase "maintenance of certification" (MOC) for "continuing board certification," a seemingly minor change that has an important backstory. This is the story of how the physician community flexed its collective muscle and how the American College of Obstetricians and Gynecologists (ACOG) helped broker an important détente and pathway in a highly contentious issue.

Founded in 1933 as a nonprofit organization dedicated to maintaining high uniform standards among physicians, the ABMS and many of its specialty boards have found themselves, for more than a decade, under heavy fire from physicians (especially family physicians, internists, and surgeons), their 24 subspecialties, and the state medical societies representing them.

The ObGyn experience with the American Board of Obstetrics and Gynecology (ABOG), however, is better for a number of reasons. Historically, ABOG and ACOG have worked closely together, which is an anomaly among boards as many boards have an arms-length or even an antagonistic relationship with their specialty society.

The discussion below outlines physician concerns with the ABMS and related boards and describes efforts to address and rebuild the continuing board certification process.

Ms. DiVenere is Officer, Government and Political Affairs, at the American College of Obstetricians and Gynecologists in Washington, DC. She is an OBG MANAGEMENT Contributing Editor.

The author reports no financial relationships relevant to this article.

Direct and indirect costs

Physicians are very concerned with the costs involved in MOC. Measurable costs include testing fees, while indirect costs include time, stress, travel to test centers, and threats to livelihood for failing a high-stakes examination. Physicians want the high-stakes exam eliminated.

Relevance to practice

Physicians often feel that the MOC has little relevance to their practice, which fuels a sense of resentment toward boards that they believe are dominated by physicians who no longer practice. Subspecialists feel farther away from general practice and the base exams. Generalists feel that the exams miss the points of their daily practice.

Lack of data to show improved quality of care

Physicians want to know that the MOC is worth their time, effort, and money because it improves patient care. To date, however,

CONTINUED ON PAGE 28

MDedge™ | OBG MANAGEMENT

Keeping you informed. Saving you time.

MDedge: The Information access platform that makes you a better Doctor.

Consolidates the resources of our 35 publications and websites, including *OBG Management*

Expert physician guidance – 700+ MDs/KOLs on our 35 boards

Improved patient care via superior conference coverage, original research, and expert commentary

Time-saving personal development via special reports, summarized articles, and the business of medicine

- Daily Briefing and Podcast
- Personalized content
- Digital and print access

Come visit us at **mdedge.com/obgmanagement**

...painlessly register to gain access to special reports

CONTINUED FROM PAGE 26

FAST TRACK

Physicians want to know what the best MOC practices are, what improves care, and that practices that make no difference will be discarded

empirical or clinical data on patient outcomes are absent or ambiguous; most studies lack high-level data or do not investigate the MOC requirements. Physicians want to know what the best MOC practices are, what improves care, and that practices that make no difference will be discarded. In addition, they want timely knowledge alerts when evidence changes.

Relationship to licensing, employment, privileging, credentialing, and reimbursement

Hospitals, insurers, and states increasingly—and inappropriately—use board certification as the primary (sometimes only) default measure of a physician's fitness for patient care. Physicians without board certification often are denied hospital privileges, inclusion in insurance panels, and even medical licenses. This changes certification from a voluntary physician self-improvement exercise into a can't-earn-a-living-without-it cudgel.

Variation

Boards vary significantly in their MOC requirements and costs. The importance of an equal standard across all boards is a clear theme among physician concerns.

Role and authority of the ABMS and related boards

Many physicians are frustrated with the perceived autocratic nature of their boards—boards that lack transparency, do not solicit or allow input from practicing physicians, and are unresponsive to physician concerns.

According to Susan Ramin, MD, ABOG Associate Executive Director, ABOG is leading in a number of these areas, including:

- rapidly disseminating clinical information on emerging topics, such as Zika virus infection and opioid misuse
- offering physician choice of testing categories
- exempting high scorers from the secured written exam, which saved physicians a total of $881,000 in exam fees
- crediting physicians for what they already are doing, including serving on maternal mortality review committees, participating in registries, and participating in the Alliance for Innovation on Maternal Health (AIM)
- providing Lifelong Learning and Self-Assessment (LLSA) articles that, according to 90% of diplomates surveyed, are beneficial to their clinical practice (**FIGURE**).[1,2]

Our colleague physicians are not so lucky. In a 2015 *New England Journal of Medicine* Perspective, one physician called out the American Board of Internal Medicine as "a private, self-appointed certifying organization," a not-for-profit organization that has "grown into a $55-million-per-year business."[3] He concluded that "many physicians are waking up to the fact that our profession is increasingly controlled by people not directly involved in patient care who have lost contact with the realities of day-to-day clinical practice."[3]

State and society responses to MOC requirements

Frustration with an inability to resolve these concerns has grown steadily, bubbling over into state governments. The American Medical Association developed "model state legislation intended to prohibit hospitals, health care insurers, and state boards of medicine

CONTINUED ON PAGE 29

ILLUSTRATION: PAUL ZWOLAK FOR OBG MANAGEMENT

2018

PAGS PELVIC ANATOMY and GYNECOLOGIC SURGERY SYMPOSIUM

IN COLLABORATION WITH OBG MANAGEMENT

JOINTLY PROVIDED BY University of Cincinnati | Global Academy for Medical Education

REGISTER BY SEPTEMBER 10 SAVE UP TO $620!

THE PREMIER MEETING FOR ALL FACETS OF YOUR GYNECOLOGY PRACTICE

Earn up to 34.25 CME Credits (Including Workshop Credit)





COURSE CHAIRS

Tommaso Falcone, MD
Cleveland Clinic

Mickey M. Karram, MD
The Christ Hospital

SPECIAL KEYNOTE SPEAKER

Sawsan As-Sanie, MD, MPH
University of Michigan Hospitals and Health Centers

Faculty

Michael S. Baggish, MD
St. Helena Hospital

Linda D. Bradley, MD
Cleveland Clinic

Andrew I. Brill, MD
California Pacific Medical Center

Amanda Nickles Fader, MD
Johns Hopkins Hospital

John B. Gebhart, MD, MS
Mayo Clinic

Rosanne M. Kho, MD
Cleveland Clinic

Javier F. Magrina, MD
Mayo Clinic Phoenix

Beri M. Ridgeway, MD
Cleveland Clinic

ENCORE AT WYNN Las Vegas

OPTIONAL OPIOID REMS COURSE *NEW!*
December 4, 2018

OPTIONAL HANDS-ON WORKSHOPS
December 5, 2018

SCIENTIFIC GENERAL SESSIONS
December 6-8, 2018

OPTIONAL HANDS-ON WORKSHOPS

LIMITED SPACE AVAILABLE. FIRST COME. FIRST SERVED!

- Tissue Extraction Techniques
- Laparoscopic Suturing - The "Vertical Zone"
- Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
- Office-Based Gynecologic Procedures *NEW!*

SPECIAL KEYNOTES

- Management of Chronic Pelvic Pain
- Non-Opioid Pain Management after Minimally Invasive Hysterectomy

PLUS

- Hysterectomy Techniques
  Vaginal • Single Port • Robotic • Total Laparoscopic • Morcellation • Preserving Level 1 Support • When is it Appropriate to Remove the Ovaries?
- Incontinence and Prolapse Surgery
- Avoiding and Managing Complications
- Gynecologic Oncology for the Generalist
- Medical Legal Cases
- Fibroid Management
- Safe Use of Energy Devices in Gynecologic Surgery
- Surgical Tips for Successful Pelvic Surgery Video Session

AND, Optional Post-Conference P.E.P. Practice Management Workshop

To register and for complete information please see our website: **PAGS-cme.org**.

PAGS AGENDA

Agenda and faculty is subject to change. Please see website for updates.

TUESDAY, DECEMBER 4, 2018

Optional Opioid REMS Course NEW!
Optional, free course. Pre-registration required
Pain Management and Opioids: Balancing Risks and Benefits
3:00 PM - 6:15 PM

WEDNESDAY, DECEMBER 5, 2018

Optional Hands-On Workshops

Tissue Extraction Techniques
8:30 AM–12:30 PM

Laparoscopic Suturing - The "Vertical Zone"
8:30 AM–12:30 PM

Office-Based Gynecologic Procedures
8:30 AM–5:30 PM

Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
1:30 PM–5:30 PM

THURSDAY, DECEMBER 6, 2018

6:30 AM **Registration/Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

7:55 AM **Course Overview**
Mickey M. Karram, MD

PELVIC ANATOMY

8:00 AM **Pelvic and Abdominal Anatomy from the Laparoscopic Surgeon's View**
Tommaso Falcone, MD

8:40 AM **Anatomic Considerations: Facilitating Vaginal Procedures Safely and Effectively**
Mickey M. Karram, MD

INCONTINENCE AND PROLAPSE SURGERY

9:10 AM **Panel Discussion: Evaluation and Non-Surgical Management of Female Pelvic Floor Disorders: What Every Generalist Should Know**
John B. Gebhart, MD
Mickey M. Karram, MD
Beri M. Ridgeway, MD

9:55 AM **Question and Answer Session**

10:25 AM **Break/Exhibits**

11:10 AM **Surgery for Stress Incontinence and the Future of Synthetic Slings**
Beri M. Ridgeway, MD

11:40 AM **Surgery for Pelvic Organ Prolapse: Do We Need to Perform and Teach More Transvaginal Native Tissue Suture Repairs?**
John B. Gebhart, MD

12:10 PM **Mesh-Augmented Prolapse Repair: Is There Any Role for Vaginal Mesh: Indication and Technique of Sacral Colpopexy**
Beri M. Ridgeway, MD

12:40 PM **Question and Answer Session**

1:10 PM **Luncheon Symposium**

2:10 PM **Dessert Break/ Exhibits**

THURSDAY'S KEYNOTE LECTURE

2:40 PM **Management of Chronic Pelvic Pain in Women**
Sawsan As-Sanie, MD, MPH

FIBROID MANAGEMENT & PRINCIPLES OF ELECTROSURGERY

3:25 PM **Safe Use of Energy-Based Devices for Gynecologic Surgery**
Andrew I. Brill, MD

3:55PM **Myomectomy: Open to Robotic Approaches**
Tommaso Falcone, MD

4:25 PM **Break/Exhibits**

4:40 PM **The Hysteroscopic Treatment of Submucosal Fibroids and Polyps**
Linda D. Bradley, MD

5:10 PM **Question and Answer Session**

FRIDAY, DECEMBER 7, 2018

7:00 AM **Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

HYSTERECTOMY - TECHNIQUE

8:15 AM **The Difficult Vaginal Hysterectomy**
Rosanne M. Kho, MD

8:50 AM **When is it Appropriate to Remove Ovaries at Hysterectomy?**
Amanda Nickles Fader, MD

9:25 AM **Total Laparoscopic Hysterectomy**
Andrew I. Brill, MD

10:00 AM **Break /Exhibits**

10:45 AM **Robotic Hysterectomy**
Javier F. Magrina, MD

11:15 AM **Tissue Extraction Techniques (Morcellation)**
Tommaso Falcone, MD

11:45 AM **Techniques to Preserve Level 1 Support at the Time of Vaginal Laparoscopic and Robotic Hysterectomy**
Beri M. Ridgeway, MD

12:15 PM **Which Hysterectomy Approach is Best?**
Case Presentation and
Audience Participation – all speakers

12:45 PM **Question and Answer Session**

1:00 PM **Luncheon Symposium**

2:00 PM **Dessert Break/Exhibits**

FRIDAY'S KEYNOTE LECTURE

2:30 PM **Non-Opioid Pain Management after Minimally Invasive Hysterectomy**
Sawsan As-Sanie, MD, MPH

ONCOLOGY FOR THE GENERALIST

3:15 PM **Surgical Management of Pre-Cancer Vulvovaginal Lesions**
Amanda Nickles Fader, MD

4:00 PM **Laparoscopic and Robotic Management of the Adnexal Mass**
Javier F. Magrina, MD

4:45 PM **Spectrum of Vulvovaginal Disorders**
Michael S. Baggish, MD

5:30 PM **Question and Answer Session**

SATURDAY, DECEMBER 8, 2018

6:30 AM **Breakfast**

7:30 AM **Management of Endometriosis**
Tommaso Falcone, MD

8:30 AM **Avoiding and Managing Urogynecologic Complications**
John B. Gebhart, MD
Mickey M. Karram, MD

9:30 AM **Avoiding and Managing Laparoscopic Complications**
Tommaso Falcone, MD

10:30 AM **Break**

10:45 AM **Medical Legal Cases**
Michael S. Baggish, MD
Tommaso Falcone, MD

11:30 AM **Surgical Tips for Successful Pelvic Surgery: Video Session**
Surgical Management of Cornual Ectopic & Dermoid Cysts
Tommaso Falcone, MD

Techniques to Suspend the Apex at the Time of Vaginal Surgery
Mickey M. Karram, MD

1:00 PM **PAGS Scientific Program Adjournment**

P.E.P. PRACTICE ENHANCEMENT PROGRAM AGENDA (Optional, separate fee required)

Open to Non-Attendees—So bring your staff!

3.25 CME Credits Available

Make Your Practice More Profitable, Efficient, and Productive!

Director
Neil H. Baum, MD
Former Associate Clinical Professor of Urology
Tulane Medical School
Louisiana State University
New Orleans, Louisiana

Dr. Neil Baum is the author of *The Complete Business Guide to a Successful Medical Practice* and *3-Stages of a Physician's Career*

SATURDAY, DECEMBER 8, 2018

2:00 PM **Course Overview**

2:10 PM **Looking at the 4 Pillars of a Successful Practice in the Current Healthcare Environment**
- The 4 Pillars of a Successful Practice
- How to Improve the Efficiency, Productivity, and Profitability of Your Practice
- Online Reputation Management
- Why Market and Promote Your ObGyn Practice

3:30 PM **Break**

3:45 PM
- Using Social Media to Get to the Top of Google
- Numbers You Need to Know
- Moving from Volume to Value

5:00 PM **Q and A**

5:30 PM **P.E.P. Adjournment**

PAGS Scientific Faculty

Course Chairs

Tommaso Falcone, MD
Chief of Staff
Chief Academic Officer
Cleveland Clinic London
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
Cleveland, Ohio

Mickey M. Karram, MD
Director of Urogynecology
The Christ Hospital
Volunteer Professor of OB/GYN
University of Cincinnati
Cincinnati, Ohio

Special Keynote Speaker

Sawsan As-Sanie, MD, MPH
Associate Professor
University of Michigan
Michigan Medical
Von Voigtlander Women's Hospital
Ann Arbor, Michigan

Faculty

Michael S. Baggish, MD
Professor of Obstetrics and Gynecology
University of California San Francisco
St. Helena Hospital
St. Helena, California

Linda D. Bradley, MD
Vice Chair
Obstetrics, Gynecology, and Women's Health Institute
Director
Center for Menstrual Disorders
Professor of Surgery
Cleveland Clinic
Cleveland, Ohio

Andrew I. Brill, MD
Director
Minimally Invasive Gynecology & Surgical Education
California Pacific Medical Center
San Francisco, California

Amanda Nickles Fader, MD
Associate Professor and Director
Kelly Gynecologic Oncology Service
Director of Minimally Invasive Surgery
Department of Gynecology/Obstetrics
Johns Hopkins Hospital
Baltimore, Maryland

John B. Gebhart, MD, MS
Professor, Obstetrics and Gynecology
Mayo Clinic
Rochester, Minnesota

Rosanne M. Kho, MD
Head, Section Benign Gynecology
Director
Benign Gyn Surgery
Women's Health Institute
Cleveland Clinic
Cleveland, Ohio

Javier F. Magrina, MD
Professor of Obstetrics and Gynecology
Barbara Woodward Lips Professor
Mayo Clinic
Phoenix, Arizona

Beri M. Ridgeway, MD
Department Chair, Regional Ob/Gyn
Cleveland Clinic
Assistant Professor
Cleveland Clinic Learner College of Medicine
Cleveland, Ohio

Optional Workshops

For complete information please see PAGS-CME.org.

Tuesday, December 4, 2018, Encore at Wynn Las Vegas

Optional Opioid REMS Course

OPIOID RISK EVALUATION AND MITIGATION STRATEGIES (REMS) COURSE "PAIN MANAGEMENT AND OPIOIDS: BALANCING RISKS AND BENEFITS"
3.0 CME/CNE Credits Available
3:00 PM - 6:00 PM
(Free course. Pre-registration required. See PAGS website for complete details)

Wednesday, December 5, 2018, Encore at Wynn Las Vegas

Optional Hands-on Workshops

PAGS hands-on workshops have limited space available and will sell out. *First come. First served!* (See PAGS website for complete details.)

WORKSHOP A
TISSUE EXTRACTION TECHNIQUES
4 CME Credits Available
8:30 AM - 12:30 PM
Led by: Rosanne M. Kho, MD
Faculty: Andrew I. Brill, MD;
Keith B. Isaacson, MD

WORKSHOP B
HANDS-ON LAPAROSCOPIC SUTURING - THE "VERTICAL ZONE" (SIMULATION LAB)
4 CME Credits Available
8:30 AM - 12:30 PM
Led by: Charles H. Koh, MD

WORKSHOP C
OFFICE-BASED GYNECOLOGIC PROCEDURES: THE GYNECOLOGIST OF THE FUTURE NEW!
FULL-DAY WORKSHOP
8 CME Credits Available
8:30 AM - 5:30 PM
Includes a morning lecture series and afternoon practicum on vulvar/vaginal injections and excisions, ultrasound and hysteroscopy

Led by: Tommaso Falcone, MD
Faculty: Andrew Brill, MD; Linda D. Bradley, MD; Mark Dassel, MD; Laura Detti, MD; Oluwatosin Goje, MD; Keith Isaacson, MD; Mickey Karram, MD; James M. Shwayder, MD, JD

WORKSHOP D
TECHNICAL ASPECTS OF VAGINAL HYSTERECTOMY & CYSTOURETHROSCOPY FOR THE GYNECOLOGIST
4 CME Credits Available
1:30 PM - 5:30 PM
Led by: Mickey Karram, MD
Faculty: Rosanne M. Kho, MD;
Doug Miyazaki, MD

Who Should Attend?

The PAGS conference is designed for obstetricians/gynecologists, second, third and fourth-year residents in OB/GYN, as well as sub-specialty fellows and advanced practice clinicians. Residents and advanced practice health clinicians are welcome at reduced rates.

ACCREDITATION

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Cincinnati and Global Academy for Medical Education, Inc. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

The University of Cincinnati designates this Live Activity for 20 *AMA PRA CME Category 1 credits*™ for the conference and (1) 8-hour pre-conference workshops at 8.0 *AMA PRA CME Category 1 credits*™, (3) 4-hour pre-conference workshops at 4.0 *AMA PRA CME Category 1 credits*™ each and (1) post workshop at 3.25 *AMA PRA CME Category 1 credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

2018

PAGS PELVIC ANATOMY and GYNECOLOGIC SURGERY SYMPOSIUM

Earn up to 34.25 CME Credits (Including Workshop Credit)

REGISTER BY SEPTEMBER 10 SAVE UP TO $620!

The Premier Meeting for all Facets of Your Gynecology Practice

ENCORE AT WYNN Las Vegas

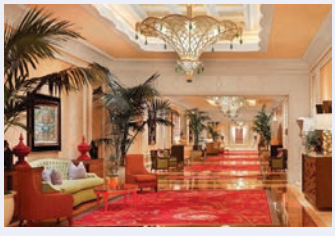
Optional **OPIOID REMS COURSE 3 CME Credits Available**
December 4, 2018

Optional **HANDS-ON WORKSHOPS 8 CME Credits Available**
December 5, 2018

SCIENTIFIC SESSIONS 20 CME Credits Available
December 6-8, 2018

Optional **"P.E.P." PRACTICE MANAGEMENT PROGRAM 3.25 CME Credits Available**
December 8, 2018

About Our Venue Encore at Wynn Las Vegas



The 2018 Pelvic Anatomy and Gynecologic Surgery Symposium (PAGS) will take place at the Encore Wynn Las Vegas where we have arranged for a discount room rate of **just $189* a night** for PAGS participants. To make your reservation, please call (866) 770-7555. You must identify yourself as a Pelvic Anatomy and Gynecologic Surgery Symposium 2018 attendee or reference the block code: 6PAG1218 to receive the discounted rate.

Discount room rate expires November 6, but we urge you to make your arrangements as soon as possible as our room block will sell out.

*Plus $25 amenity fee

To register and for complete information please see our website: PAGS-cme.org.

Highlights Include

- *Optional* Opioid REMS Course
- *Optional* Hands-on Workshops
  Limited space available. First come. First served!
  - Tissue Extraction Techniques Workshop
  - Laparoscopic Suturing
  - Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
  - Office-Based Gynecologic Procedures
- Incontinence and Prolapse Surgery
- Gynecologic Oncology for the Generalist
- Hysterectomy Techniques
- Avoiding and Managing Complications
- Fibroid Management & Principles of Electrosurgery
- Surgical Tips for Successful Pelvic Surgery

SPECIAL KEYNOTES:

- Management of Chronic Pelvic Pain
- Non-Opioid Pain Management after Minimally Invasive Hysterectomy

How to Register for PAGS

Online: www.PAGS-CME.org Inquiries: PAGS@globalacademycme.com

Mail: See website registration page for downloadable registration form

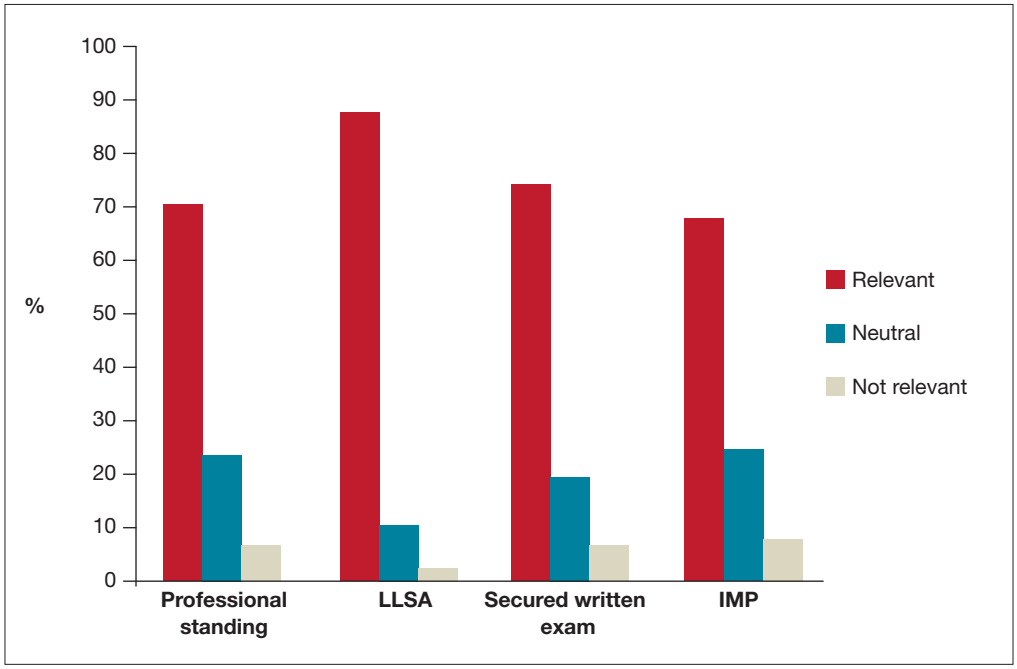
PAGS 2018 c/o Global Academy for Medical Education
7 Century Drive, Suite 301, Parsippany, NJ 07054

	Until Sept 10	Sept 11-Nov 5	After Nov 5
Price Schedule			
■ Physicians	$795	$895	$995
■ Residents, Fellows, Allied Health	$595	$695	$795
■ **P.E.P. Program only** Also open to non-attendees	$295	$395	$495
■ **Best Buy!** PAGS + P.E.P. Discount Combination Package	$995	$1,195	$1,395
■ **Office-Based Gynecologic Procedures: The Gynecologist of the Future** All Day Workshop	$445	$495	$595
■ **Laparoscopic Suturing** Morning Workshop	$245	$275	$345
■ **Tissue Extraction Techniques** Morning Workshop	$245	$275	$345
■ **Vaginal Hysterectomy & Cystourethroscopy** Afternoon Workshop	$275	$325	$395
■ **Opioid REMS Course** *Pre-registration required*	Free	Free	Free

Cancellation Policy: Full refund less a $50 administrative fee as follows: Cancellations can be made using our online registration system until November 6, 2018. After November 6, 2018 no refunds will be granted. After the refund date, you have two options: you can send someone in your place, or we can mark a credit in the amount you paid minus $50 administration fee (plus additional $35 administration fee per workshop) to be applied to your registration for next year's conference. Refunds will not be issued to no-shows.

CONTINUED FROM PAGE 28

FIGURE Relevance of specialty MOC requirements to ObGyn practice according to an ABOG survey of diplomates[2]



Abbreviations: ABOG, American Board of Obstetrics and Gynecology; IMP, improvement in medical practice; LLSA, lifelong learning and self-assessment; MOC, maintenance of certification.

and osteopathic medicine from requiring participation in MOC processes as a condition of credentialing, privileging, insurance panel participation, licensure, or licensure renewal."[4]

Some states are proposing or have enacted legislation that prohibits the use of MOC as a criterion for licensure, privileging, employment, reimbursement, and/or insurance panel participation. Eight states (Arizona, Georgia, Kentucky, Maryland, Maine, Missouri, Oklahoma, Tennessee) have enacted laws to prohibit the use of MOC for initial and renewal licensure decisions. Many states are actively considering MOC-related legislation, including Alaska, Florida, Iowa, Indiana, Maryland, Massachusetts, Michigan, Missouri, New Hampshire, New York, Ohio, Oklahoma, Rhode Island, South Carolina, Tennessee, Utah, Washington, and Wisconsin.

Legislation is not the only outlet for physician frustration. Some medical specialty societies are considering dropping board certification as a membership requirement; physicians are exploring developing alternative boards; and some physicians are defying the board certification requirement altogether, with thousands signing anti-MOC petitions.

ACOG asserts importance of maintaining self-regulation

While other specialties are actively advocating state legislation, ACOG and ABOG have worked together to oppose state legislation, believing that physician self-regulation is paramount. In fact, in 2017, ACOG and ABOG issued a joint statement urging state lawmakers to "not interfere with our decades of successful self-regulation and to realize that each medical society has its own experience with its MOC program."[5]

Negotiations lead to new initiative

This brings us to an interesting situation. ACOG's Executive Vice President and CEO

FAST TRACK

ACOG and ABOG have worked together to oppose state legislation, believing that physician self-regulation is paramount

Make your voice heard

The Vision Initiative offers physicians an important opportunity to help shape the future of continuing education and certification. ObGyns and other physicians should consider reviewing and commenting on the draft report, due in November, during the public comment period. Visit https://visioninitiative.org for more information and to sign up for email updates.

FAST TRACK

The Vision Initiative is a process designed to fundamentally rebuild the continuing certification process with input and guidance from practicing physicians

Hal Lawrence III, MD, was tapped (in his position as Chair of the Specialty Society CEO Consortium) to represent physician specialties in negotiations and discussions with the boards, which were represented by Lois Nora, MD, JD, President and CEO of the ABMS, and state medical societies, represented by Donald Palmisano Jr, JD, Executive Director and CEO of the Medical Association of Georgia. Many state medical societies, boards, and physician specialty organizations participated in these meetings.

Throughout months of debate, Dr. Lawrence urged his colleagues to stay at the table and do the hard work of reaching an agreement, rather than ask politicians to solve medicine's problems. This approach was leveraged by the serious efforts and threats of state legislation, which brought the boards to the table. In August 2017, 41 state medical societies and 33 national medical specialty societies wrote to Dr. Nora expressing their concerns that "professional self-regulation is under attack. Concerns regarding the usefulness of the high-stakes exam, the exorbitant costs of the MOC process, and the lack of transparent communication from the certifying boards have led to damaging the MOC brand, and creating state-based attacks on the MOC process."[6]

In December 2017, Dr. Lawrence and Mr. Palmisano led a meeting of principals from the national medical specialty societies and state medical societies with leaders of ABMS and 8 specialty boards, including ABOG, an opportunity to secure meaningful change. Dr. Lawrence began by stressing that the interests of physicians and patients would be best served by all parties coming together and collaborating on a meaningful solution, to repair trust and preserve physician self-regulation.

Dr. Ramin presented ABOG's approach to continuous certification, lifelong learning, and self-assessment. The American Board of Urology and the American Board of Psychiatry and Neurology indicated that they were basing important changes in their MOC process on ABOG's work, including using 5 modules (1 general and 4 specific to the physician's practice) and multiple open-book mini-exams based on selected journal articles as an alternative to the 10-year MOC exam.

The Vision Initiative. At that meeting and others, the ABMS and other boards heard physicians' candid and sometimes blunt concerns. Dr. Nora spoke to the recently announced Continuing Board Certification: Vision for the Future program, also known as the "Vision Initiative," a process designed to fundamentally rebuild the continuing certification process with input and guidance from practicing physicians. Physician response seemed uniform: Seeing is believing.

Importantly, all participants at the December meeting agreed to work together to rebuild trust and ensure professionalism and professional self-regulation, reflected in this Statement of Shared Purpose:

> ABMS certifying boards and national medical specialty societies will collaborate to resolve differences in the process of ongoing certification and

CONTINUED ON PAGE 32

Ob.Gyn. News®

STAY TUNED

for coverage of the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology

DON'T MISS

our exclusive columns

- > Drugs, Pregnancy, & Lactation
- > Gynecologic Oncology Consult
- > Master Class

GET BREAKING NEWS

on the web at **obgynnews.com**

CONTINUED FROM PAGE 30

to fulfill the principles of professional self-regulation, achieving appropriate standardization, and assuring that ongoing certification is relevant to the practices of physicians without undue burden. Furthermore, the boards and societies, and their organizations (ABMS and CMSS [Council of Medical Specialty Societies]), will undertake necessary changes in a timely manner, and will commit to ongoing communication with state medical associations to solicit their input.[4]

Two ObGyns participating in the Vision Initiative are Haywood Brown, MD, ACOG's Immediate Past President, and George Wendel, MD, ABOG's Executive Director. The Vision Initiative is composed of 3 parts. Part 1, Organization, is complete. The committee is currently working on part 2, Envisioning the Future, an information-gathering component that includes physician surveys, hearings, open solicited input, and identifying new and better approaches. After the final report is delivered to the ABMS in February 2019, part 3, Implementation, will begin. ●

References

1. American Board of Obstetrics and Gynecology. From pilot to permanent: ABOG's program offering an innovative pathway integrating lifelong learning and self-assessment and external assessment is approved. https://www.abog.org/new/ABOG_PilotToPermanent.aspx. Accessed July 6, 2018.
2. Ramin S. American Board of Obstetrics and Gynecology MOC program. PowerPoint presentation; December 4, 2017.
3. Teirstein PS. Boarded to death—why maintenance of certification is bad for doctors and patients. N Engl J Med. 2015;372(2):106–108.
4. AMA Council on Medical Education. Executive summary. 2017. https://www.ama-assn.org/sites/default/files/media-browser/public/council-on-med-ed/a18-cme-02.pdf. Accessed July 6, 2018.
5. American College of Obstetricians and Gynecologists. ACOG-ABOG joint statement: political interference in physician maintenance of skills threatens women's health care. https://www.acog.org/-/media/Departments/State-Legislative-Activities/2017ACOG-ABMS-MOC-Statement.pdf?dmc=1&ts=20180706T1615538746. Accessed July 6, 2018.
6. Letter to Lois Nora, MD, JD. August 18, 2017. https://www.mainemed.com/sites/default/files/content/MOC%20Letter%20082117.pdf. Accessed July 6, 2018.

Contraceptive considerations for women with headache and migraine

What are the benefits and risks of using hormonal contraceptives in women with headache and migraine?

Ronald T. Burkman, MD

The use of hormonal contraception in women with headaches, especially migraine headaches, is an important topic. Approximately 43% of women in the United States report migraines.[1] Roughly the same percentage of reproductive-aged women use hormonal contraception.[2] Data suggest that all migraineurs have some increased risk of stroke. Therefore, can women with migraine headaches use combination hormonal contraception? And can women with severe headaches that are nonmigrainous use combination hormonal contraception? Let's examine available data to help us answer these questions.

Risk factors for stroke

Migraine without aura is the most common subset, but migraine with aura is more problematic relative to the increased incidence of stroke.[1]

A migraine aura is visual 90% of the time.[1] Symptoms can include flickering lights, spots, zigzag lines, a sense of pins and needles, or dysphasic speech. Aura precedes the headache and usually resolves within 1 hour after the aura begins.

In addition to migraine headaches, risk factors for stroke include increasing age, hypertension, the use of combination oral contraceptives (COCs), the contraceptive patch and ring, and smoking.[1]

Data indicate that the risk for ischemic stroke is increased in women with migraines even without the presence of other risk factors. In a meta-analysis of 14 observational studies, the risk of ischemic stroke among all migraineurs was about 2-fold (relative risk [RR], 2.2; 95% confidence interval [CI], 1.9–2.5) compared with the risk of ischemic stroke in women of the same age group who did not have migraine headaches. When there is migraine without aura, it was slightly less than 2-fold (RR, 1.8; 95% CI, 1.1–3.2). The risk of ischemic stroke among migraineurs with aura is increased more than 2 times compared with women without migraine (RR, 2.27; 95% CI, 1.61–3.19).[3] However, the absolute risk of ischemic stroke among reproductive-aged women is 11 per 100,000 women years.[4]

Two observational studies show how additional risk factors increase that risk (**TABLE**).[5,6] There are similar trends in terms of overall risk of stroke among women with

At the time of this writing, Dr. Burkman was Professor, Department of Obstetrics and Gynecology, Tufts University School of Medicine, Boston, Massachusetts, and an obstetrician-gynecologist at Baystate Medical Center, Springfield. He is an OBG Management Contributing Editor.

The author reports no financial relationships relevant to this article.

IN THIS ARTICLE

TABLE Migraine headache and the risk of stroke

Risk factors	Tzourio,[5] RR	Chang,[6] OR
Migraine	3.5	3.7
Migraine + smoking	10.2	7.4
Migraine + COCs	13.9	6.6
Migraine + smoking + COCs	–	34.4

Abbreviations: COCs, combination oral contraceptives; OR, odds ratio; RR, relative risk.

FAST TRACK

There are 2 ways to treat estrogen withdrawal or menstrual migraines: COCs or NSAIDs

all types of migraine. However, when you add smoking as an additional risk factor for women with migraine headaches, there is a substantial increase in the risk of stroke. When a woman who has migraines uses COCs, there is increased risk varying from 2-fold to almost 4-fold. When you combine migraine, smoking, and COCs, a very, very large risk factor (odds ratio [OR], 34.4; 95% CI, 3.27–3.61) was reported by Chang and colleagues.[6]

Although these risks are impressive, it is important to keep in mind that even with a 10-fold increase, we are only talking about 1 case per 1,000 migraineurs.[4] Unfortunately, stroke often leads to major disability and even death, such that any reduction in risk is still important.

Preventing estrogen withdrawal or menstrual migraines

How should we treat a woman who uses hormonal contraception and reports estrogen withdrawal or menstrual migraines? Based on clinical evidence, there are 2 ways to reduce her symptoms:

- **COCs.** Reduce the hormone-free interval by having her take COCs for 3 to 4 days instead of 7 days, or eliminate the hormone-free interval altogether by continuous use of COCs, usually 3 months at a time.[7]
- **NSAIDs.** For those who do not want to alter how they take their hormonal product, use nonsteroidal anti-inflammatory drugs (NSAIDs) starting 7 days before the onset of menses and continuing for 13 days. In a clinical trial by Sances and colleagues, this plan reduced the frequency, duration, and severity of menstrual migraines.[8]

Probably altering how she takes the COC would make the most sense for most individuals instead of taking NSAIDs for 75% of each month.

Recommendations from the US MEC

The US Medical Eligibility Criteria (US MEC) from the Centers for Disease Control and Prevention (CDC) offers recommendations for contraceptive use[9]:

- **For nonmigrainous headache,** the CDC suggests that the benefits of using COCs outweigh the risks unless the headaches persist after 3 months of COC use.
- **For migraine without aura,** the benefits outweigh the risks in starting women who are younger than age 35 years on oral contraceptives. However, the risks of COCs outweigh the benefits in women who are age 35 years and older who develop migraine headache while on

CONTINUED ON PAGE 51

JOIN YOUR COLLEAGUES AT THESE
CME/CE COURSES

Global Academy for Medical Education

RHEUMATOLOGY

11TH ANNUAL PERSPECTIVES IN RHEUMATIC DISEASES

SEPTEMBER 14-15, 2018
Encore at Wynn Las Vegas

14 CME/CE Credits, 13.5 AAFP Prescribed Credits Available

GlobalAcademyCME.com/Rheumatology

PAIN CARE/PRIMARY CARE

PAIN CARE FOR PRIMARY CARE

NOVEMBER 16-17, 2018
San Diego, California
Pre-conference Addiction Workshop November 15

19 CME/CE credits Credits Available including Opioid REMS Course & Workshop

PCPC-cme.com

PRIMARY CARE/ENDOCRINOLOGY

Advanced Education Presented by and for NPs and PAs

MEDS
Metabolic & Endocrine Disease Summit

OCTOBER 10-13, 2018
Orlando, FL

24.25 CE/CME Credits Available

MEDSummit-cecme.org

PRIMARY CARE

Advanced Education Presented by and for NPs and PAs

Cardiovascular, Allergy & Respiratory SUMMIT CARPS

NOVEMBER 8-10, 2018
Pre-conference Workshops November 7
San Diego, CA

24 CE/CME Credits Available Including Workshop Credit

CARPS-cme.org

EMERGENCY MEDICINE

Created especially for primary care physicians, NPs, and PAs

ADVANCED EMERGENCY MEDICINE BOOT CAMP
THE MASTER PRACTITIONER

SEPTEMBER 13-16, 2018
Las Vegas, Nevada

31.5 CME/CE Credits Available

EMBootCamp2.com/cme

EMERGENCY MEDICINE

Created especially for primary care physicians, NPs, and PAs

ORIGINAL EMERGENCY MEDICINE BOOT CAMP
THE CORE EM KNOWLEDGE BASE

DECEMBER 13-16, 2018
Las Vegas, Nevada

26 CME/CE Credits Available

EMBootCamp.com/cme

To register and for complete information, including accreditation information, please see our websites.

UPDATE Abnormal uterine bleeding

Howard T. Sharp, MD
Dr. Sharp is Professor and Vice Chair for Clinical and Quality Activities, Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake City.

Marisa R. Adelman, MD
Dr. Adelman is Assistant Professor, Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake City.

The authors report no financial relationships relevant to this article.

Coverage and clinical perspective on recent AUB studies, including optimal procedure order for evaluation, cost-effectiveness of 4 treatment options, and ulipristal for leiomyoma-related bleeding

IN THIS ARTICLE

Over the past year, a few gems have been published to help us manage and treat abnormal uterine bleeding (AUB). One study suggests an order of performing hysteroscopy and endometrial biopsy, another emphasizes the continued cost-effectiveness of the levonorgestrel-releasing intrauterine system (LNG-IUS), while a third provides more evidence that ulipristal acetate is effective in the management of leiomyomas.

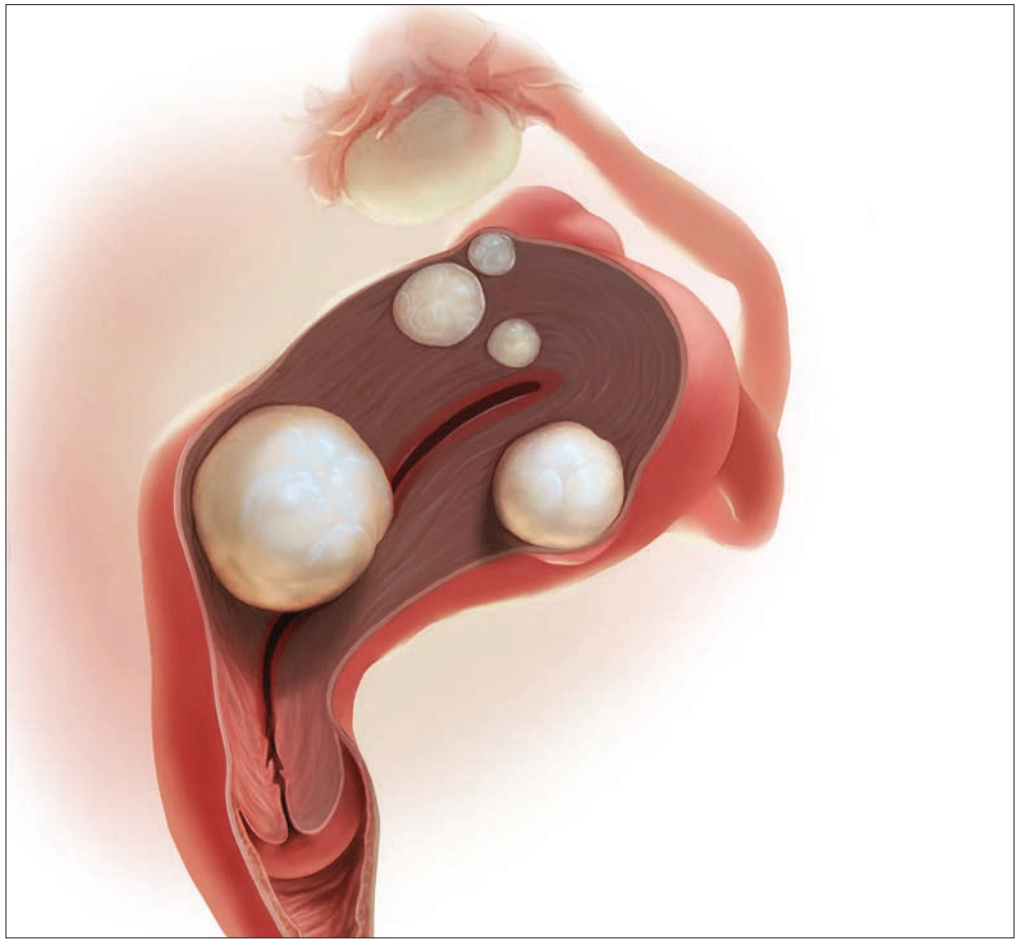
Optimal order of office hysteroscopy and endometrial biopsy?

Sarkar P, Mikhail E, Schickler R, Plosker S, Imudia AN. Optimal order of successive office hysteroscopy and endometrial biopsy for the evaluation of abnormal uterine bleeding: a randomized controlled trial. Obstet Gynecol. 2017;130(3):565–572.

Office hysteroscopy and endometrial biopsy are frequently used in the evaluation of women presenting with AUB. Sarkar and colleagues conducted a study aimed at estimating the optimal order of office hysteroscopy and endometrial biopsy when performed successively among premenopausal women.

Pain perception, procedure duration, and other outcomes

This prospective single-blind randomized trial included 78 consecutive patients. The primary outcome was detection of any difference in patients' global pain perception based on the order of the procedures. Secondary outcome measures included determining whether the procedure order affected the duration of the procedures, the adequacy of the endometrial biopsy sample, the number of attempts to obtain an adequate tissue sample, and optimal visualization of the endometrial cavity during office hysteroscopy.



Uterine leiomyomas are common in reproductive-age women, affecting up to 70% of white women and more than 80% of black women. A recent study suggested that an oral medication currently under investigation in the United States may be useful for the medical management of abnormal uterine bleeding associated with uterine leiomyomas.

Order not important, but other factors may be

Not surprisingly, the results showed that the order in which the procedures were performed had no effect on patients' pain perception or on the overall procedure duration. Assessed using a visual analog scale scored from 1 to 10, global pain perception in the hysteroscopy-first patients (group A, n = 40) compared with the biopsy-first patients (group B, n = 38) was similar (7 vs 7, $P = .57$; 95% confidence interval [CI], 5.8–7.1). Procedure duration also was similar in group A and group B (3 vs 3, $P = .32$; 95% CI, 3.3–4.1).

However, when hysteroscopy was performed first, the quality of endometrial cavity images was superior compared with images from patients in whom biopsy was performed first. The number of endometrial biopsy curette passes required to obtain an adequate tissue sample was lower in the biopsy-first patients. The endometrial biopsy specimen was adequate for histologic evaluation regardless of whether hysteroscopy or biopsy was performed first.

FAST TRACK

The order in which the procedures were performed had no effect on patients' pain perception or on the overall procedure duration

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Sarkar and colleagues suggested that their study findings emphasize the importance of individualizing the order of successive procedures to achieve the most clinically relevant result with maximum ease and comfort. They proposed that patients who have a high index of suspicion for occult malignancy or endometrial hyperplasia should have a biopsy procedure first so that adequate tissue samples can be obtained with fewer attempts. In patients with underlying uterine anatomic defects, performing hysteroscopy first would be clinically relevant to obtain the best images for optimal surgical planning.

CONTINUED ON PAGE 38

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

CONTINUED FROM PAGE 37

Which treatment for AUB is most cost-effective?

Spencer JC, Louie M, Moulder JK, et al. Cost-effectiveness of treatments for heavy menstrual bleeding. Am J Obstet Gynecol. 2017;217(5):574.e1–574e.9.

The costs associated with heavy menstrual bleeding are significant. Spencer and colleagues sought to evaluate the relative cost-effectiveness of 4 treatment options for heavy menstrual bleeding: hysterectomy, resectoscopic endometrial ablation, nonresectoscopic endometrial ablation, and the LNG-IUS in a hypothetical cohort of 100,000 premenopausal women. No previous studies have examined the cost-effectiveness of these options in the context of the US health care setting.

FAST TRACK

The LNG-IUS was superior to all alternatives in both cost and quality, making it the dominant strategy

Decision tree used for analysis

The authors formulated a decision tree to evaluate private payer costs and quality-adjusted life-years over a 5-year time horizon for premenopausal women with heavy menstrual bleeding and no suspected malignancy. For each treatment option, the authors used probabilities to estimate frequencies of complications and treatment failure leading to additional therapies. They compared the treatments in terms of total average costs, quality-adjusted life years, and incremental cost-effectiveness ratios.

Comparing costs, quality of life, and complications

Quality of life was fairly high for all treatment options; however, the estimated costs and the complications of each treatment were markedly different between treatment options. The LNG-IUS was superior to all alternatives in terms of both cost and quality, making it the dominant strategy. The 5-year cost for the LNG-IUS was $4,500, about half the cost of endometrial ablation ($9,500) and about one-third the cost of hysterectomy ($13,500). When examined over a range of possible values, the LNG-IUS was cost-effective compared with hysterectomy in the large majority of scenarios (90%).

If the LNG-IUS is removed from consideration because of either patient preference or clinical judgment, the decision between hysterectomy and ablation is more complex. Hysterectomy results in better quality of life in the majority of simulations, but it is cost-effective in just more than half of the simulations compared with either resectoscopic or nonresectoscopic ablation. Therefore, consideration of cost, procedure-specific complications, and patient preferences may guide the therapeutic decision between hysterectomy and endometrial ablation.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The 52-mg LNG-IUS was superior to all treatment alternatives in both cost and quality, making it the dominant strategy for the treatment of heavy menstrual bleeding.

WATCH FOR... ›› **Update on contraception**
from Mitchell Creinin, MD

Ulipristal may be useful for managing AUB associated with uterine leiomyomas

Simon JA, Catherino W, Segars JH, et al. Ulipristal acetate for treatment of symptomatic uterine leiomyomas: a randomized controlled trial. Obstet Gynecol. 2018;131(3):431–439.

Managing uterine leiomyomas is a common issue for gynecologists, as up to 70% of white women and more than 80% of black women of reproductive age in the United States have leiomyomas.

Ulipristal acetate is an orally administered selective progesterone-receptor modulator that decreases bleeding and reduces leiomyoma size. Although trials conducted in Europe found ulipristal to be superior to placebo and noninferior to leuprolide acetate in controlling bleeding and reducing leiomyoma size, those initial trials were conducted in a predominantly white population.

Study assessed efficacy and safety

Simon and colleagues recently conducted a randomized double-blind, placebo-controlled trial designed to assess the safety and efficacy of ulipristal in a more diverse population, such as patients in the United States. The 148 participants included in the study were randomly assigned on a 1:1:1 basis to once-daily oral ulipristal 5 mg, ulipristal 10 mg, or placebo for 12 weeks, with a 12-week drug-free follow-up.

Amenorrhea achieved and quality of life improved

The investigators found that ulipristal in 5-mg and 10-mg doses was well tolerated and superior to placebo in both the rate of and the time to amenorrhea (the coprimary end points) in women with symptomatic leiomyomas. In women treated with ulipristal 5 mg, amenorrhea was achieved in 25 of 53 (47.2%; 97.5% CI, 31.6–63.2), and of those treated with the 10-mg dose, 28 of 48 (58.3%; 97.5% CI, 41.2–74.1) achieved amenorrhea ($P<.001$ for both groups), compared with 1 of 56 (1.8%; 97.5% CI, 0.0–10.9) in the placebo group.

Ulipristal treatment also was shown to improve health-related quality of life, including physical and social activities. No patient discontinued ulipristal because of lack of efficacy, and 1 patient in the placebo group stopped taking the drug because of an adverse event. Estradiol levels were maintained at midfollicular levels during ulipristal treatment, and endometrial biopsies did

FAST TRACK

Ulipristal acetate was well tolerated and superior to placebo in the rate of and time to amenorrhea in women with symptomatic leiomyomas

Consider quality and cost in AUB treatment

AUB continues to be a significant issue for many women. As women's health care providers, it is important that we deliver care with high value (Quality ÷ Cost). Therefore, consider these takeaway points:

- The LNG-IUS consistently delivers high value by affecting both sides of this equation. We should use it more.
- Although we do not yet know what ulipristal acetate will cost in the United States, effective medical treatments usually affect both sides of the Quality ÷ Cost equation, and new medications on the horizon are worth knowing about.
- Last, efficiency with office-based hysteroscopy is also an opportunity to increase value by improving biopsy and visualization quality.

not show any atypical or malignant changes. These results are consistent with those of the studies conducted in Europe in a predominantly white, nonobese population.

Results of this study help to define a niche for ulipristal when hysterectomy is not an option for women who wish to preserve fertility. Further, although leuprolide is used for preoperative hematologic improvement of anemia, its use results in hypoestrogenic adverse effects. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The findings from this and other studies suggest that ulipristal may be useful for the medical management of AUB associated with uterine leiomyomas, especially for patients desiring uterine- and fertility-sparing treatment. Hopefully, this treatment will be available soon in the United States.

Examining the EVIDENCE

CONTINUED FROM PAGE 25

Study strengths and weaknesses

This study is one of the first of its kind to compare laser therapy alone and in combination with local estriol to vaginal estriol alone for the treatment of GSM. The trial's strength is in its design as a double-blind, placebo-controlled block randomized trial, which adds to the prospective cohort trials that generally show favorable outcomes for fractionated laser for the treatment of GSM.

The study's weaknesses include its small sample size, single trial site, and short-term follow-up. Findings from this trial should be considered preliminary and not generalizable. Other weaknesses are the 3 of 45 participants lost to follow-up and the significant baseline differences among the women, with lower bothersome baseline VAS scores in the estriol arm.

Furthermore, this study was not powered for multiple comparisons, and conclusions favoring laser therapy cannot be overinflated. Lasers such as CO2 target the chromophore water, and indiscriminate use in severely dry vaginal epithelium may cause more pain or scarring. Longer-term follow-up is needed.

More research also is needed to develop guidelines related to pre-laser treatment to achieve optimal vaginal pH and ideal vaginal maturation, including, for example, vaginal priming with estrogen, DHEA, or other moisturizers.

This study also suggests the use of vaginal laser therapy as a drug delivery mechanism for combination therapy. Many vaginal estrogen treatments are expensive (despite prescription drug coverage), and laser treatments are very expensive (and not covered by insurance), so research to optimize outcomes and minimize patient expense is needed. ●

References

1. Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med. 2013;10(7):1790–1799.
2. Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause. 2014;21(10):1063–1068.
3. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24(7):728–753.
4. Thomas K. Prices keep rising for drugs treating painful sex in women. New York Times. June 3, 2018. https://www.nytimes.com/2018/06/03/health/vagina-womens-health-drug-prices.html. Accessed July 15, 2018.
5. Tadir Y, Gaspar A, Lev-Sagie A, et al. Light and energy based therapeutics for genitourinary syndrome of menopause: consensus and controversies. Lasers Surg Med. 2017;49(2):137–159.
6. Athanasiou S, Pitsouni E, Antonopoulou S, et al. The effect of microablative fractional CO2 laser on vaginal flora of postmenopausal women. Climacteric. 2016;19(5):512–518.
7. Sokol ER, Karram MM. Use of a novel fractional CO2 laser for the treatment of genitourinary syndrome of menopause: 1-year outcomes. Menopause. 2017;24(7):810–814.

Obesity: When to consider medication

These 4 cases illustrate how weight loss drugs—including the 4 newest—can be integrated into a treatment plan that includes diet, exercise, and behavior modification

Katherine H. Saunders, MD; Alpana P. Shukla, MD, MRCP; Leon I. Igel, MD; and Louis J. Aronne, MD

Modest weight loss of 5% to 10% among patients who are overweight or obese can result in a clinically relevant reduction in cardiovascular (CV) disease risk.[1] This amount of weight loss can increase insulin sensitivity in adipose tissue, liver, and muscle, and have a positive impact on blood sugar, blood pressure, triglycerides, and high-density lipoprotein cholesterol.[1,2]

All patients who are obese or overweight with increased CV risk should be counseled on diet, exercise, and other behavioral interventions.[3] Weight loss secondary to lifestyle modification alone, however, leads to adaptive physiologic responses, which increase appetite and reduce energy expenditure.[4–6]

Pharmacotherapy can counteract this metabolic adaptation and lead to sustained weight loss. Antiobesity medication can be considered if a patient has a body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 with obesity-related comorbidities such as hypertension, type 2 diabetes, dyslipidemia, or obstructive sleep apnea.[3,7]

Comprehensive Weight Control Center, Division of Endocrinology, Diabetes and Metabolism, Cornell Medicine, New York, New York.

Drs. Saunders, Shukla, and Igel reported no potential conflicts of interest relevant to this article. Dr. Aronne reported various financial relationships with Aspire Bariatrics, AstraZeneca, BMIQ, Eisai, Gelesis, GI Dynamics, Jamieson Laboratories, Janssen Pharmaceuticals, MYOS RENS Technology Inc., Novo Nordisk, Pfizer, Real Appeal, UnitedHealth Group Ventures, and Zafgen.

Adapted from The Journal of Family Practice. 2017;66(10): 608–616.

Until recently, there were few pharmacologic options approved by the US Food and Drug Administration (FDA) for the management of obesity. The mainstays of treatment were phentermine (Adipex-P, Ionamin, Suprenza) and orlistat (Alli, Xenical). Since 2012, however, 4 agents have been approved as adjuncts to a reduced-calorie diet and increased physical activity for long-term weight management.[8,9] Phentermine/topiramate extended-release (ER) (Qsymia) and lorcaserin (Belviq) were approved in 2012,[10,11] and naltrexone sustained release (SR)/bupropion SR (Contrave) and liraglutide 3 mg (Saxenda) were approved in 2014[12,13] (**TABLE**[9,14–39]). These medications have the potential to not only limit weight

Practice recommendations

For patients with a body mass index (BMI) ≥30 kg/m^2 or BMI ≥27 kg/m^2 with weight-related comorbidities:

- Consider antiobesity pharmacotherapy when diet, exercise, and behavior modification do not produce sufficient weight loss. **A**
- Continue an antiobesity medication if it is deemed effective and well tolerated. **A**

Strength of recommendation:

A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

IN THIS ARTICLE

TABLE Antiobesity medications: What to expect and who makes a good candidate[9,14–39]

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects	Good candidates	Poor candidates
Phentermine (Adipex-P,[15] Ionamin,[16] Lomaira,[17] Suprenza[18]) Schedule IV controlled substance NOTE: Approved for short-term use	Adrenergic agonist 8–37.5 mg/d Capsule, tablet	Aronne LJ, et al[19] 28 weeks	15 mg/d 7.5 mg/d Placebo (topiramate ER and phentermine/topiramate ER arms excluded)	6.06[a] 5.45[a] 1.71	Dry mouth, insomnia, dizziness, irritability	Younger patients who need assistance with appetite suppression	Patients with uncontrolled hypertension, active or unstable coronary disease, hyperthyroidism, glaucoma, anxiety, insomnia, or patients who are generally sensitive to stimulants; patients with a history of drug abuse or recent MAOI use; patients who are pregnant
Orlistat (Alli,[20] Xenical[21]) Schedule IV controlled substance	Lipase inhibitor 60–120 mg three times per day with meals Capsule	XENDOS[22] 208 weeks	120 mg three times per day Placebo	9.6 (Week 52)[a] 5.25 (Week 208)[a] 5.61 (Week 52) 2.71 (Week 208)	Fecal urgency, oily stool, flatus with discharge, fecal incontinence	Patients with hypercholesterolemia and/or constipation who can limit their intake of dietary fat	Patients with malabsorption syndromes or other GI conditions that predispose to GI upset/diarrhea; patients who cannot modify the fat content of their diets; patients who are pregnant
Phentermine/topiramate ER (Qsymia)[23] Schedule IV controlled substance	Adrenergic agonist/neurostabilizer 3.75/23–15/92 mg/d Capsule	EQUIP[24] 56 weeks	15/92 mg/d 3.75/23 mg/d Placebo	10.9[a] 5.1[a] 1.6	Paresthesias, dizziness, dysgeusia, insomnia, constipation, dry mouth	Younger patients who need assistance with appetite suppression	Patients with uncontrolled hypertension, active or unstable coronary disease, hyperthyroidism, glaucoma, anxiety, insomnia, or patients who are generally sensitive to stimulants; patients with a history of drug abuse or recent MAOI use; patients with a history of nephrolithiasis; patients who are pregnant
		CONQUER[25] 56 weeks	15/92 mg/d 7.5/46 mg/d Placebo	9.8[a] 7.8[a] 1.2			
		SEQUEL[26] 108 weeks (52-week extension of CONQUER trial)	15/92 mg/d 7.5/46 mg/d Placebo	10.5[a] 9.3[a] 1.8 (Weeks 0–108)			

gain but also promote weight loss and, thus, improve blood pressure, cholesterol, glucose, and insulin.[40]

Despite the growing obesity epidemic and the availability of several additional medications for chronic weight management, use of antiobesity pharmacotherapy has been limited. Barriers to use include inadequate training of health care professionals, poor insurance coverage for new agents, and low reimbursement for office visits to address weight.[41]

In addition, the number of obesity medicine specialists, while increasing, is still not sufficient. Therefore, it is imperative for other health care professionals—including ObGyns—to be aware of the treatment options available to patients who are overweight

TABLE Antiobesity medications: What to expect and who makes a good candidate[9,14–39] **(continued)**

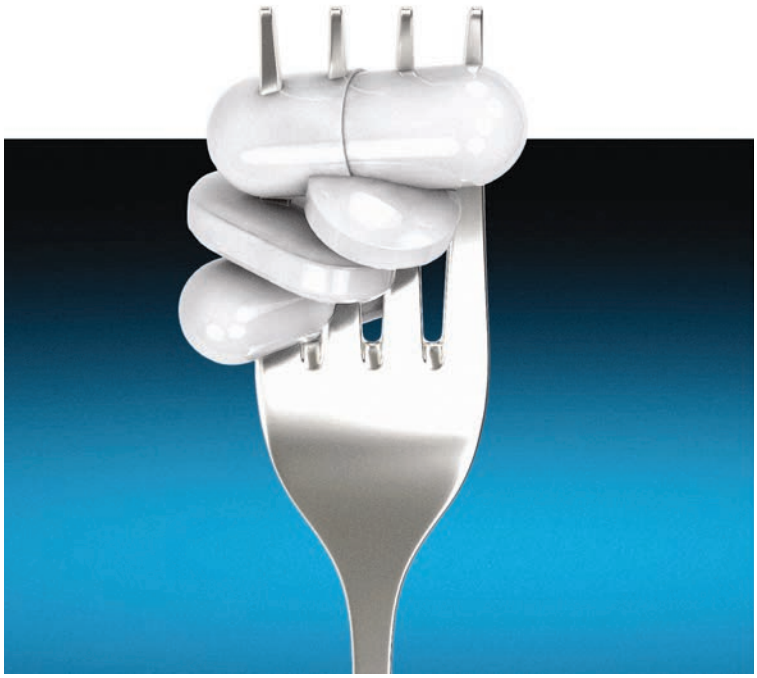
Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects	Good candidates	Poor candidates
Lorcaserin (Belviq, Belviq XR)[27] Schedule IV controlled substance	Serotonin 5-HT2C receptor agonist 10 mg twice per day or 20 mg/d ER Tablet	BLOOM[28] 52 weeks	10 mg twice per day Placebo	5.8[a] 2.2	Headache, dizziness, fatigue, nausea, dry mouth, constipation	Patients who report inadequate meal satiety	Patients on other serotonin modulating medications; patients with known cardiac valvular disease; patients who are pregnant
		BLOSSOM[29] 52 weeks	10 mg twice per day 10 mg/d Placebo	5.8[a] 4.7[a] 2.8			
		BLOOM-DM[30] 52 weeks	10 mg twice per day 10 mg/d Placebo	4.5[a] 5.0[a] 1.5			
Naltrexone SR/bupropion SR (Contrave)[31]	Opioid receptor antagonist/ dopamine and norepinephrine reuptake inhibitor 8/90 mg/d–16/180 mg twice per day Tablet	COR-I[32] 56 weeks	16/180 mg twice per day 8/180 mg twice per day Placebo	6.1[a] 5.0[a] 1.3	Nausea, vomiting, constipation, headache, dizziness, insomnia, dry mouth	Patients who describe cravings for food and/ or addictive behaviors related to food; patients who are trying to quit smoking, reduce alcohol intake, and/or have concomitant depression	Patients with uncontrolled hypertension, uncontrolled pain, recent MAOI use, history of seizures, or any condition that predisposes to seizure such as anorexia/ bulimia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs; patients who are pregnant
		COR-II[33] 56 weeks	16/180 mg twice per day Placebo	6.4[a] 1.2			
		COR-BMOD[34] 56 weeks	16/180 mg twice per day Placebo	9.3[a] 5.1			
		COR-DIABETES[35] 56 weeks	16/180 mg twice per day Placebo	5.0[a] 1.8			
Liraglutide 3 mg (Saxenda)[36]	GLP-1 receptor agonist 0.6–3 mg/d Prefilled pen for subcutaneous injection	SCALE Obesity and Prediabetes[37] 56 weeks	3 mg/d Placebo	8.0[a] 2.6	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain	Patients who report inadequate meal satiety, and/or have type 2 diabetes, prediabetes, or impaired glucose tolerance; patients requiring use of concomitant psychiatric medications	Patients with an aversion to needles, history of pancreatitis, personal or family history of medullary thyroid carcinoma, or multiple endocrine neoplasia syndrome type 2; patients who are pregnant
		SCALE Diabetes[38] 56 weeks	3 mg/d 1.8 mg/d Placebo	6[a] 4.7[a] 2			
		SCALE Maintenance[39] 56 weeks (after initial ≥5% weight loss with LCD)	3 mg/d Placebo	6.2[a] 0.2			

Abbreviations: ER, extended release; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; LCD, low-calorie diet; MAOI, monoamine oxidase inhibitor; XR, extended release.

[a]*P*<.001 vs placebo.

CONTINUED ON PAGE 44

CONTINUED FROM PAGE 43



or obese and to be adept at using them.

In this review, we present 4 cases that depict patients who could benefit from the addition of antiobesity pharmacotherapy to a comprehensive treatment plan that includes diet, physical activity, and behavioral modification.

CASE 1 Young obese woman is unable to lose weight

A 27-year-old woman with obesity (BMI 33 kg/m^2), hyperlipidemia, and migraine headaches, presents for weight management. Despite a calorie-reduced diet and 200 minutes per week of exercise for the past 6 months, she has been unable to lose weight. The only medications she is taking are oral contraceptive pills and sumatriptan, as needed. She suffers from migraines 3 times a month and has no anxiety. Laboratory test results are normal with the exception of an elevated low-density lipoprotein (LDL) level.

Which medication is an appropriate next step for this patient?

Ask 2 important questions

When considering an antiobesity agent for any patient, there are 2 important questions to ask:

- Are there contraindications, drug-drug interactions, or undesirable adverse effects associated with this medication that could be problematic for the patient?
- Can this medication improve other symptoms or conditions the patient has?

In addition, see "Before prescribing antiobesity medication . . ." on page 45.

Phentermine/topiramate ER

Phentermine/topiramate ER is a good first choice for this young patient with class I (BMI 30–34.9 kg/m^2) obesity and migraines, as she can likely tolerate a stimulant and her migraines might improve with topiramate. Before starting the medication, ask about insomnia and nephrolithiasis in addition to anxiety and other contraindications (ie, glaucoma, hyperthyroidism, recent monoamine oxidase inhibitor use, or a known hypersensitivity or idiosyncrasy to sympathomimetic amines).[23] The most common adverse events reported in phase III trials were dry mouth, paresthesia, and constipation.[24–26]

Not for pregnant women. Women of childbearing age must have a negative pregnancy test before starting phentermine/topiramate ER and every month while taking the medication. The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) to inform prescribers and patients about the increased risk of congenital malformation, specifically orofacial clefts, in infants exposed to topiramate during the first trimester of pregnancy.[42] REMS focuses on the importance of pregnancy prevention, the consistent use of birth control, and the need to discontinue phentermine/topiramate ER immediately if pregnancy occurs.

Flexible dosing. Phentermine/topiramate ER is available in 4 dosages: phentermine 3.75 mg/topiramate 23 mg ER; phentermine 7.5 mg/topiramate 46 mg ER; phentermine 11.25 mg/topiramate 69 mg ER; and phentermine 15 mg/topiramate 92 mg ER. Gradual dose escalation minimizes risks and adverse events.[23]

Monitor patients frequently to evaluate for adverse effects and ensure adherence to diet, exercise, and lifestyle modifications. If weight loss is slower or less robust than expected, check for dietary indiscretion, as medications have limited efficacy without appropriate behavioral changes.

Discontinue phentermine/topiramate ER if the patient does not achieve 5% weight loss after 12 weeks on the maximum dose, as it is unlikely that she will achieve and sustain clinically meaningful weight loss with continued treatment.[23] In this case, consider another agent with a different mechanism of action. Any of the other antiobesity medications could be appropriate for this patient.

CASE 2 Overweight woman with comorbidities

A 52-year-old overweight woman (BMI 29 kg/m^2) with type 2 diabetes, hyperlipidemia, osteoarthritis, and glaucoma has recently hit a plateau with her weight loss. She lost 45 lb secondary to diet and exercise, but hasn't been able to lose any more. She also struggles with constant hunger. Her medications include metformin 1,000 mg twice per day, atorvastatin 10 mg/d, and occasional acetaminophen/oxycodone for knee pain until she undergoes a left knee replacement. Laboratory values are normal except for a hemoglobin A_{1c} of 7.2%.

The patient is afraid of needles and cannot tolerate stimulants due to anxiety. Which medication is an appropriate next step for this patient?

What are good choices for this patient?

Lorcaserin is a good choice for this patient who is overweight and has several weight-related comorbidities. She has worked hard to lose a significant number of pounds and is now at high risk of regaining them. That's because her appetite has increased with her new exercise regimen, but her energy expenditure has decreased secondary to metabolic adaptation.

Narrowing the field. Naltrexone SR/bupropion SR cannot be used because of her opioid use. Phentermine/topiramate ER is contraindicated for patients with glaucoma, and liraglutide 3 mg is not appropriate given the patient's fear of needles.

She could try orlistat, especially if she struggles with constipation, but the gastrointestinal adverse effects are difficult for many patients to tolerate. While not an antiobesity medication, a sodium-glucose co-transporter 2 (SGLT2) inhibitor could be prescribed for her diabetes and also may promote weight loss.[43]

An appealing choice. The glucose-lowering effect of lorcaserin could provide an added benefit for the patient. The BLOOMDM (Behavioral modification and lorcaserin for overweight and obesity management in diabetes mellitus) study reported a mean reduction in hemoglobin A_{1c} of 0.9% in the treatment group compared with a 0.4% reduction in the placebo group,[30] and the effect of lorcaserin on A_{1c} appeared to be independent of weight loss.

Mechanism of action: Cause for concern? Although lorcaserin selectively binds to serotonin 5-HT2C receptors, the theoretical risk of cardiac valvulopathy was evaluated in phase III studies, as fenfluramine, a 5-HT2B-receptor agonist, was withdrawn from the US market in 1997 for this reason.[44] Both the BLOOM (Behavioral modification

Before prescribing antiobesity medication . . .

Have a frank discussion with the patient and be sure to cover the following points:

- The rationale for pharmacologic treatment is to counteract adaptive physiologic responses, which increase appetite and reduce energy expenditure, in response to diet-induced weight loss.
- Antiobesity medication is only one component of a comprehensive treatment plan, which also includes diet, physical activity, and behavior modification.
- Antiobesity agents are intended for long-term use, as obesity is a chronic disease. If/when you stop the medication, there may be some weight regain, similar to an increase in blood pressure after discontinuing an antihypertensive agent.
- Because antiobesity medications improve many parameters including glucose/hemoglobin A_{1c}, lipids, blood pressure, and waist circumference, it is possible that the addition of one antiobesity medication can reduce, or even eliminate, the need for several other medications.

Remember that many patients who present for obesity management have experienced weight bias. It is important to not be judgmental, but rather explain why obesity is a chronic disease. If patients understand the physiology of their condition, they will understand that their limited success with weight loss in the past is not just a matter of willpower. Lifestyle change and weight loss are extremely difficult, so it is important to provide encouragement and support for ongoing behavioral modification.

and lorcaserin for overweight and obesity management) and BLOSSOM (Behavioral modification and lorcaserin second study for obesity management) studies found that lorcaserin did not increase the incidence of FDA-defined cardiac valvulopathy.[28,29]

Formulations/adverse effects. Lorcaserin is available in 2 formulations: 10-mg tablets, which are taken twice daily, or 20-mg XR tablets, which are taken once daily. Both are generally well tolerated.[27,45] The most common adverse event reported in phase III trials was headache.[28,30,43] Discontinue lorcaserin if the patient does not lose 5% of her initial weight after 12 weeks, as weight loss at this stage is a good predictor of longer-term success.[46]

Some patients don't respond. Interestingly, a subset of patients do not respond to lorcaserin. The most likely explanation for different responses to the medication is that there are many causes of obesity, only some of which respond to 5-HT2C agonism. Currently, we do not perform pharmacogenomics testing before prescribing lorcaserin, but perhaps an inexpensive test to identify responders will be available in the future.

FAST TRACK

Naltrexone SR/bupropion SR is a good choice for patients who describe debilitating cravings and addictive behavior surrounding food

CASE 3 A preoccupation with food

A 38-year-old woman with obesity (BMI 42 kg/m^2), obstructive sleep apnea, gastroesophageal reflux disease, and depression is eager to get better control over her weight. Her medications include lansoprazole 30 mg/d and a multivitamin. She reports constantly thinking about food and not being able to control her impulses to buy large quantities of unhealthy snacks. She is so preoccupied by thoughts of food that she has difficulty concentrating at work.

The patient smokes a quarter of a pack of cigarettes daily, but she is ready to quit. She views bariatric surgery as a "last resort" and has no anxiety, pain, or history of seizures. Which medication is appropriate for this patient?

Discuss all options

This patient with class III obesity (BMI ≥40 kg/m^2) is eligible for bariatric surgery; however, she is not interested in pursuing it at this time. It is important to discuss all of her options before deciding on a treatment plan. For patients like this, who would benefit from more than modest weight loss, consider a multidisciplinary approach including lifestyle modifications, pharmacotherapy, devices (eg, an intragastric balloon), and/or surgery. You would need to make clear to the patient that she may still be eligible for insurance coverage for surgery if she changes her mind after pursuing other treatments as long as her BMI remains ≥35 kg/m^2 with obesity-related comorbidities.

Naltrexone SR/bupropion SR is a good choice for this patient because she describes debilitating cravings and addictive behavior surrounding food. Patients taking naltrexone SR/bupropion SR in the Contrave Obesity Research (COR)-I and COR-II phase III trials experienced a reduced frequency of food cravings, reduced difficulty in resisting food cravings, and an increased ability to control eating compared with those assigned to placebo.[32,33]

Added benefits. Bupropion also could help this patient quit smoking and improve her mood, as it is FDA-approved for smoking cessation and depression. She denies anxiety and seizures, so bupropion is not contraindicated. Even if a patient denies a history of seizure, ask about any conditions that predispose to seizures, such as anorexia nervosa or bulimia or the abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs.

Opioid use. Although the patient denies pain, ask about potential opioid use, as naltrexone is an opioid receptor antagonist. Patients should be informed that opioids may be ineffective if they are required unexpectedly (eg, for trauma) and that naltrexone SR/bupropion SR should be withheld for any planned surgical procedure potentially requiring opioid use.

Other options. While naltrexone SR/bupropion SR is the most appropriate choice for this patient because it addresses her problematic eating behaviors while potentially improving mood and assisting with smoking cessation, phentermine/topiramate ER, lorcaserin, and liraglutide 3 mg also could be used and certainly should be tried if

naltrexone SR/bupropion SR does not produce the desired weight loss.

Adverse effects. Titrate naltrexone SR/bupropion SR slowly to the treatment dose to minimize risks and adverse events.[31] The most common adverse effects reported in phase III trials were nausea, constipation, and headache.[34,35,45,46] Discontinue naltrexone SR/bupropion SR if the patient does not achieve 5% weight loss at 16 weeks (after 12 weeks at the maintenance dose).[31]

CASE 4 Regaining weight after gastric bypass

A 65-year-old woman with obesity (BMI 39 kg/m^2) who underwent Roux-en-Y gastric bypass surgery and who has type 2 diabetes, congestive heart failure, coronary artery disease, hypertension, and hyperlipidemia, remains concerned about her weight. She lost 100 lb following surgery and maintained her weight for 3 years, but then regained 30 lb. She comes in for an office visit because she is concerned about her increasing blood sugar and wants to prevent further weight gain. Her medications include metformin 1,000 mg twice per day, lisinopril 5 mg/d, carvedilol 12.5 mg twice per day, simvastatin 20 mg/d, and aspirin 81 mg/d. Laboratory test results are normal except for a hemoglobin A_{1c} of 8%. She denies pancreatitis and a personal or family history of thyroid cancer.

Which medication is an appropriate next step for this patient?

Pharmacotherapy is an option

Pharmacotherapy is a great option for this patient, who is regaining weight following bariatric surgery. Phentermine/topiramate ER is the only medication that would be contraindicated because of her heart disease. Lorcaserin and naltrexone SR/bupropion SR could be considered, but liraglutide 3 mg is the most appropriate option, given her need for further glucose control.

Furthermore, the recent LEADER (Liraglutide effect and action in diabetes: evaluation of CV outcome results) trial reported a significant mortality benefit with liraglutide 1.8 mg/d among patients with type 2 diabetes and high CV risk.[47] The study found that liraglutide was superior to placebo in reducing CV events.

Contraindications. Ask patients about a history of pancreatitis before starting liraglutide 3 mg, given the possible increased risk. In addition, liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Thyroid C-cell tumors have been found in rodents given supratherapeutic doses of liraglutide[48]; however, there is no evidence of liraglutide causing C-cell tumors in humans.

For patients taking a medication that can cause hypoglycemia, such as insulin or a sulfonylurea, monitor blood sugar and consider reducing the dose of that medication when starting liraglutide.

Administration and titration. Liraglutide is injected subcutaneously once daily. The dose is titrated up weekly to reduce gastrointestinal symptoms.[36] The most common adverse effects reported in phase III trials were nausea, diarrhea, and constipation.[37–39] Discontinue liraglutide 3 mg if the patient does not lose at least 4% of baseline body weight after 16 weeks.[49]

FAST TRACK

Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in those with multiple endocrine neoplasia syndrome type 2

References

1. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34:1481–1486.
2. Magkos F, Fraterrigo G, Yoshino J. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. Cell Metab. 2016;23:591–601.
3. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol. 2014;63(25 pt B):2985–3023.
4. Sumithran P, Predergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011;365:1597–1604.
5. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. Int J Obes (Lond). 2015;39:1188–1196.
6. Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity (Silver Spring). 2016;24:1612–1619.
7. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;100:342–362.

CONTINUED ON PAGE 48

CONTINUED FROM PAGE 47

8. Saunders KH, Shukla AP, Igel LI, et al. Pharmacotherapy for obesity. Endocrinol Metab Clin North Am. 2016;45:521–538.
9. Saunders KH, Kumar RB, Igel LI, et al. Pharmacologic approaches to weight management: recent gains and shortfalls in combating obesity. Curr Atheroscler Rep. 2016;18:36.
10. US Food and Drug Administration. Drug approval package. Qsymia. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022580Orig1s000_qsymia_toc.cfm. Accessed August 28, 2017.
11. Arena Pharmaceuticals. Arena Pharmaceuticals and Eisai announce FDA approval of BELVIQR (lorcaserin HCl) for chronic weight management in adults who are overweight with a comorbidity or obese. http://invest.arenapharm.com/releasedetail.cfm?ReleaseID=687182. Accessed August 28, 2017.
12. Drugs.com. Contrave approval history. https://www.drugs.com/history/contrave.html. Accessed August 28, 2017.
13. US Food and Drug Administration. Drugs@FDA: FDA approved drug products. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=206321. Accessed August 28, 2017.
14. Igel LI, Kumar RB, Saunders KH, et al. Practical use of pharmacotherapy for obesity. Gastroenterology. 2017;152:1765–1779.
15. Adipex-P package insert. http://www.iodine.com/drug/phentermine/fda-package-insert. Accessed August 28, 2017.
16. Ionamin package insert. http://druginserts.com/lib/rx/meds/ionamin/. Accessed August 28, 2017.
17. Lomaira package insert. https://www.lomaira.com/Prescribing_Information.pdf. Accessed August 28, 2017.
18. Suprenza package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202088s001lbl.pdf. Accessed August 28, 2017.
19. Aronne LJ, Wadden TA, Peterson C, et al. Evaluation of phentermine and topiramate versus phentermine/topiramate extended release in obese adults. Obesity (Silver Spring). 2013;21:2163–2171.
20. Alli package labeling. http://druginserts.com/lib/otc/meds/alli-1/. Accessed August 28, 2017.
21. Xenical package insert. https://www.gene.com/download/pdf/xenical_prescribing.pdf. Accessed August 28,2017.
22. Torgerson JS, Hauptman J, Boldrin MN, et al. XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004;27:155–161.
23. Qsymia package insert. https://www.qsymia.com/pdf/prescribing-information.pdf. Accessed August 28, 2017.
24. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring). 2012;20:330–342.
25. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase 3 trial. Lancet. 2011;377:1341–1352.
26. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr. 2012;95:297–308.
27. Belviq package insert. https://www.belviq.com/-/media/Files/BelviqConsolidation/PDF/Belviq_Prescribing_information-pdf.PDF?la=en. Accessed August 28, 2017.
28. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med. 2010;363:245–256.
29. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab. 2011;96:3067–3077.
30. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring). 2012;20:1426–1436.
31. Contrave package insert. https://contrave.com/wpcontent/uploads/2017/05/Contrave_PI.pdf. Accessed August 28, 2017.
32. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2010;376:595–605.
33. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring). 2013;21:935–943.
34. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring). 2011;19:110–120.
35. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care. 2013;36:4022–4029.
36. Saxenda package insert. http://www.novo-pi.com/saxenda.pdf. Accessed August 28, 2017.
37. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373:11–22.
38. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. JAMA. 2015;314:687–699.
39. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2013;37:1443–1451.
40. Saunders KH, Igel LI, Aronne LJ. An update on naltrexone/bupropion extended-release in the treatment of obesity. Expert Opin Pharmacother. 2016. 10.1080/14656566.2016.1244527.
41. Thomas CE, Mauer EA, Shukla AP, et al. Low adoption of weight loss medications: a comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. Obesity (Silver Spring). 2016;24:1955–1961.
42. Qsymia Risk Evaluation and Mitigation Strategy (REMS). VIVUS, Inc. http://www.qsymiarems.com. Accessed January 16, 2017.
43. Zinman B, Wanner C, Lachin JM, et al. Empaglifozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128.
44. US Food and Drug Administration. FDA announces withdrawal fenfluramine and dexfenfluramine (Fen-Phen). https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafety-InformationforPatientsandProviders/ucm179871.htm. Accessed August 28, 2017.
45. Belviq XR package insert. https://www.belviq.com/-/media/Files/BelviqConsolidation/PDF/belviqxr_prescribing_information-pdf.PDF?la=en. Accessed January 16, 2017.
46. Smith SR, O'Neil PM, Astrup A. Early weight loss while on lorcaserin, diet and exercise as a predictor of week 52 weight-loss outcomes. Obesity (Silver Spring). 2014;22:2137–2146.
47. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–322.
48. Madsen LW, Knauf JA, Gotfredsen C, et al. GLP-1 receptor agonists and the thyroid: C-cell effects in mice are mediated via the GLP-1 receptor and not associated with RET activation. Endocrinology. 2012;153:1538–1547.
49. Fujioka K, O'Neil PM, Davies M, et al. Early weight loss with liraglutide 3.0 mg predicts 1-year weight loss and is associated with improvements in clinical markers. Obesity (Silver Spring). 2016;24:2278–2288.

CDC apps specific for ObGyns

Useful information at your fingertips

Katherine T. Chen, MD, MPH

The Centers for Disease Control and Prevention (CDC) is a US federal agency under the Department of Health and Human Services. It is the nation's leading public health institute. Its main goal is to save lives and protect people from health, safety, and security threats. The CDC website lists 25 no-cost applications that the agency has developed: https://www.cdc.gov/mobile/mobileapp.html.

This review will focus on 3 CDC apps (**TABLE**, page 50) that I feel are useful to ObGyn health care providers: Prevent Group B Strep (GBS), STD Tx Guide, and US Medical Eligibility Criteria for Contraceptive Use. In fact, in an evaluation of contraception apps for providers of family planning services, US Medical Eligibility Criteria for Contraceptive Use was one of the highest scoring apps.[1] I will evaluate each app by a shortened version of the APPLICATIONS scoring system, APPLI (app comprehensiveness, price, platform, literature use, and important special features).[2] I commend the CDC for developing these useful tools to assist health care providers.

Dr. Chen is Professor of Obstetrics, Gynecology, and Reproductive Science and Medical Education, Vice-Chair of Ob-Gyn Education for the Mount Sinai Health System, Icahn School of Medicine, Mount Sinai, New York, New York. She is an OBG MANAGEMENT Contributing Editor.

The author reports being an advisory board member and receiving royalties from UpToDate, Inc.

References

1. Perry R, Lunde B, Chen KT. An evaluation of contraception mobile applications for providers of family planning services. Contraception. 2016;93(6):539-544.
2. Chyjek K, Farag S, Chen KT. Rating pregnancy wheel applications using the APPLICATIONS scoring system. Obstet Gynecol. 2015;125(6):1478-1483.

IN THIS ARTICLE

Details on recommended apps

page 50

CONTINUED ON PAGE 50

CONTINUED FROM PAGE 49

TABLE CDC applications for ObGyn health care providers

App	App comprehensiveness	Price	Platform	Literature used	Important special features
Prevent Group B Strep (GBS) iTunes: https://itunes.apple.com/us/app/prevent-group-b-strep-gbs/id689290789?mt=8 Google Play: https://play.google.com/store/apps/details?id=gov.cdc.ncird.dbd.GBS&hl=en_US	Clinical decision-making (clinical decision support system, clinical treatment guidelines)	Free	iTunes and Google Play store	• Prevention of Perinatal GBS Disease (MMWR Recomm Rep. 2010;59[RR-10]) • Developed in collaboration with AAP, ACOG, AAFP, and ACNM	Tools for neonatal providers, obstetric providers, and choosing antibiotic regimen
STD Tx Guide iTunes: https://itunes.apple.com/us/app/std-tx-guide/id655206856?mt=8 Google Play: https://play.google.com/store/apps/details?id=gov.cdc.stdtxguide&hl=en_US	• Reference and information gathering (drug reference guides) • Clinical decision-making (clinical treatment guidelines)	Free	iTunes and Google Play store	Sexually Transmitted Diseases Treatment Guidelines (MMWR Recomm Rep. 2010;59 [No. RR-12])	
US Medical Eligibility Criteria for Contraceptive Use iTunes: https://itunes.apple.com/us/app/contraception/id595752188?mt=8 Google Play: https://play.google.com/store/apps/details?id=gov.cdc.ondieh.nccdphp.contraception2&hl=en_US	Clinical decision-making (clinical decision support system, clinical treatment guidelines)	Free	iTunes and Google Play store	• US Medical Eligibility Criteria for Contraceptive Use (MMWR Recomm Rep. 2016;65 [No. RR-3]) • US Selected Practice Recommendations for Contraceptive Use (MMWR 2016;65 [No. RR-4])	• >60 characteristics and medical conditions that may affect people seeking family-planning services • Select practice recommendations for contraceptive use

Abbreviations: AAFP, American Academy of Family Physicians; AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists; ACNM, American College of Nurse-Midwives.

CONTINUED FROM PAGE 34

COCs, or who have risk factors for stroke.

- **For migraine with aura,** COCs are contraindicated.
- **Progestin-only contraceptives.** The CDC considers that the benefits of COC use outweigh any theoretical risk of stroke, even in women with risk factors or in women who have migraine with aura. Progestin-only contraceptives do not alter one's risk of stroke, unlike contraceptives that contain estrogen.

My bottom line

Can women with migraine headaches begin the use of combination hormonal methods? Yes, if there is no aura in their migraines and they are not older than age 35.

Can women with severe headaches that are nonmigrainous use combination hormonal methods? Possibly, but you should discontinue COCs if headache severity persists or worsens, using a 3-month time period for evaluation.

How do you manage women with migraines during the hormone-free interval? Consider the continuous method or shorten the hormone-free interval.

Recommendations for complicated patients. Consulting the CDC's US MEC database[7] can provide assistance in your care of more complicated patients requesting contraception. I also recommend the book, "Contraception for the Medically Challenging Patient," edited by Rebecca Allen and Carrie Cwiak.[10] It links nicely with the CDC guidelines and presents more detail on each subject. ●

References

1. Stewart WF, Wood C, Reed MD, et al. Cumulative lifetime migraine incidence in women and men. Cephalalgia. 2008;28(11):1170–1178.
2. Finer LB, Frohwirth LF, Dauphinee LA, Singh S, Moore AM. Reasons U.S. women have abortions: quantitative and qualitative perspectives. Perspect Sex Reprod Health. 2005;37(3):110–118.
3. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ. 2005;330(7482):63–66.
4. Petitti DB, Sydney S, Bernstein A, Wolf S, Quesenberry C, Ziel HK. Stoke in users of low-dose oral contraceptives. N Engl J Med. 1996;335(1):8–15.
5. Tzourio C, Tehindrazanarivelo A, Iglesias S, et al. Case-control study of migraine and risk of ischemic stroke in young women. BMJ. 1995;310:830–833.
6. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. BMJ. 1999;318(7175):13–18.
7. Edelman A, Gallo MF, Nichols MD, Jensen JT, Schulz KF, Grimes DA. Continuous versus cyclic use of combined oral contraceptives for contraception: systematic Cochrane review of randomized controlled trials. Hum Reprod. 2006;21(3):573–578.
8. Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. Headache. 1990;30(11):705–709.
9. US Medical Eligibility Criteria for Contraceptive Use, 2010. MMWR Recomm Rep. 2010;59(RR-4):1–86. https://www.cdc.gov/mmwr/pdf/rr/rr59e0528.pdf. Accessed October 4, 2016.
10. Allen RH, Cwiak CA, eds. Contraception for the medically challenging patient. New York, New York: Springer New York; 2014.

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

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

WARNINGS

1. Intrauterine Pregnancy

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

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

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

2. Ectopic Pregnancy

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

3. Pelvic Infection

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

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

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

4. Immunocompromise

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

5. Embedment

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

6. Perforation

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

7. Expulsion

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

8. Wilson's Disease

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

PRECAUTIONS

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

1. Information for patients

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

2. Insertion precautions, continuing care, and removal.

3. Vaginal bleeding

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

4. Vasovagal reactions, including fainting

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

5. Expulsion following placement after a birth or abortion

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

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

6. Magnetic resonance imaging (MRI)

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

7. Medical diathermy

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

8. Pregnancy

ParaGard® is contraindicated during pregnancy.

9. Nursing mothers

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

10. Pediatric use

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

ADVERSE REACTIONS

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

Intrauterine pregnancy	Pelvic infection
Septic abortion	Perforation
Ectopic pregnancy	Embedment

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

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

CooperSurgical, Inc
95 Corporate Drive
Trumbull, CT 06611

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.

CooperSurgical

*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.

Visit hcp.paragard.com