MDEDGE.COM/OBGMANAGEMENT | VOL 30, NO 9 | SEPTEMBER 2018

OBG MANAGEMENT

30th ANNIVERSARY

The MAVEN Project: Tackling health care disparities in retirement

Arnold Advincula's Video Series: Bartholin gland cyst excision

The most effective EC is hard to obtain from US pharmacies
Andrew Kaunitz, MD

The techno vagina

High-tech energy device boom leaves unanswered questions, prompts FDA action

Update on hysteroscopic permanent contraception
Mitchell Creinin, MD;
Suji Uhm, MD, MPH

ARRIVE trial takeaways, at mdedge.com/obgmanagement

Hypertension in pregnancy: Practice recommendations
p. 21

FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

TO LEARN MORE, SIMPLY VISIT
IMVEXXY.COM/HCP
OR CALL
1-855-351-5311
TO SPEAK TO A SALES REPRESENTATIVE AND REQUEST SAMPLES

DISCOVER A TREATMENT EXPERIENCE WITH

SIMPLICITY AT ITS CORE[1]

IMPORTANT SAFETY INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older

Estrogen Plus Progestin Therapy

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia
- The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE) and myocardial infarction (MI)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older

Imvexxy™
(estradiol vaginal inserts)
4 mcg • 10 mcg

NOW AVAILABLE

IMVEXXY is the only ultra-low-dose vaginal estradiol available in both 4-mcg and 10-mcg doses, offering comfortable and convenient, any time of day, applicator-free, mess-free administration.[1-3]

CONTRAINDICATIONS

- IMVEXXY™ is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to IMVEXXY; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

WARNINGS AND PRECAUTIONS

- IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY.
- The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.
- The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.
- Other warnings include: gallbladder disease; severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice.
- Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
- Women on thyroid replacement therapy should have their thyroid function monitored.

ADVERSE REACTIONS

- The most common adverse reaction with IMVEXXY (incidence ≥3 percent) and greater than placebo was headache.

INDICATION

IMVEXXY™ (estradiol vaginal inserts) is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Please see Brief Summary of the Full Prescribing Information, including the Boxed Warning, on the following pages.

References: 1. Imvexxy [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2018. **2.** Data on file. Clinical Study Report-Protocol No. TXV14-01. **3.** Data on file, TherapeuticsMD, Inc. **4.** Test ID: EEST—estradiol, serum. Mayo Clinic. https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/81816. Accessed on May 29, 2018.

IVXY-20116 08/2018

TherapeuticsMD®
For Her. For Life.

IMPORTANT IMVEXXY FEATURES

Applicator-free, any time of day administration[1]

Mess-free administration with no applicator, dose preparation, or cleanup needed[1,2]

Freedom to enjoy her everyday activities without interruption after insertion[1]

Improvement in moderate to severe dyspareunia seen at week 12 and beginning as early as week 2 (a secondary endpoint)[1,2]

Both doses of IMVEXXY resulted in average systemic hormone levels that were within the normal postmenopausal range[1,4*]

*Systemic absorption may occur with IMVEXXY. The risks associated with systemic estrogen therapy should be considered.

IMVEXXY™ (estradiol vaginal inserts)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use **IMVEXXY™** safely and effectively. See package insert for Full Prescribing Information.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.3) in full prescribing information]*.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information]*.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg] relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information]*.

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age of older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.3), and Clinical Studies (14.2) in full prescribing information]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.3, 5.15) in full prescribing information]*.

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

CONTRAINDICATIONS

IMVEXXY is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction (MI)), or a history of these conditions
- Known anaphylactic reaction or angioedema with IMVEXXY
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

WARNINGS AND PRECAUTIONS

Risks from Systemic Absorption

IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY (*Pharmacokinetics [12.3] in full prescribing information*). The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account.

Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.2) in full prescribing information]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.2) in full prescribing information]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.2) in full prescribing information]*.

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

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.2) in full prescribing information]*.

In postmenopausal women with documented heart disease (n=2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3] *[see Clinical Studies (14.2) in full prescribing information]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[4] *[see Clinical Studies (14.2) in full prescribing information]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80][5] *[see Clinical Studies (14.2) in full prescribing information]*.

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely

(continued on next page)

to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[6] *[see Clinical Studies (14.2)* ***in full prescribing information****].*

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77 to 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7]

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)* ***in full prescribing information****].*

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)* ***in full prescribing information****].*

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)* ***in full prescribing information****].*

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogen-alone is prescribed.

Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

Exacerbation of Endometriosis

Cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

Drug Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

ADVERSE REACTIONS

In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reaction with IMVEXXY (incidence ≥ 3 percent) and greater than placebo was headache.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with IMVEXXY.

Metabolic Interactions

In-vitro and *in-vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort *(Hypericum perforatum)* preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

USE IN SPECIFIC POPULATIONS

IMVEXXY is not indicated for use in pregnancy, in females of reproductive potential, or in children.

Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing IMVEXXY to determine whether those over 65 years of age differ from younger subjects in their response to IMVEXXY.

The Women's Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.2)* ***in full prescribing information****].*

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.2)* ***in full prescribing information****].*

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.4), and Clinical Studies (14.3)* ***in full prescribing information****].*

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Warnings and Precautions (5.4), and Clinical Studies (14.3)* ***in full prescribing information****].*

OVERDOSAGE

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of IMVEXXY therapy with institution of appropriate symptomatic care.

PATIENT COUNSELING INFORMATION

See FDA-approved PATIENT COUNSELING INFORMATION

Based on IVXY-20009
Revised: 05/2018

TherapeuticsMD®

#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.

femVue®

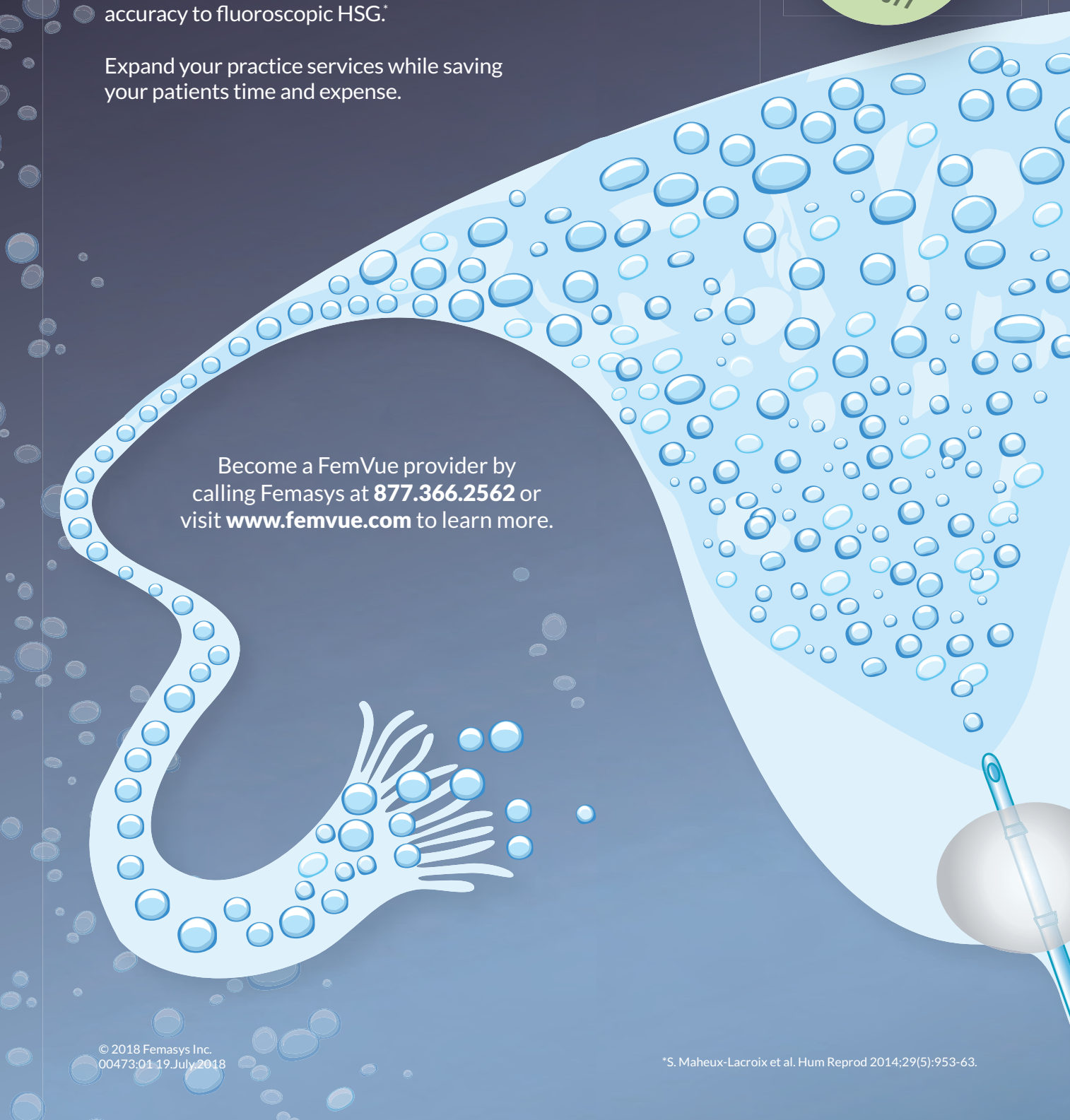
In-office **tubal patency** diagnostic test

VISIT US AT ASRM BOOTH 975 & 977

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.

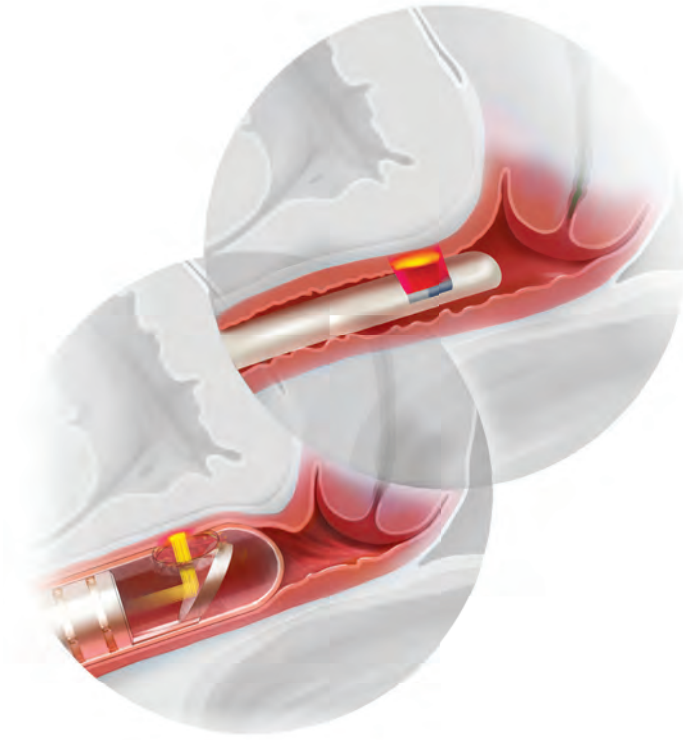


Become a FemVue provider by calling Femasys at **877.366.2562** or visit **www.femvue.com** to learn more.

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

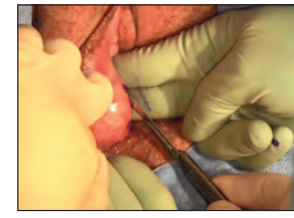
SEPTEMBER 2018 | VOL 30, NO 9

OBG MANAGEMENT



See what's ON THE WEB! page 8

Hypertension in pregnancy **21**



Bartholin gland cyst **52**

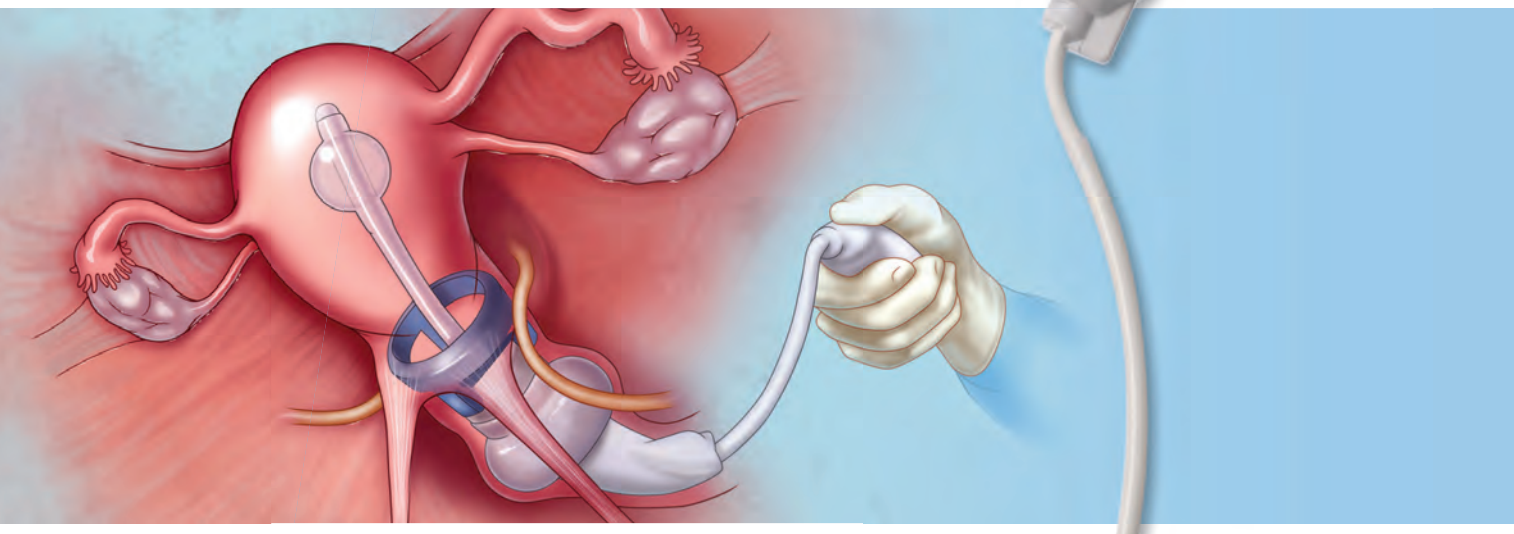
FAST TRACK is a system to enable you as a reader to move quickly through each issue of **OBG MANAGEMENT**, identifying articles or sections of articles to read in depth.

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

The Advincula Delineator™

Exceptional Strength. Single-use Convenience.



The Advincula Delineator is engineered to combine exceptional strength and safety with the ease and convenience of a disposable uterine manipulator. The shaft and Koh-Efficient® colpotomy system are fully integrated, providing unprecedented access, visualization and safety during TLH, LSH and LAVH procedures.

- Rigid colpotomy cup clearly delineates vaginal fornices with proper cephalad pressure.
- Best in class pneumo occluder balloon is built into the Koh-Efficient.
- Exceptional control and strength.
- No assembly required.

Advincula
DELINEATOR™
with Koh-Efficient® Technology

CooperSurgical

To place an order, or to learn more, contact your CooperSurgical representative, visit CooperSurgical.com, or call 800.243.2974 or 203.601.5200.

82612 Rev. 9/15

ON THE WEB at obgmanagement.com

FROM ENDOMETRIOSIS JOURNEY

Modern surgical techniques for gastrointestinal endometriosis

Endometriosis care: The importance of a multidisciplinary approach

Visit the Endometriosis Journey online at endometriosisjourney.com

WEB EXCLUSIVE

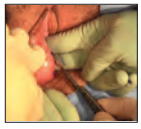
Medical Verdicts: Hemorrhagic shock following hysteroscopic removal of fibroid

Visit us online for daily news

VIDEO LIBRARY

Takeaways from the ARRIVE trial

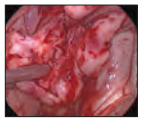
JOHN T. REPKE, MD



Excision of a Bartholin gland cyst

LISA R. GABOR, MD; PATRICIA J. MATTINGLY, MD; AND JIN HEE KIM, MD

See page 52 for QR code



Morcellation at the time of vaginal hysterectomy

M. ISLAM, MD; J. MAGRINA, MD; AND M. WASSON, DO

Brought to you by the Society of Gynecologic Surgeons

See page 17 for QR code

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

THE CURE FOR INFORMATION OVERLOAD

ALLMEDx.com

Introducing a new and better search engine for physicians!

- Unique search algorithm with no consumer links
- Essential and refined physician-based content
- Less is more results saves you time!

What physicians are saying about ALLMEDx.com

"ALLMEDx.com got me where I wanted to go faster and more precisely than other search sites—and that's key!"

"ALLMEDx.com eliminates the irrelevant without effort on my part. That's useful!"

"ALLMEDx.com separates the wheat from the chaff, saving me time and effort"

*Go to **ALLMEDx.com** and compare!*

An oath to save lives against a backdrop of growing disparities

The MAVEN Project, which began patient care in 2016 and has provided more than 2,000 consultations to date, closes the health care access gap with volunteer retired physicians from across the United States

Laurie Green, MD

Dr. Green is Vice-Chair of the Department of Obstetrics and Gynecology at California Pacific Medical Center in San Francisco. She also is the founder of the MAVEN Project and Past President of the Harvard Medical Alumni Association, the San Francisco Gynecological Society, and the California Academy of Medicine. She is a full-time ObGyn in San Francisco.

Practicing in the field of obstetrics and gynecology affords us a special privilege: we are part of the most important and unforgettable events in our patients' lives, both in sickness and in health. Along with the great joys we share comes profound responsibility and the recognition that we are only as effective as the team with whom we work. Although we live in a country that is home to some of the best health care systems in the world, the maternal mortality rates and disease burden among women in underserved communities belie this fact. A University of Washington study demonstrated a more than 20-year gap in life expectancy between wealthy and poor communities in the United States from 1980 to 2014.[1] Not surprisingly, access to medical care was a contributing factor.

Poverty only partly explains this disparity. Racial differences are at play as well. In 1992, a seminal study by Schoendorf and colleagues[2] demonstrated that the death rates of babies born to educated African American parents were higher due to lower birth weights. Concern recently has been amplified, and many lay publications have publicly raised the alarm.[3] Several states have started investigating the causes, and the American College of Obstetrics and Gynecology, as well as other organizations, are studying possible solutions.

With nearly 50% of US births financed by Medicaid,[5] there was great hope that the Patient Protection and Affordable Care Act and expansion of Medicaid would result in improved access and quality of health care for underserved patients; however, it has become apparent that coverage did not confer improved access to quality care, especially for medical specialties.

Urban and rural poor populations generally seek medical services from safety net clinics staffed by midlevel and physician primary care providers whose tight schedules, documentation demands, and low reimbursement rates are coupled with complex medical and socioeconomic patient populations. While these providers may be skilled in basic primary care, their patients often present with conditions outside their scope of practice. Our country's growing physician shortage, along with patient location and personal logistics, adds to the challenges for patients and providers alike. And who among us is not asked several times a week, even by our well-insured patients, for a primary care or specialist physician recommendation? The barriers for seeking medical care in rural populations are even greater, as local hospitals and clinics are closing at an alarming rate.

Alumni at work

Communities of physicians across the country recognize both the access problem and the potential to create solutions. Organizations such as Project ECHO, launched in 2003 through

The author reports no financial relationships relevant to this article.

Instant Poll

Do you feel that the MAVEN Project could be a valuable resource for you in the future and that it could fill a need in your community?

Tell us at rbarbieri@mdedge.com Please include your name and city and state.

the University of New Mexico, connect rural providers with university physicians to aid in treatment of hepatitis C and other illnesses.

As the date for implementation of the Patient Protection and Affordable Care Act approached, a group of medical school alumni leaders recognized that we could come together and offer our services to address growing health care disparities. Galvanized by the challenge, the Medical Alumni Volunteer Expert Network, or MAVEN Project, was, in our parlance, "born."

While the concept of the MAVEN Project was germinating, we interviewed numerous colleagues for advice and input and were struck by their desire—especially among the newly retired—to continue to give back. Medicine is a calling, not just a job, and for many of us the joy of helping—the exhilaration of that first birth that sold us on our specialty—gives us meaning and purpose. Many physicians who had left full-time clinical medicine missed the collegiality of the "doctors' lounge." Throughout our careers, we are part of a cohort: our medical school class, our residency partners, our hospital staff—we all crave community. With 36% of US physicians older than age 55 and 240,000 retired doctors in the country, we realized a motivated, previously untapped workforce could be marshaled to form a community to serve the most vulnerable among us.[5]

At the same time, telemedicine had come into its own. Simple technology could enable us to see each other on smartphones and computers and even perform portions of a physical examination from afar.

We realized we could marry opportunity (the workforce), need (underserved populations across the country), and technology. The Harvard Medical School Center Primary Care supported a feasibility study, and the MAVEN Project began "seeing" patients in 2016.

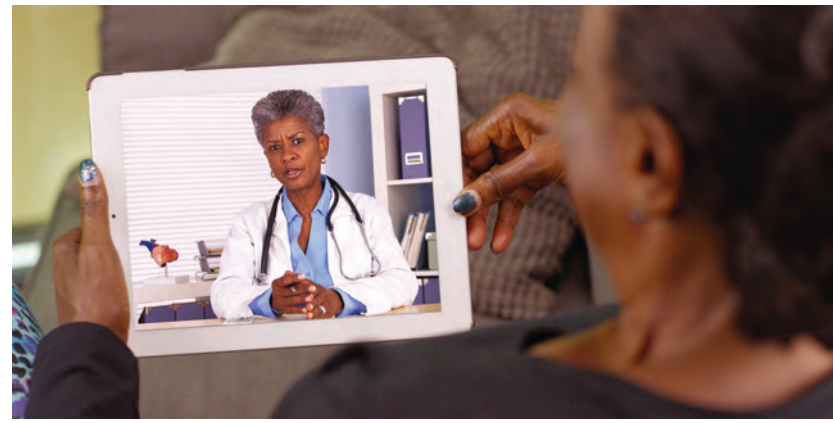


PHOTO: SHUTTERSTOCK

A model of hope

The MAVEN Project matches physician volunteers with safety net clinics serving patients in need and provides malpractice insurance and a Health Information Portability and Accountability Act–compliant technology platform to facilitate remote communication. Our volunteers mentor and educate primary care providers in the field and offer both immediate and asynchronous advisory consults. Clinic providers can group cases for discussion, ask urgent questions, or receive advice and support for the day-to-day challenges facing clinicians today. Clinics choose educational topics, focusing on tools needed for patient care rather than esoteric mechanisms of disease. Patients receive best-in-class care conveniently and locally, and by making volunteering easy, we build partnerships that augment patient and provider satisfaction, support long-term capacity building, and improve service delivery.

Our volunteer physicians now represent more than 30 medical specialties and 25 medical schools, and we have completed more than 2,000 consultations to date. Our clinics are located in 6 states (California, Florida, Massachusetts, New York, South Dakota, and Washington), and thanks to our model, physician state of licensure is not an impediment to volunteering. Several colleagues in our specialty are providing advice in women's health.

Driving innovative solutions

Elizabeth Kopin, MD, an ObGyn who practiced for 28 years in Worcester, Massachusetts, and volunteers for the MAVEN Project, eloquently described in correspondence with Project coordinators the spirit that embodies the pursuit of medicine and the organization's mission. As Dr. Kopin stated, "The driving force behind my entering medicine was to help people in an essential and meaningful way. I was especially driven to participate in the care of women. I wanted to gain knowledge and skills to help women with health care throughout their lives."

Dr. Kopin's capacity to care for patients in the clinic and hospital was progressively reduced as her multiple sclerosis advanced. As a result, she retired from clinical practice, but her desire to participate and contribute to medicine with the

CONTINUED ON PAGE 16

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

WARNINGS and PRECAUTIONS

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

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

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

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

>99% effective†

Placed subdermally in the inner upper arm just under the skin

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

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

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information.

MERCK

Nexplanon®

(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

1. **Complications of Insertion and Removal**

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

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

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

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

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

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

2. **Changes in Menstrual Bleeding Patterns**

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

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

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

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

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

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

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

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

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

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

3. **Ectopic Pregnancies**

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

4. **Thrombotic and Other Vascular Events**

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

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

5. **Ovarian Cysts**

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

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

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

7. **Liver Disease**

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

8. **Weight Gain**

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

9. **Elevated Blood Pressure**

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

10. **Gallbladder Disease**

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

11. **Carbohydrate and Lipid Metabolic Effects**

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

12. **Depressed Mood**

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

13. **Return to Ovulation**

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

Nexplanon®
(etonogestrel implant) 68mg

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Effects of Other Drugs on Hormonal Contraceptives

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

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

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

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

Effects of Hormonal Contraceptives on Other Drugs

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

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

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

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

For more detailed information, please read the Prescribing Information.

USPI-MK8415-IPTX-1705r019
Revised: 05/17

MERCK

CONTINUED FROM PAGE 11

passion with which she entered it remained.

Her father was an internist who started a charitable clinic in Georgia. Like her father, Dr. Kopin began her medical career in academic medicine. Her father felt that his last 15 years in medicine were the most meaningful of his career because of his work with underserved populations. Dr. Kopin is following in his footsteps. For her, "Looking for a telehealth vehicle helping communities in need gives me the opportunity to use my abilities in the best way possible." Dr. Kopin also stated, "Helping the underserved was something I wanted to devote my time to and The MAVEN Project has given me that possibility."

We like to think of ourselves as Match.com meets the Peace Corps, with the goal to reach underserved patients in all 50 states in both rural and urban communities. We ask for as little as 4 hours of your time per month, and all you need is a computer or smartphone and a medical license. We welcome volunteers in active or part-time practice, academics, and industry: your years of wisdom are invaluable.

The vast complexities of the US health care system are by no measure easy to address, but standing by and allowing a fractured system to rupture is not an option. Each of us has an expertise and an opportunity to make incremental steps to ensure that those who need health care do not slip through the cracks. Dr. Kopin and I are fortunate to have a skill to help others and, in the MAVEN Project, a robust, dedicated network of individuals who share our vision.

There are many who have and continue to inspire a guiding conscience to serve beyond oneself. George H.W. Bush said it best when explaining why he founded the Points of Light organization nearly 3 decades ago[6]:

> I have pursued life itself over many years now and with varying degrees of happiness. Some of my happiness still comes from trying to be in my own small way a true "point of light." I believe I was right when I said, as President, there can be no definition of a successful life that does not include service to others. So I do that now, and I gain happiness. I do not seek a Pulitzer Prize. I do not want press attention…. I have found happiness. I no longer pursue it, for it is mine.

Please join us on our mission!

How to join

We are actively seeking specialty and primary care physicians to provide advisory consultations, mentorship, and education via telehealth technology. We welcome physician volunteers who:

- are newly retired, semi-retired, in industry, or in clinical practice
- have a minimum of 2 years of clinical practice experience
- have been active in the medical community in the past 3 years
- have an active or volunteer US medical license (any state)
- are able to provide 3 professional references
- are willing to commit a minimum of 4 hours per month for 6 months.

Visit us online to complete our physician volunteer inquiry form (http://www.mavenproject.org/get-involved/volunteer-physician/). ●

The MAVEN Project at work

What happens when a safety net clinic receives a donation of life-altering oral diabetes medications but their providers lack the expertise to use them appropriately? A closet full of drugs. That is what the MAVEN Project discovered at one of our partner clinics. Enter our volunteer endocrinologist. She consulted with the medical team, reviewed how each medication should be prescribed and monitored, and gave instructions on which patients with diabetes would benefit the most from them.

The closet is emptying, the clinic providers are confidently prescribing the newest therapies, and patients are enjoying improved blood sugars and quality of life!

References

1. Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, et al. Inequalities in life expectancy among US counties, 1980 to 2014: temporal trends and key drivers. *JAMA Intern Med*. 2017;177:1003-1011.
2. Schoendorf KC, Hogue CJ, Kleinman JC, et al. Mortality among infants of black as compared with white college-educated parents. *N Engl J Med*. 1992;326:1522-1526.
3. 3. Villarosa L. Why America's black mothers and babies are in a life-or-death crisis. *New York Times*. April 11, 2018. https://www.nytimes.com/2018/04/11/magazine/black-mothers-babies-death-maternal-mortality.html. Accessed August 14, 2018.
4. Smith VK, Gifford K, Ellis E, et al; The Henry J. Kaiser Family Foundation; The National Association of Medical Directors. Implementing coverage and payment initiatives: results from a 50-state Medicaid budget survey for state fiscal years 2016 and 2017. http://files.kff.org/attachment/Report-Implementing-Coverage-and-Payment-Initiatives. Published October 2006. Accessed August 14, 2018.
5. Association of American Medical Colleges. 2016 Physician Specialty Data Report: Executive Summary. https://www.aamc.org/download/471786/data/2016physicianspecialtydatareportexecutivesummary.pdf. Accessed August 23, 2018.
6. Miller RW. Jenna Bush Hager shares George H.W. Bush 'point of light' letter after Trump jab. *USA TODAY*. July 7, 2018. https://www.usatoday.com/story/news/politics/onpolitics/2018/07/07/jenna-bush-hager-shares-george-h-w-bush-point-light-letter-donald-trump/765248002/. Accessed August 14, 2018.

SGS video series!

SOCIETY OF GYNECOLOGIC SURGEONS

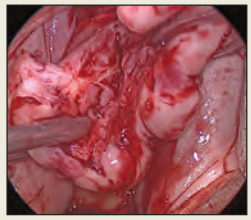
View this new video at
obgmanagement.com

Brought to you by the Society of Gynecologic Surgeons

OBG MANAGEMENT

Morcellation at the time of vaginal hysterectomy

MOHAMMAD ISLAM, MD; JAVIER MAGRINA, MD; AND MEGAN WASSON, DO



In this video, the authors demonstrate techniques for performing morcellation at the time of vaginal hysterectomy in properly selected patients. Techniques include intramyometrial coring, anterior wedge resection, myomectomy, and posterior wedge resection. Important concepts to remember include the need for complete devascularization prior to morcellation, adequate visualization, and correct orientation of the scalpel toward the midline to avoid uterine perforation and injury to surrounding structures. A bayonet-shaped scalpel may be used to allow the cutting blade to be better visualized.

◀ Use this QR code* to view the video at **mdedge.com/obgmanagement**

*Free QR readers are available for smartphones at the iPhone App Store, Android Market, and BlackBerry App World.

A Supplement to OBG MANAGEMENT

This supplement is sponsored by Lupin Pharmaceuticals, Inc.

Effective Management and Counseling of Patients with Recurrent Bacterial Vaginosis

Bacterial vaginosis (BV) affects women worldwide and recurrent BV can be a frustrating condition for both patients and providers. In this new supplement, expert Khady Diouf, MD, discusses her treatment approach and suggested counseling for patients with recurrent BV.

This supplement can be found in the June issue of OBG MANAGEMENT, in the Education Center at the OBG MANAGEMENT website, and directly at **www.mdedge.com/obgmanagement/BV**

Is the most effective emergency contraception easily obtained at US pharmacies?

The availability of ulipristal acetate (Ella) for emergency contraception is limited (either immediately or via order placement), according to a national secret shopper telephone survey of 344 retail pharmacies in 10 major US cities. Only 10% of pharmacies (33 of 344) reported having ulipristal acetate immediately available, including 12% of chain pharmacies (28 of 233) and 5% of independent pharmacies (5 of 111).

FAST TRACK

Available only by prescription, ulipristal acetate provides emergency contraception that is more effective than emergency contraception provided by levonorgestrel

EXPERT COMMENTARY

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

Shigesato M, Elia J, Tschann M, et al. Pharmacy access to ulipristal acetate in major cities throughout the United States. Contraception. 2018;97(3):264–269.

Although it is available only by prescription, ulipristal acetate provides emergency contraception that is more effective than the emergency contraception provided by levonorgestrel (LNG), which is available without a prescription (**TABLE**). In addition, ulipristal acetate appears more effective than LNG in obese and overweight women.[1,2] Package labeling for ulipristal acetate indicates that a single 30-mg tablet should be taken orally within 5 days of unprotected sex.

According to a survey of pharmacy availability of ulipristal acetate in Hawaii, 2.6% of retail pharmacies had the drug immediately available, compared with 82.4% for LNG, and 22.8% reported the ability to order it.[3] To assess pharmacy availability of ulipristal acetate on a nationwide scale, Shigesato and colleagues conducted a national "secret shopper" telephone survey in 10 cities (each with a population of at least 500,000) in all major regions of the United States.

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

Details of the study

Independent pharmacies (defined as having fewer than 5 locations within the city) and chain pharmacies were included in the survey. The survey callers, representing themselves as uninsured 18-year-old women attempting to fill a prescription for ulipristal acetate, followed a semistructured questionnaire and recorded the responses. They asked about the immediate availability of ulipristal acetate and LNG, the pharmacy's ability to order ulipristal acetate if not immediately available, out-of-pocket costs, instructions for use, and the differences between ulipristal acetate and LNG. Questions were directed to whichever pharmacy staff member answered the phone; callers did not specifically ask to speak to a pharmacist.

Of the 344 pharmacies included in this analysis, 10% (33) indicated that they could

TABLE FDA-approved emergency contraceptive pills available in the United States

Drug	Dosage and administration	Availability
Ulipristal acetate (Ella)	30-mg tablet to be taken within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure	• Rx only
Levonorgestrel (Plan B One-Step; My Way; Next Choice One Dose; Take Action)	1.5-mg tablet to be taken as soon as possible within 72 hours after unprotected intercourse	• OTC for women 17 years and older • Available by Rx for women younger than 17 years

Abbreviations: FDA, US Food and Drug Administration; OTC, over the counter; Rx, prescription.

fill a prescription for ulipristal acetate immediately. While availability did not vary by region, there was a difference in immediate availability by city.

Almost three-quarters of pharmacies without immediate drug availability indicated that they could order ulipristal acetate, with a median predicted time for availability of 24 hours. Of the chain pharmacies, 81% (167 of 205) reported the ability to order ulipristal acetate, compared with 55% (57 of 106) of independent pharmacies.

When asked if ulipristal acetate was different from LNG, more than one-third of pharmacy personnel contacted stated either that there was no difference between ulipristal acetate and LNG or that they were not sure of a difference.

Study strengths and weaknesses

The authors noted that the secret shopper methodology, along with having callers speak to the pharmacy staff person who answered the call (rather than asking for the pharmacist), provided data that closely approximates real-world patient experiences.

Since more pharmacies than anticipated met exclusion criteria for the study, the estimate of ulipristal acetate immediate availability was less precise than the power analysis predicted. Further, results from the 10 large, geographically diverse cities may not be representative of all similarly sized cities nationally or all areas of the United States. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

As the authors point out, a low prevalence of pharmacies stock ulipristal acetate, and more than 25% are not able to order this emergency contraception. This underscores the fact that access to the most effective oral emergency contraception is limited for US women. I agree with the authors' speculation that access to ulipristal acetate may be even lower in rural areas. In many European countries, ulipristal acetate is available without a prescription. Clinicians caring for women who may benefit from emergency contraception, particularly those using short-acting or less effective contraceptives, may wish to prescribe ulipristal acetate in advance of need.

ANDREW M. KAUNITZ, MD

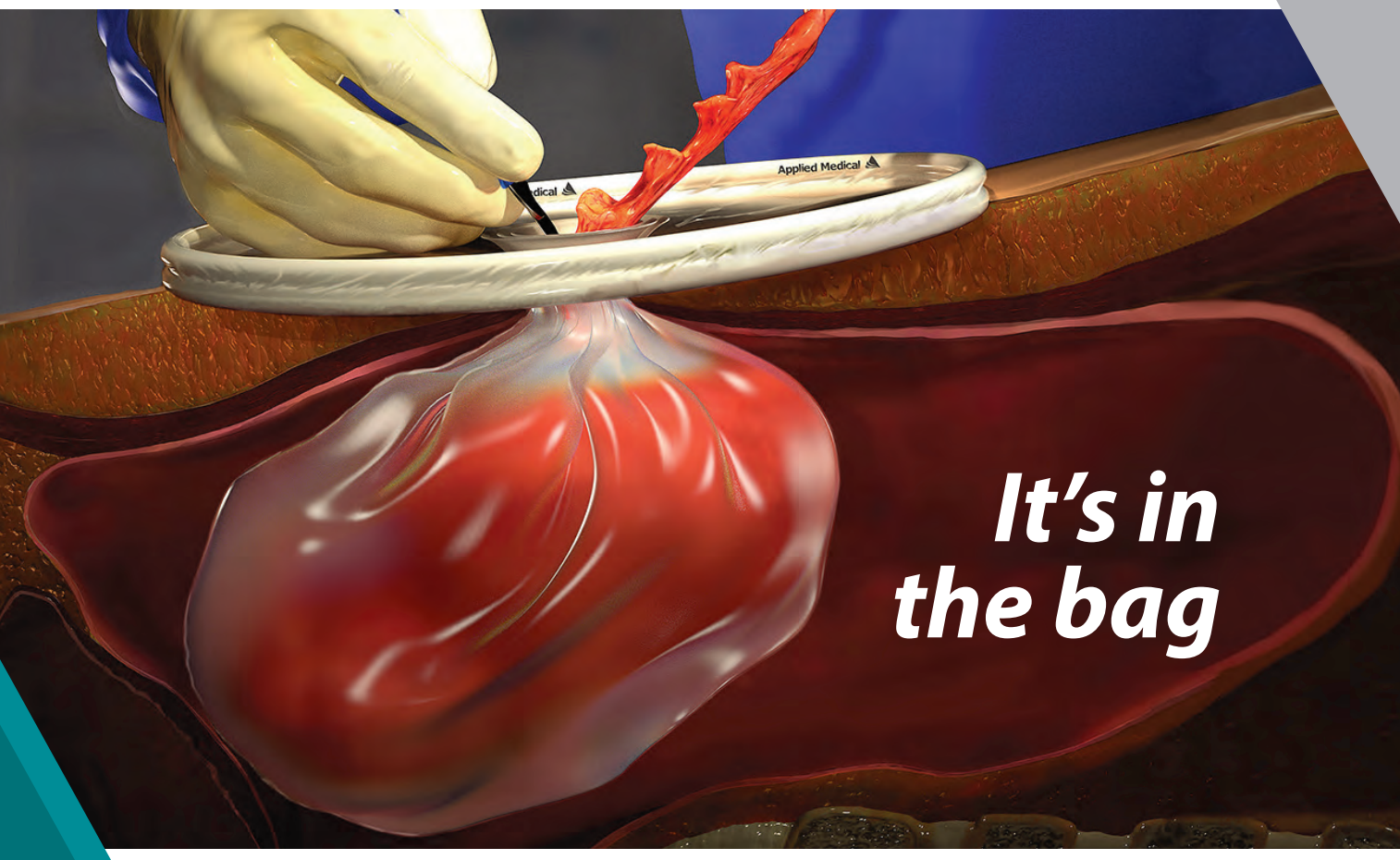
FAST TRACK

Of 344 pharmacies, 10% (33) could fill a prescription for ulipristal acetate immediately; three-quarters without immediate drug availability could order it with a median predicted time for availability of 24 hours

References

1. Kapp N, Abitbol JL, Mathé H, et al. Effect of body weight and BMI on the efficacy of levonorgestrel emergency contraception. Contraception. 2015;91(2):97–104.
2. Glasier A, Cameron ST, Blithe D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. Contraception. 2011;84(4):363–367.
3. Bullock H, Steele S, Kurata N, et al. Pharmacy access to ulipristal acetate in Hawaii: is a prescription enough? Contraception. 2016;93(5):452–454.

Minimally Invasive Tissue Extraction



When it comes to minimally invasive tissue extraction, the **Alexis® Contained Extraction System (CES)** has it in the bag. Featuring a secure specimen-containment bag, an adjustable guard to protect the bag from sharp instrumentation, and kit configurations to support your multiport, reduced-port or single-site techniques, the Alexis CES offers a complete solution for contained tissue extraction that stand-alone bags cannot.

View procedural videos,
register for a course and more at
www.appliedmedical.com/alexis_ces

Applied Medical

Importance of providing standardized management of hypertension in pregnancy

Good outcomes depend on following best-practice recommendations for preventive, emergent, and routine care, based on our improving understanding of pathophysiology and risk

Marc H. Incerpi, MD

CASE Onset of nausea and headache, and elevated BP, at full term

A 24-year-old woman (G1P0) at 39 2/7 weeks of gestation without significant medical history and with uncomplicated prenatal care presents to labor and delivery reporting uterine contractions. She reports nausea and vomiting, and reports having a severe headache this morning. Blood pressure (BP) is 154/98 mm Hg. Urine dipstick analysis demonstrates absence of protein.

How should this patient be managed?

Although we have gained a greater understanding of hypertensive disorders in pregnancy—most notably, preeclampsia—during the past 15 years, management of these patients can, as evidenced in the case above, be complicated. Providers must respect this disease and be cognizant of the significant maternal, fetal, and neonatal complications that can be associated with hypertension during pregnancy—a leading cause of preterm birth and maternal mortality in the United States.[1-3] Initiation of early and aggressive antihypertensive medical therapy, when indicated, plays a key role in preventing catastrophic complications of this disease.

Dr. Incerpi is Clinical Professor of Obstetrics and Gynecology (Clinician Educator), Division of Maternal-Fetal Medicine, Keck School of Medicine of USC, University of Southern California, Los Angeles.

The author reports no financial relationships relevant to this article.

Terminology and classification

Hypertension of pregnancy is classified as:

- **chronic hypertension:** BP ≥140/90 mm Hg prior to pregnancy or prior to 20 weeks of gestation. Patients who have persistently elevated BP 12 weeks after delivery are also in this category.
- **preeclampsia–eclampsia:** hypertension along with multisystem involvement that occurs after 20 weeks of gestation.
- **gestational hypertension:** hypertension alone after 20 weeks of gestation; in approximately 15% to 25% of these patients, a diagnosis of preeclampsia will be made as pregnancy progresses.
- **chronic hypertension with superimposed preeclampsia**: hypertension complicated by development of multisystem involvement during the course of the pregnancy—often a challenging diagnosis, associated with greater perinatal morbidity than either chronic hypertension or preeclampsia alone.

IN THIS ARTICLE

CONTINUED ON PAGE 22

CONTINUED FROM PAGE 21

PHOTO: SHUTTERSTOCK

FAST TRACK

Evaluate for secondary causes and comorbidities of hypertension; conduct lab testing for serum creatinine, electrolyte, and liver enzyme levels; and order complete blood count, including early screen for gestational diabetes

Evaluation of the hypertensive gravida

Although most pregnant patients (approximately 90%) who have a diagnosis of chronic hypertension have primary or essential hypertension, a secondary cause—including thyroid disease, systemic lupus erythematosus (SLE), and underlying renal disease—might be present and should be sought out. It is important, therefore, to obtain a comprehensive history along with a directed physical examination and appropriate laboratory tests.

Ideally, a patient with chronic hypertension should be evaluated prior to pregnancy, but this rarely occurs. At the initial encounter, the patient should be informed of risks associated with chronic hypertension, as well as receive education on the signs and symptoms of preeclampsia. Obtain a thorough history—not only to evaluate for secondary causes of hypertension or end-organ involvement (eg, kidney disease), but to identify comorbidities (such as pregestational diabetes mellitus). The patient should be instructed to immediately discontinue any teratogenic medication (such as an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker).

Routine laboratory evaluation

Testing should comprise a chemistry panel to evaluate serum creatinine, electrolytes, and liver enzymes. A 24-hour urine collection for protein excretion and creatinine clearance or a urine protein–creatinine ratio should be obtained to record baseline kidney function.[4] (Such testing is important, given that new-onset or worsening proteinuria is a manifestation of superimposed preeclampsia.) All pregnant patients with chronic hypertension also should have a complete blood count, including a platelet count, and an early screen for gestational diabetes.

Depending on what information is obtained from the history and physical examination, renal ultrasonography and any of several laboratory tests can be ordered, including thyroid function, an SLE panel, and vanillylmandelic acid/metanephrines. If the patient has a history of severe hypertension for greater than 5 years, is older than 40 years, or has cardiac symptoms, baseline electrocardiography or echocardiography, or both, are recommended.

Clinical manifestations of chronic hypertension during pregnancy include[5]:

- **in the mother:** accelerated hypertension, with resulting target-organ damage involving heart, brain, and kidneys
- **in the fetus**: placental abruption, preterm birth, fetal growth restriction, and fetal death.

What should treatment seek to accomplish?

The goal of antihypertensive medication during pregnancy is to reduce maternal risk of stroke, congestive heart failure, renal failure, and severe hypertension. No convincing evidence exists that antihypertensive medications decrease the incidence of superimposed preeclampsia, preterm birth, placental abruption, or perinatal death.

According to the American College of Obstetricians and Gynecologists (ACOG), antihypertensive medication is *not* indicated in patients with uncomplicated chronic hypertension unless systolic BP is ≥160 mm Hg or diastolic BP is ≥105 mm Hg.[3] The goal is to

CONTINUED ON PAGE 25

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

A new choice for balanced control

Patient Savings
$21 for 21*

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 22

TABLE 1 Oral antihypertensive therapy in pregnancy[3]

Drug (brand names)[a]	Dosage	Comments
Labetalol (Normodyne, Trandate)	200–2,400 mg/d orally in 2 or 3 divided doses	• Well tolerated • Potential bronchoconstrictive effects • Avoid in patients with asthma and congestive heart failure
Nifedipine (Adalat, Afeditab, Nifediac, Procardia)	30–120 mg/d orally (use slow-release preparation)	• Do not use sublingual form
Methyldopa (Aldomet)	0.5–3 g/d orally in 2 or 3 divided doses	• Childhood safety data to 7 years of age • Might not be as effective in controlling severe hypertension
Thiazide diuretics (Diuril, Enduron, Esidrix, Lozol, Microzide, Mykrox, Zaroxolyn)	Varies by agent	• Second-line agents
Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers	—	• Associated with fetal anomalies • Contraindicated in pregnancy and preconception period

[a]Not an exhaustive list.

maintain systolic BP at 120–160 mm Hg and diastolic BP at 80–105 mm Hg. The National Institute for Health and Care Excellence recommends treatment of hypertension when systolic BP is ≥150 mm Hg or diastolic BP is ≥100 mm Hg.[6] In patients with end-organ disease (chronic renal or cardiac disease) ACOG recommends treatment with an antihypertensive when systolic BP is >140 mm Hg or diastolic BP is >90 mm Hg.

First-line antihypertensives considered safe during pregnancy are methyldopa, labetalol, and nifedipine. Thiazide diuretics, although considered second-line agents, may be used during pregnancy—especially if BP is adequately controlled prior to pregnancy. Again, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are contraindicated during pregnancy (**TABLE 1**).[3]

Continuing care in chronic hypertension

Given the maternal and fetal consequences of chronic hypertension, it is recommended that a hypertensive patient be followed closely as an outpatient; in fact, it is advisable that she check her BP *at least* twice daily. Beginning at 24 weeks of gestation, serial ultrasonography should be performed every 4 to 6 weeks to evaluate interval fetal growth. Twice-weekly antepartum testing should begin at 32 to 34 weeks of gestation.

During the course of the pregnancy, the chronically hypertensive patient should be observed closely for development of superimposed preeclampsia. If she does not develop preeclampsia or fetal growth restriction, and has no other pregnancy complications that necessitate early delivery, 3 recommendations regarding timing of delivery apply[7]:

- If the patient is *not* taking antihypertensive medication, delivery should occur at 38 to 39 6/7 weeks of gestation
- If hypertension is controlled with medication, delivery is recommended at 37 to 39 6/7 weeks of gestation.
- If the patient has severe hypertension that is difficult to control, delivery might be advisable as early as 36 weeks of gestation.

Be vigilant for maternal complications (including cardiac compromise, congestive heart failure, cerebrovascular accident, hypertensive encephalopathy, and worsening

FAST TRACK

First-line antihypertensives considered safe during pregnancy are methyldopa, labetalol, and nifedipine; thiazide diuretics are second-line agents

renal disease) and fetal complications (such as placental abruption, fetal growth restriction, and fetal death). If any of these occur, management must be tailored and individualized accordingly. Study results have demonstrated that superimposed preeclampsia occurs in 20% to 30% of patients who have underlying mild chronic hypertension. This increases to 50% in women with underlying severe hypertension.[8]

The complex challenge of managing preeclampsia

Chronic hypertension is not the only risk factor for preeclampsia; others include nulliparity, history of preeclampsia, multifetal gestation, underlying renal disease, SLE, antiphospolipid syndrome, thyroid disease, and pregestational diabetes. Furthermore, preeclampsia has a bimodal age distribution, occurring more often in adolescent pregnancies and women of advanced maternal age. Risk is also increased in the presence of abnormal levels of various serum analytes or biochemical markers, such as a low level of pregnancy-associated plasma protein A or estriol or an elevated level of maternal serum α-fetoprotein, human chorionic gonadotropin, or inhibin—findings that might reflect abnormal placentation.[9]

In fact, the findings of most studies that have looked at the pathophysiology of preeclampsia appear to show that several noteworthy pathophysiologic changes are evident in early pregnancy[10,11]:

- incomplete trophoblastic invasion of spiral arteries
- retention of thick-walled, muscular arteries
- decreased placental perfusion
- early placental hypoxia
- placental release of factors that lead to endothelial dysfunction and endothelial damage.

Ultimately, vasoconstriction becomes evident, which leads to clinical manifestations of the disorder. In addition, there is an increase in the level of thromboxane (a vasoconstrictor and platelet aggregator), compared to the level of prostacyclin (a vasodilator).

FAST TRACK

Upgrade a preeclampsia diagnosis to "with severe features" if SBP >160 mm Hg or DBP >110 mm Hg (determined by 2 measurements 4 hours apart) or if "severe"-range BP occurs so rapidly that acute antihypertensive medication is required

ACOG revises nomenclature, provides recommendations

The considerable expansion of knowledge about preeclampsia over the past 10 to 15 years has not translated to better outcomes. In 2012, ACOG, in response to troubling observations about the condition (see "ACOG finds compelling motivation to boost understanding, management of preeclampsia," page 31), created a Task Force to investigate hypertension in pregnancy.

Findings and recommendations of the Task Force were published in November 2013,[3] and have been endorsed and supported by professional organizations, including the American Academy of Neurology, American Society of Hypertension, Preeclampsia Foundation, and the Society for Maternal-Fetal Medicine. A major premise of the Task Force that has had a direct impact on recommendations for management of preeclampsia is that the condition is a progressive and dynamic process that involves multiple organ systems and is not specifically confined to the antepartum period.

The nomenclature of mild preeclampsia and severe preeclampsia was changed in the Task Force report to *preeclampsia without severe features* and *preeclampsia with severe features*. **Preeclampsia without severe features** is diagnosed when a patient has:

- systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg (measured twice at least 4 hours apart)
- proteinuria, defined as a 24-hour urine collection of ≥300 mg of protein or a urine protein–creatinine ratio of ≥0.3.

If a patient has elevated BP by those criteria, plus any of several laboratory indicators of multisystem involvement (platelet count, $<100 \times 10^3/\mu L$; serum creatinine level, >1.1 mg/dL; doubling in the serum creatinine concentration; liver transaminase concentrations twice normal) or other findings (pulmonary edema, visual disturbance, headaches), she has **preeclampsia with severe features**. A diagnosis of preeclampsia without severe features is upgraded to preeclampsia with severe features if systolic BP increases to >160 mm Hg or diastolic BP increases to >110 mm Hg

CONTINUED ON PAGE 28

START THE CONVERSATION TO START THEIR RELIEF

Sexual discomfort due to vaginal dryness can have a simple solution: **K-Y® ULTRAGEL®.**

Start discussing the benefits of a lubricant with your patients and you can start improving their sexual health.

RECOMMEND:

K-Y® ULTRAGEL®
WATER-BASED PERSONAL LUBRICANT

An advanced, hormone-free liquid gel formula for silky lubrication

ALSO AVAILABLE:

K-Y® LIQUIBEADS®
LESS-MESS MOISTURIZER

A discreet OVULE® insert that gently dissolves within minutes for hydration that lasts all day and all night

COMFORT STARTS WHEN YOU ADD K-Y® TO THE CONVERSATION

Discover more at www.k-y.com

CONTINUED FROM PAGE 26

TABLE 2 Options for emergent treatment of acute-onset severe hypertension of pregnancy[12]

IV labetalol
Administer 20 mg
Measure BP in 10 minutes
If BP remains elevated, administer 40 mg
Measure BP in 10 minutes
If BP remains elevated, administer 80 mg
Measure BP in 10 minutes
If BP remains elevated, administer IV *hydralazine* 10 mg
Measure BP in 20 minutes
If BP remains elevated, obtain emergency consultation
IV hydralazine
Administer 5 or 10 mg
Measure BP in 20 minutes
If BP remains elevated, administer 10 mg
Measure BP in 20 minutes
If BP remains elevated, administer IV *labetalol* 20 mg
Measure BP in 10 minutes
If BP remains elevated, administer IV *labetalol,* 40 mg
Obtain emergency consultation
Oral nifedipine
Administer 10 mg
Measure BP in 20 minutes
If BP remains elevated, administer 20 mg
Measure BP in 20 minutes
If BP remains elevated, administer 20 mg
Measure BP in 20 minutes
If BP remains elevated, administer IV *labetalol,* 40 mg
Obtain emergency consultation

Abbreviations: BP, blood pressure; IV, intravenous.

(determined by 2 measurements 4 hours apart) or if "severe"-range BP occurs with such rapidity that acute antihypertensive medication is required.

Pharmacotherapy for hypertensive emergency

Acute BP control with intravenous (IV) labetalol or hydralazine or oral nifedipine is recommended when a patient has a hypertensive emergency, defined as acute-onset severe hypertension that persists for ≥15 minutes (**TABLE 2**).[12] The goal of management is not to completely normalize BP but to lower BP to the range of 140 to 155 mm Hg (systolic) and 90 to 105 mm Hg (diastolic). Of all proposed interventions, these agents are likely the most effective in preventing a maternal cerebrovascular or cardiovascular event. (Note: Labetalol is contraindicated in patients with severe asthma and in the setting of acute cocaine or methamphetamine intoxication. Hydralazine can cause tachycardia.)[13,14]

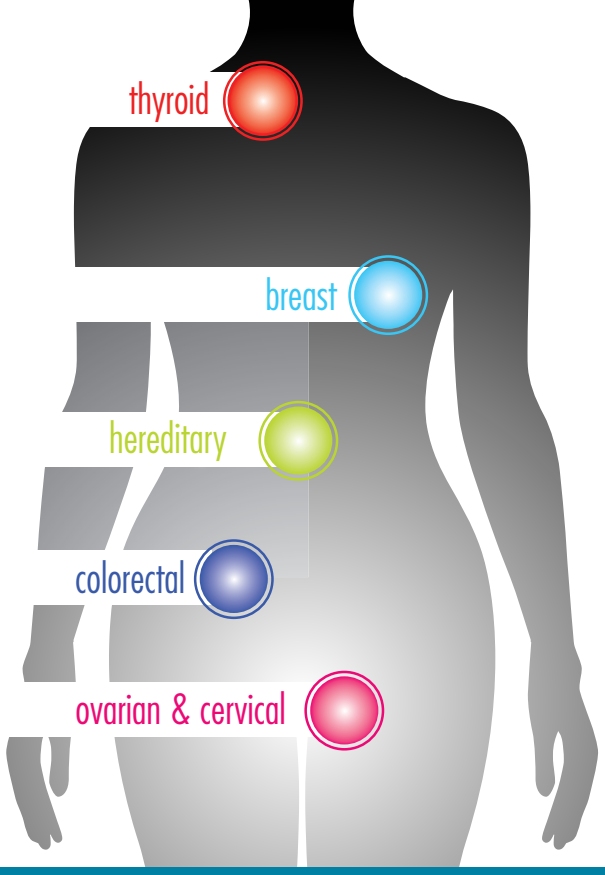
Once a diagnosis of preeclampsia with severe features or superimposed preeclampsia with severe features is made, the patient should remain hospitalized until delivery. If either of these diagnoses is made at ≥34 weeks of gestation, there is no reason to prolong pregnancy. Rather, the patient should be given prophylactic magnesium sulfate to prevent seizures and delivery should be accomplished.[15,16] Earlier than 36 6/7 weeks of gestation, consider a late preterm course of corticosteroids; however, do not delay delivery in this situation.[17]

Planning for delivery

Route of delivery depends on customary obstetric indications. Before 34 weeks of gestation, corticosteroids, magnesium sulfate, and prolonging the pregnancy until 34 weeks of gestation are recommended. If, at any time, maternal or fetal condition deteriorates, delivery should be accomplished regardless of gestational age. If the patient is unwilling to accept the risks of expectant management of preeclampsia with severe features remote from term, delivery is indicated.[18,19] If delivery is not likely to occur, magnesium sulfate can be discontinued after the patient has received a second dose of corticosteroids, with the plan to resume magnesium sulfate if she develops signs of worsening preeclampsia or eclampsia, or once the plan for delivery is made.

In patients who have either gestational hypertension or preeclampsia without severe features, the recommendation is to accomplish delivery no later than 37 weeks of gestation. While the patient is being expectantly managed, close maternal and fetal surveillance are necessary, comprising serial assessment of maternal symptoms and fetal

CONTINUED ON PAGE 30



Everything **she** needs

with the services **you** expect.

LabCorp offers a comprehensive test menu that supports the continuum of care. From screening to diagnosis, treatment decisions, and surveillance, LabCorp is a one-source laboratory provider. LabCorp's advanced technologies enable clinicians to detect and define the disease more accurately for informed treatment decisions.

Tests **She** Needs - cancer prevention, detection, and management

- Breast Cancer
- Cervical Cancer
- Colorectal Cancer
- Hereditary Cancers
- Ovarian Cancer
- Thyroid Cancer

Services **You** Expect - from patient encounter to follow-up

- Scientific expertise
- Genetic counselors
- Patient information and counseling reports
- Patient portal
- Online appointments for blood draws at LabCorp collection sites
- EMR interface solutions
- Monthly cytology summary reports

LabCorp

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

CONTINUED FROM PAGE 28

My practice recommendations

Antihypertensive medication is the mainstay of treatment for severely elevated blood pressure (BP). To avoid fetal heart rate decelerations and possible emergent cesarean delivery, however, do not decrease BP too quickly or lower to values that might compromise perfusion to the fetus. The BP goal should be 140–155 mm Hg (systolic) and 90–105 mm Hg (diastolic). **A**

Be prepared for eclampsia, which is unpredictable and can occur in patients without symptoms or severely elevated BP and even postpartum in patients in whom the diagnosis of preeclampsia was never made prior to delivery. The response to eclamptic seizure includes administering magnesium sulfate, which is the approved initial therapy for an eclamptic seizure. **A**

Make algorithms for acute treatment of severe hypertension and eclampsia readily available or posted in labor and delivery units and in the emergency department. **C**

Counsel high-risk patients about the potential benefit of low-dosage aspirin to prevent preeclampsia. **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

movement; serial BP measurement (twice weekly); and weekly measurement of the platelet count, serum creatinine, and liver enzymes. At 34 weeks of gestation, conventional antepartum testing should begin. Again, if there is deterioration of the maternal or fetal condition, the patient should be hospitalized and delivery should be accomplished according to the recommendations above.[3]

Seizure management

If a patient has a tonic–clonic seizure consistent with eclampsia, management should be as follows:

1. Preserve the airway and immediately tilt the head forward to prevent aspiration.
2. If the patient is not receiving magnesium sulfate, immediately administer a loading dose of 4–6 g IV or 10 mg intramuscularly if IV access has not been established.[20]
3. If the patient is already receiving magnesium sulfate, administer a loading dose of 2 g IV over 5 minutes.
4. If the patient continues to have seizure activity, administer anticonvulsant medication (lorazepam, diazepam, midazolam, or phenytoin).

Eclamptic seizures are usually self-limited, lasting no longer than 1 or 2 minutes. Regrettably, these seizures are unpredictable and contribute significantly to maternal morbidity and mortality.[21,22] A maternal seizure causes a significant interruption in the oxygen pathway to the fetus, with resultant late decelerations, prolonged decelerations, or bradycardia.

Resist the temptation to perform emergent cesarean delivery when eclamptic seizure occurs; rather, allow time for fetal recovery and then proceed with delivery in a controlled fashion. In many circumstances, the patient can undergo vaginal delivery after an eclamptic seizure. Keep in mind that the differential diagnosis of new-onset seizure in pregnancy includes cerebral pathology, such as a bleeding arteriovenous malformation or ruptured aneurysm. Therefore, brain-imaging studies might be indicated, especially in patients who have focal neurologic deficits, or who have seizures either while receiving magnesium sulfate or 48 to 72 hours after delivery.

Preeclampsia postpartum

More recent studies have demonstrated that preeclampsia can be exacerbated *after* delivery or might even present *initially* postpartum.[23,24] In all women in whom gestational hypertension, preeclampsia, or superimposed preeclampsia is diagnosed, therefore, recommendations are that BP be monitored in the hospital or on an outpatient basis for at least 72 hours postpartum and again 7 to 10 days after delivery. For all women postpartum, the recommendation is that discharge instructions 1) include information about signs and symptoms of preeclampsia and 2) emphasize the importance of promptly reporting such developments to providers.[25] Remember: Sequelae of preeclampsia have been reported as late as 4 to 6 weeks postpartum.

Magnesium sulfate is recommended when a patient presents postpartum with new-onset hypertension associated with headache or blurred vision, or with preeclampsia with severe hypertension. Because

nonsteroidal anti-inflammatory drugs can be associated with elevated BP, these medications should be replaced by other analgesics in women with hypertension that persists for more than 1 day postpartum.

Prevention of preeclampsia

Given the significant maternal, fetal, and neonatal complications associated with preeclampsia, a number of studies have sought to determine ways in which this condition can be prevented. Currently, although no interventions appear to prevent preeclampsia in all patients, significant strides have been made in prevention for high-risk patients. Specifically, beginning low-dosage aspirin (most commonly, 81 mg/d, beginning at less than 16 weeks of gestation) has been shown to mitigate—although not eliminate—risk in patients with a history of preeclampsia and those who have chronic hypertension, multifetal gestation, pregestational diabetes, renal disease, SLE, or antiphospholipid syndrome.[26,27] Aspirin appears to act by preferentially blocking production of thromboxane, thus reducing the vasoconstrictive properties of this hormone.

Summing up

Hypertensive disorders during pregnancy are associated with significant morbidity and mortality for mother, fetus, and newborn. Preeclampsia, specifically, is recognized as a dynamic and progressive disease that has the potential to involve multiple organ systems, might present for the first time *after* delivery, and might be associated with long-term risk of hypertension, heart disease, stroke, and venous thromboembolism.[28,29]

ACOG finds compelling motivation to boost understanding, management of preeclampsia

- Incidence of preeclampsia in the United States has increased by 25% over the past 2 decades
- Etiology remains unclear
- Leading cause of maternal and perinatal morbidity and mortality
- Risk factor for future cardiovascular disease and metabolic disease in women
- Hypertensive disorders of pregnancy are major contributors to prematurity
- New best-practice recommendations are urgently needed to guide clinicians in the care of women with all forms of preeclampsia and hypertension during pregnancy
- Improved patient education and counseling strategies are needed to convey, more effectively, the dangers of preeclampsia and hypertension during pregnancy

Reference

1. The American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. November 2013. https://www.acog.org/Clinical-Guidance-and-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy. Accessed August 8, 2018.

FAST TRACK

Low-dosage aspirin mitigates (but does not eliminate) risk of eclampsia in patients with a history of the disorder

CONTINUED ON PAGE 50

References

1. Callaghan WM, Mackay AP, Berg CJ. Identification of severe maternal morbidity during delivery hospitalizations, United States, 1991–2003. Am J Obstet Gynecol. 2008; 199:133.e1–e8.
2. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. Obstet Gynecol. 2009;113:1299–1306.
3. The American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. November 2013. https://www.acog.org/Clinical-Guidance-and-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy. Accessed August 8, 2018.
4. Wheeler TL 2nd, Blackhurst DW, Dellinger EH, Ramsey PS. Usage of spot urine protein to creatinine ratios in the evaluation of preeclampsia. Am J Obstet Gynecol. 2007;196:465.e1–e4.
5. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LL. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014;348:g2301.
6. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. CG107, August 2010. https://www.nice.org.uk/guidance/cg107. Accessed August 27, 2018. Last updated January 2011.
7. Spong CY, Mercer BM, D'Alton M, et al. Timing of indicated late-preterm and early-term birth. Obstet Gynecol. 2011;118:323–333.
8. Sibai BM. Chronic hypertension in pregnancy. Obstet Gynecol. 2002;100(2):369–377.
9. Dugoff L; Society for Maternal-Fetal Medicine. First- and second-trimester maternal serum markers or aneuploidy and adverse obstetric outcomes. Obstet Gynecol. 2010;115:1052–1061.
10. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "great obstetrical syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol. 2011;204:193–201.
11. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. Hypertension. 2008;51:970–975.
12. The American College of Obstetricians and Gynecologists Committee on Obstetric Practice; El-Sayed YY, Borders AE. Committee Opinion Number 692. Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period; April 2017. https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co692.pdf?dmc=1. Accessed August 8, 2018.
13. Hollander JE. The management of cocaine-associated myocardial ischemia. N Engl J Med. 1995;333:1267–1272.
14. Ghuran A, Nolan J. Recreational drug misuse: issues for the cardiologist. Heart. 2000;83:627–633.

UPDATE Contraception

Suji Uhm, MD, MPH
Dr. Uhm is a Family Planning Fellow in the Department of Obstetrics and Gynecology at the University of California, Davis; Sacramento, California.

Mitchell D. Creinin, MD
Dr. Creinin is Professor and Director of Family Planning in the Department of Obstetrics and Gynecology at the University of California, Davis.

Dr. Uhm reports no financial relationships relevant to this article. Dr. Creinin reports receiving speaking honoraria from Merck & Co; serving on an advisory board for Merck & Co; and being a consultant for Exeltis, Estetra, Gedeon Richter, Icebreaker Health, and Medicines360. The Department of Obstetrics and Gynecology, University of California–Davis, receives contraceptive research funding from Contramed (now Sebela), Medicines360, Merck & Co., National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the Society of Family Planning.

The Essure permanent hysteroscopic contraceptive device will disappear from the market in 2019. We present a timeline of events leading to product withdrawal, examine recent studies comparing efficacy and safety of permanent contraceptive methods, and look at device removal techniques to assist those considering such procedures. We also ask the question: Given the availability and uptake of LARC, have permanent contraceptive needs of patients shifted?

IN THIS ARTICLE

Female permanent contraception is among the most widely used contraceptive methods worldwide. In the United States, more than 640,000 procedures are performed each year and it is used by 25% of women who use contraception.[1–4] Female permanent contraception is achieved via salpingectomy, tubal interruption, or hysteroscopic techniques.

Essure, the only currently available hysteroscopic permanent contraception device, approved by the US Food and Drug Administration (FDA) in 2002,[5,6] has been implanted in more than 750,000 women worldwide.[7] Essure was developed by Conceptus Inc, a small medical device company that was acquired by Bayer in 2013. The greatest uptake has been in the United States, which accounts for approximately 80% of procedures worldwide.[7,8]

Essure placement involves insertion of a nickel-titanium alloy coil with a stainless-steel inner coil, polyethylene terephthalate fibers, platinum marker bands, and silver-tin solder.[9] The insert is approximately 4 cm in length and expands to 2 mm in diameter once deployed.[9]

Potential advantages of a hysteroscopic approach are that intra-abdominal surgery can be avoided and the procedure can be performed in an office without the need for general anesthesia.[7] Due to these potential benefits, hysteroscopic permanent contraception with Essure underwent expedited review and received FDA approval without any comparative trials.[1,5,10] However, there

also are disadvantages: the method is not always successfully placed on first attempt and it is not immediately effective. Successful placement rates range between 60% and 98%, most commonly around 90%.[11–15] Additionally, if placement is successful, alternative contraception must be used until a confirmatory radiologic test is performed at least 3 months after the procedure.[9,11] Initially, hysterosalpingography was required to demonstrate a satisfactory insert location and successful tubal occlusion.[11,16] Compliance with this testing is variable, ranging in studies from 13% to 71%.[11] As of 2015, transvaginal ultrasonography showing insert retention and location has been approved as an alternative confirmatory method.[9,11,16,17] Evidence suggests that the less invasive ultrasound option increases follow-up rates; while limited, one study noted an increase in follow-up rates from 77.5% for hysterosalpingogram to 88% ($P = .008$) for transvaginal ultrasound.[18]

Recent concerns about potential medical and safety issues have impacted approval status and marketing of hysteroscopic permanent contraception worldwide. In response to safety concerns, the FDA added a boxed safety warning and patient decision checklist in 2016.[19] Bayer withdrew the device from all markets outside of the United States as of May 2017.[20–22] In April 2018, the FDA restricted Essure sales in the United States only to providers and facilities who utilized an FDA-approved checklist to ensure the device met standards for safety and effectiveness.[19] Most recently, Bayer announced that Essure would no longer be sold or distributed in the United States after December 31, 2018 (See "FDA Press Release").[23]

So how did we get here? How did the promise of a "less invasive" approach for female permanent contraception get off course?

A search of the Manufacturer and User Facility Device Experience (MAUDE) database from Essure's approval date in 2002 to December 2017 revealed 26,773 medical device reports, with more than 90% of those received in 2017 related to device removal.[19] As more complications and complaints have been reported, the lack of comparative data has presented a problem for understanding the relative risk of the procedure as compared with laparoscopic techniques. Additionally, the approval studies lacked information about what happened to women who had an unsuccessful attempted hysteroscopic procedure. Without robust data sets or large trials, early research used evidence-based Markov modeling; findings suggested that hysteroscopic permanent contraception resulted in fewer women achieving successful permanent contraception and that the hysteroscopic procedure was not as effective as laparoscopic occlusion procedures with "typical" use.[24,25]

Over the past year, more clinical data have been published comparing hysteroscopic with laparoscopic permanent contraception procedures. In this article, we evaluate this information to help us better understand the relative efficacy and safety of the different permanent contraception methods and review recent articles describing removal techniques to further assist clinicians and patients considering such procedures.

FDA press release (July 20, 2018)

"The US Food and Drug Administration was notified by Bayer that the Essure permanent birth control device will no longer be sold or distributed after December 31, 2018… The decision today to halt Essure sales also follows a series of earlier actions that the FDA took to address the reports of serious adverse events associated with its use. For women who have received an Essure implant, the postmarket safety of Essure will continue to be a top priority for the FDA. We expect Bayer to meet its postmarket obligations concerning this device."

Reference

1. Statement from FDA Commissioner Scott Gottlieb, M.D., on manufacturer announcement to halt Essure sales in the U.S.; agency's continued commitment to postmarket review of Essure and keeping women informed [press release]. Silver Spring, MD; U.S. Food and Drug Administration. July 20, 2018.

FAST TRACK

As more complications with Essure have been reported, the lack of comparative data has presented a problem for understanding the relative risk of the procedure as compared with laparoscopic techniques

CONTINUED ON PAGE 34

CONTINUED FROM PAGE 33

Hysteroscopic versus laparoscopic procedures for permanent contraception

Bouillon K, Bertrand M, Bader G, et al. Association of hysteroscopic vs laparoscopic sterilization with procedural, gynecological, and medical outcomes. JAMA. 2018:319(4):375–387.

Antoun L, Smith P, Gupta J, et al. The feasibility, safety, and effectiveness of hysteroscopic sterilization compared with laparoscopic sterilization. Am J of Obstet Gynecol. 2017;217(5):570.e1–570.e6. doi:10.1016/j.ajog.2017.07.011.

Jokinen E, Heino A, Karipohja T, et al. Safety and effectiveness of female tubal sterilisation by hysteroscopy, laparoscopy, or laparotomy: a register based study. BJOG. 2017;124(12):1851–1857.

FAST TRACK

Gynecologic complications were significantly more common for women who had a hysteroscopic procedure for permanent contraception than for those who had a laparoscopic procedure

In this section, we present 3 recent studies that evaluate pregnancy outcomes and complications including reoperation or second permanent contraception procedure rates.

Data from France measure up to 3-year differences in adverse outcomes

Bouillon and colleagues aimed to identify differences in adverse outcome rates between hysteroscopic and laparoscopic permanent contraceptive methods. Utilizing national hospital discharge data in France, the researchers conducted a large database study review of records from more than 105,000 women aged 30 to 54 years receiving hysteroscopic or laparoscopic permanent contraception between 2010 and 2014. The database contains details based on the ICD-10 codes for all public and private hospitals in France, representing approximately 75% of the total population. Procedures were performed at 831 hospitals in 26 regions.

Adverse outcomes were divided into surgical, medical, and gynecologic complications (**TABLE 1**) and were assessed at 3 timepoints: at the time of procedure and at 1 and 3 years postprocedure.

Overall, 71,303 women (67.7%) underwent hysteroscopic permanent contraception procedures and 34,054 women (32.3%) underwent laparoscopic permanent contraception procedures. Immediate surgical and medical complications were significantly less common for women having hysteroscopic compared with laparoscopic procedures. Surgical complications at the time of the procedure occurred in 96 (0.13%) and 265 (0.78%) women, respectively (adjusted odds ratio [aOR], 0.18; 95% confidence interval [CI], 0.14–0.23). Medical complications at the time of procedure occurred in 41 (0.06%) and 39 (0.11%) women, respectively (aOR, 0.51; 95% CI, 0.30–0.89).

However, gynecologic outcomes, including need for a second surgery to provide permanent contraception and overall failure rates (need for salpingectomy, a second permanent contraception procedure, or pregnancy) were significantly more common for women having hysteroscopic procedures. By 1 year after the procedure, 2,955 women (4.10%) who initially had a hysteroscopic procedure, and 56 women (0.16%) who had a laparoscopic procedure required a second permanent contraception surgery (adjusted hazard ratio [aHR], 25.99; 95% CI, 17.84–37.86). By the third year, additional procedures were performed in 3,230 (4.5%) and 97 (0.28%) women, respectively (aHR, 16.63; 95% CI, 12.50–22.20). Most (65%) of the repeat procedures were performed laparoscopically. Although pregnancy rates were significantly lower at 1 year among women who initially chose a hysteroscopic procedure (0.24% vs 0.41%; aHR, 0.70; 95% CI, 0.53–0.92), the rates did not differ at 3 years (0.48% vs 0.57%, respectively; aHR, 1.04; 95% CI, 0.83–1.30).

TABLE 1 Outcomes assessed after hysteroscopic and laparoscopic permanent contraception procedures

Surgical complications	Medical complications	Gynecologic complications
• Acute hemorrhage • Abdominal injury • Complications related to implant placement • Debridement • Evacuation • Ablation of a foreign body	• Myocardial infarction/cardiac arrest • Stroke • Peripheral arterial thromboembolism • Deep vein thrombosis/pulmonary embolism • Anesthetic or anaphylactic shock/allergic reactions • Autoimmune disease • Thyroid disorders • Use of analgesics, antimigraines, antidepressants, and benzodiazepines • Respiratory complications • Infection • Suicide attempts • Death	• Sterilization failure category: - Salpingectomy - Second sterilization procedure - Pregnancy • Reoperation category: - Salpingectomy - Hysterectomy - Endometrectomy or curettage - Myomectomy - Second sterilization procedure

Source: Bouillon K, Bertrand M, Bader G, et al. Association of hysteroscopic vs laparoscopic sterilization with procedural, gynecological, and medical outcomes. JAMA. 2018:319(4):375–387.

Most importantly, overall procedure failure rates were significantly higher at 1 year in women initially choosing a hysteroscopic approach compared with laparoscopic approach (3,446 [4.83%] vs 235 [0.69%] women; aHR, 7.11; 95% CI, 5.92–8.54). This difference persisted through 3 years (4,098 [5.75%] vs 438 [1.29%] women, respectively; aHR, 4.66; 95% CI, 4.06–5.34).

UK data indicate high reoperation rate for hysteroscopic procedures

Antoun and colleagues aimed to compare pregnancy rates, radiologic imaging follow-up rates, reoperations, and 30-day adverse outcomes, between hysteroscopic and laparoscopic permanent contraception methods. Conducted at a single teaching hospital in the United Kingdom, this study included 3,497 women who underwent procedures between 2005 and 2015. The data were collected prospectively for the 1,085 women who underwent hysteroscopic procedures and retrospectively for 2,412 women who had laparoscopic permanent contraception procedures with the Filshie clip.

Over the 10-year study period, hysteroscopic permanent contraception increased from 14.2% (40 of 280) of procedures in 2005 to 40.5% (150 of 350) of procedures in 2015 ($P<.001$). Overall, 2,400 women (99.5%) underwent successful laparoscopic permanent contraception, compared with 992 women (91.4%) in the hysteroscopic group (OR, 18.8; 95% CI, 10.2–34.4).

In the hysteroscopic group, 958 women (97%) returned for confirmatory testing, of whom 902 (91% of women with successful placement) underwent satisfactory confirmatory testing. There were 93 (8.6%) unsuccessful placements that were due to inability to visualize ostia or tubal stenosis (n = 72 [77.4%]), patient intolerance to procedure (n = 15 [16.1%]), or device failure (n = 6 [6.5%]).

The odds for reoperation were 6 times greater in the hysteroscopic group by 1 year after surgery (22 [2%] vs 8 [0.3%] women; OR, 6.2; 95% CI, 2.8–14.0). However, the 1-year pregnancy risk was similar between the 2 groups, with 3 reported pregnancies after hysteroscopic permanent contraception and 5 reported pregnancies after laparoscopic permanent contraception (OR, 1.3; 95% CI, 0.3–5.6).

FAST TRACK

While the odds for reoperation were 6 times greater in the hysteroscopic group by 1 year after the procedure compared with the laparoscopic group, the 1-year pregnancy risk was similar between the 2 groups

CONTINUED ON PAGE 36

CONTINUED FROM PAGE 35

TABLE 2 Outcomes evaluated after hysteroscopic, laparoscopic, and open permanent contraception procedures in Finland between 2009 and 2014

Method	Hysteroscopic (Essure) n = 5,631	Laparoscopic (Filshie clip) n = 4,425	Minilaparotomy (Pomeroy) n = 6,216
Second permanent contraception procedure[a]	229 (4.07%)	82 (1.85%)	53 (0.85%)
Spontaneous pregnancies[b]	38 (0.67%)	34 (0.77%)	92 (1.48%)
Spontaneous pregnancies (per 100 follow-up years)	0.20	0.25	0.26

[a]*P*<.0001 for hysteroscopic versus laparoscopic.

[b]*P* = .67 for hysteroscopic versus laparoscopic.

Source: Jokinen E, Heino A, Karipohja T, et al. Safety and effectiveness of female tubal sterilisation by hysteroscopy, laparoscopy, or laparotomy: a register based study. BJOG. 2017;124(12):1851–1857.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

At a glance, these studies suggest that pregnancy rates are similar between hysteroscopic and laparoscopic permanent contraceptive approaches. But, these low failure rates were only achieved after including women who required reoperation or a second permanent contraceptive procedure. All 3 European studies showed a high follow-up rate; as method failure was identified, additional procedures were offered and performed when desired. These rates are higher than typically reported in US studies. None of the studies included discussion about the proportion of women with failed procedures who declined a second permanent contraceptive surgery. Bouillon et al[26] reported a slight improvement in perioperative safety for a hysteroscopic procedure compared with a laparoscopic procedure. While severity of complications was not reported, the risk of reoperation for laparoscopic procedures remained <1%. By contrast, based on the evidence presented here, hysteroscopic permanent contraceptive methods required a second procedure for 4% to 8% of women, most of whom underwent a laparoscopic procedure. Thus, the slight potential improvement in safety of hysteroscopic procedures does not offset the significantly lower efficacy of the method.

Finnish researchers also find high reoperation rate

Jokinen and colleagues used linked national database registries in Finland to capture data on pregnancy rate and reoperations among 16,272 women who underwent permanent contraception procedures between 2009 and 2014. The authors compared outcomes following hysteroscopic (Essure), laparoscopic (Filshie clip), and postpartum minilaparotomy (Pomeroy) permanent contraception techniques. According to the investigators, the latter method was almost exclusively performed at the time of cesarean delivery. While there was no difference in pregnancy rates, second permanent contraception procedures were significantly greater in the hysteroscopic group compared with the laparoscopic group (**TABLE 2**).

WATCH FOR...

›› Update on pelvic floor dysfunction
from Cindy Amundsen, MD

CONTINUED ON PAGE 37

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 Now Save up to $340!
Reserve Your Spot in PAGS Hands-on Workshops

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 Ridgeway, MD
Cleveland Clinic

ENCORE AT WYNN Las Vegas

Room rates start at just $189 a night!

OPTIONAL OPIOID REMS COURSE *NEW*
December 4, 2018

OPTIONAL HANDS-ON WORKSHOPS
LIMITED SPACE AVAILABLE. FIRST COME. FIRST SERVED!
December 5, 2018

SCIENTIFIC GENERAL SESSIONS
December 6-8, 2018

OPTIONAL HANDS-ON WORKSHOPS
- 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
- Non-Surgical Management of Incontinence and Pelvic Floor Disorders

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 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 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 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 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**

Open to Non-Attendees—So bring your staff!

3.25 CME Credits Available

P.E.P. PRACTICE ENHANCEMENT PROGRAM AGENDA (Optional)

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 Fellowship Program
Female Pelvic Medicine & Reconstructive Surgery
The Christ Hospital
Professor of OB/GYN & Urology
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 Foundation
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
Director
Minimally Invasive Fellowship in Gynecologic Surgery
Mayo Clinic
Phoenix, Arizona

Beri Ridgeway, MD
Assistant Professor
Cleveland Clinic Lerner 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 - 6:15 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 hands-on 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 Now Save up to $340!

Reserve Your Spot in PAGS Hands-on Workshops

The Premier Meeting for all Facets of Your Gynecology Practice

ENCORE AT WYNN Las Vegas

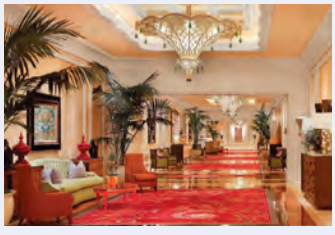
Optional **OPIOID REMS COURSE 3 CME Credits Available**
December 4, 2018

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 Nov 5	After Nov 5
Price Schedule		
■ Physicians	$895	$995
■ Residents, Fellows, Allied Health	$695	$795
■ **P.E.P. Program only** Also open to non-attendees	$395	$495
■ **Best Buy!** PAGS + P.E.P. Discount Combination Package	$1,195	$1,395
■ **Office-Based Gynecologic Procedures: The Gynecologist of the Future** All Day Workshop **NEW!**	$495	$595
■ **Laparoscopic Suturing** Morning Workshop	$275	$345
■ **Tissue Extraction Techniques** Morning Workshop	$275	$345
■ **Vaginal Hysterectomy & Cystourethroscopy** Afternoon Workshop	$325	$395
■ **Opioid REMS Course** *Pre-registration required*	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 36

Technique for hysteroscopic permanent contraception insert removal

Johal T, Kuruba N, Sule M, et al. Laparoscopic salpingectomy and removal of Essure hysteroscopic sterilisation device: a case series. Eur J Contracept Reprod Health Care. 2018;23(3):227–230.

Lazorwitz A, Tocce K. A case series of removal of nickel–titanium sterilization microinserts from the uterine cornua using laparoscopic electrocautery for salpingectomy. Contraception. 2017;96(2):96–98.

As reports of complications and concerns with hysteroscopic permanent contraception increase, there has been a rise in device removal procedures. We present 2 recent articles that review laparoscopic techniques for the removal of hysteroscopic permanent contraception devices and describe subsequent outcomes.

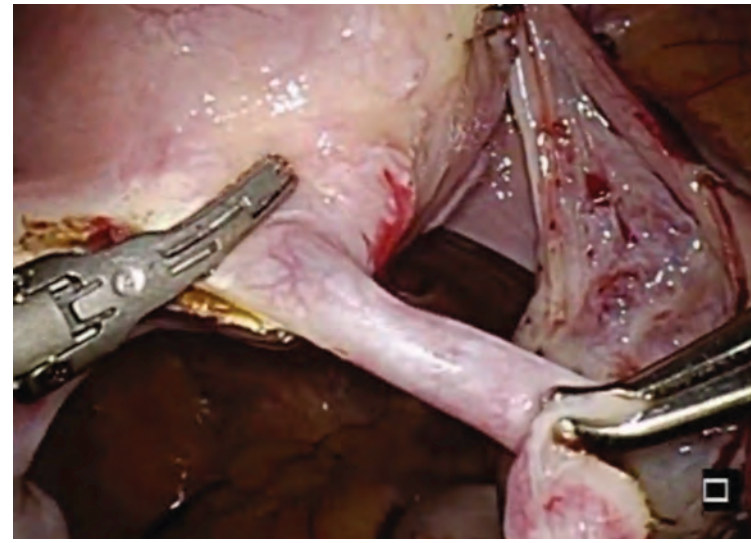
Laparoscopic salpingectomy without insert transection

In this descriptive retrospective study, Johal and colleagues reviewed hysteroscopic permanent contraception insert removal in 8 women between 2015 and 2017. The authors described their laparoscopic salpingectomy approach and perioperative complications. Overall safety and feasibility with laparoscopic salpingectomy were evaluated by identifying the number of procedures requiring intraoperative conversion to laparotomy, cornuectomy, or hysterectomy. The authors also measured operative time, estimated blood loss, length of stay, and incidence of implant fracture.

Indications for insert removal included pain (n = 4), dyspareunia (n = 2), abnormal uterine bleeding (n = 1), and unsuccessful placement or evidence of tubal occlusion failure during confirmatory imaging (n = 4). The surgeons divided the mesosalpinx and then transected the fallopian tube approximately 1 cm distal to the cornua exposing the permanent contraception insert while avoiding direct electrosurgical application to the insert. The inserts were then removed intact with gentle traction. All 8 women underwent laparoscopic removal with salpingectomy. One patient had a surgical complication of serosal bowel injury due to laparoscopic entry that was repaired in the usual fashion. Operative time averaged 65 minutes (range, 30 to 100 minutes), blood loss was minimal, and there were no implant fractures.

Laparoscopic salpingectomy with insert transection

In this case series, Lazorwitz and Tocce described the use of laparoscopic salpingectomy for hysteroscopic permanent contraception insert removal in 20 women between 2011 and 2017. The authors described their surgical technique, which included division of the mesosalpinx followed by transection of the fallopian tube about 0.5 to 1 cm distal to the cornua. This process often resulted in transection of the insert, and the remaining



WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although both case series were small in sample size, they demonstrated the feasibility of laparoscopic removal of hysteroscopic permanent contraceptive implants. These papers described techniques that can likely be performed by individuals with appropriate laparoscopic skill and experience. The indication for most removals in these reports was pain, unsuccessful placement, or the inability to confirm tubal occlusion by imaging. Importantly, most women do not have these issues, and for those who have been using it successfully, removal is not indicated.

insert was grasped and removed with gentle traction. If removal of the insert was incomplete, hysteroscopy was performed to identify remaining parts.

Indications for removal included pelvic pain (n = 14), abnormal uterine bleeding (n = 2), rash (n = 1), and unsuccessful placement or evidence of tubal occlusion failure during confirmatory imaging (n = 6). Three women underwent additional diagnostic hysteroscopy for retained implant fragments after laparoscopic salpingectomy. Fragments in all 3 women were 1 to 3 mm in size and left in situ as they were unable to be removed or located hysteroscopically. There were no reported postoperative complications including injury, infection, or readmission within 30 days of salpingectomy.

FAST TRACK

Since the introduction of hysteroscopic permanent contraception in 2002, the landscape of contraception has changed in the United States

Shift in method use

Hysteroscopic permanent contraception procedures have low immediate surgical and medical complication rates but result in a high rate of reoperation to achieve the desired outcome. Notably, the largest available comparative trials are from Europe, which may affect the generalizability to US providers, patients, and health care systems.

Importantly, since the introduction of hysteroscopic permanent contraception in 2002, the landscape of contraception has changed in the United States. Contraception use has shifted to fewer permanent procedures and more high-efficacy reversible options. Overall, reliance on female permanent contraception has been declining in the United States, accounting for 17.8% of contracepting women in 1995 and 15.5% in 2013.[27,28] Permanent contraception has begun shifting from tubal interruption to salpingectomy as mounting evidence has demonstrated up to a 65% reduction in a woman's lifetime risk of ovarian cancer.[29–32] A recent study from a large Northern California integrated health system reported an increase in salpingectomy for permanent contraception from 1% of interval procedures in 2011 to 78% in 2016.[33]

Long-acting reversible contraceptive (LARC) methods are also becoming more prevalent and are used by 7.2% of women using contraception in the United States.[28,34] Typical use pregnancy rates with the levonorgestrel 52-mg intrauterine system, etonogestrel implant, and copper T380A intrauterine device are 0.2%, 0.2%, and 0.4% in the first year, respectively.[35,37] These rates are about the same as those reported for Essure in the articles presented here.[13,26] Because these methods are easily placed in the office and are immediately effective, their increased availability over the past decade changes demand for a permanent contraceptive procedure.

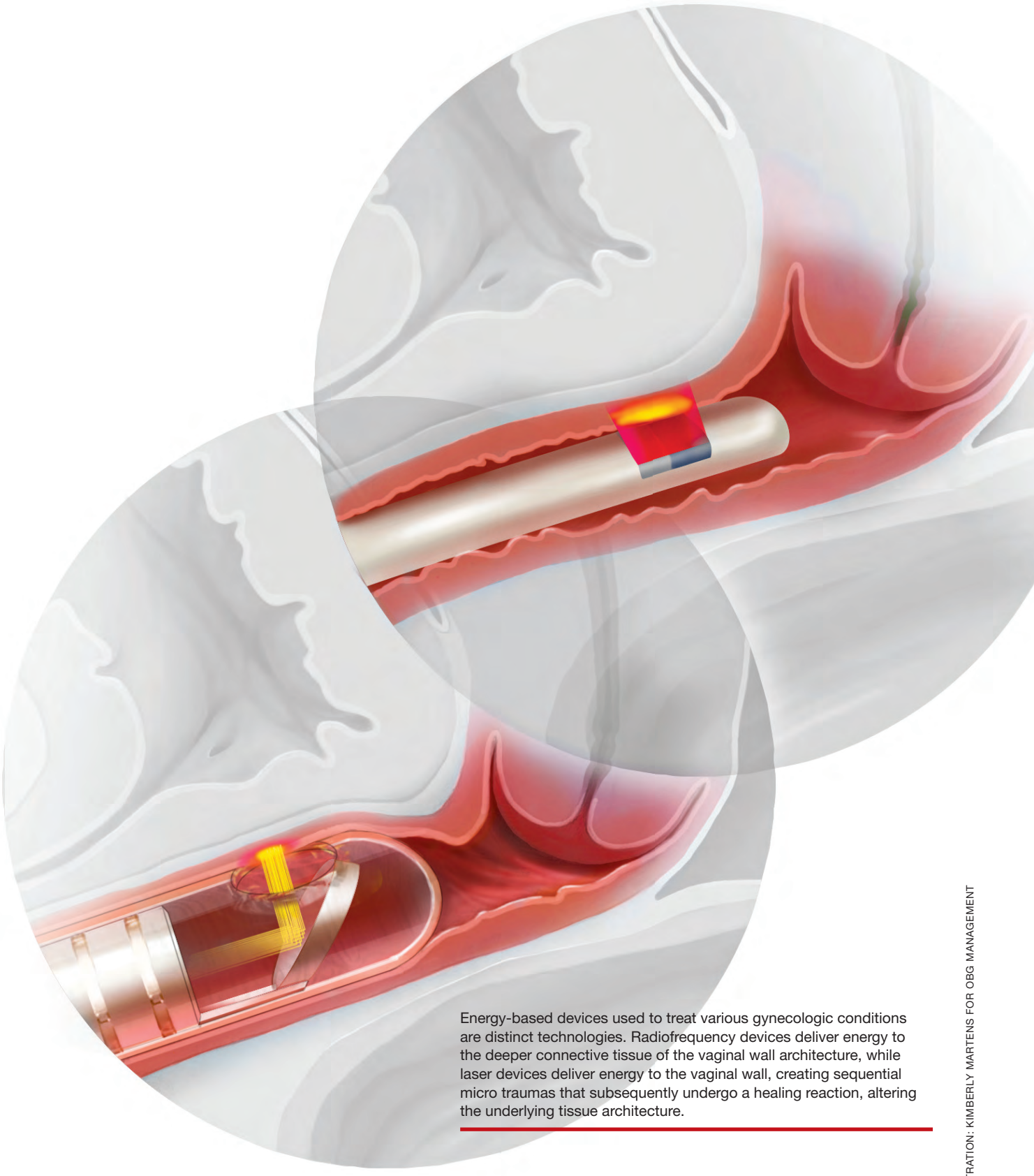
Essure underwent expedited FDA review because it had the potential to fill a contraceptive void—it was considered permanent, highly efficacious, low risk, and accessible to women regardless of health comorbidities or access to hospital operating rooms. The removal of Essure from the market is not only the result of a collection of problem reports (relatively small given the overall number of women who have used the device) but also the aggregate result of a changing marketplace and the differential needs of pharmaceutical companies and patients.

For a hysteroscopic permanent contraception insert to survive as a marketed product, the company needs high volume use. However, the increase in LARC provision and permanent contraceptive procedures using opportunistic salpingectomy have matured the market away from the presently available hysteroscopic method. This technology, in its current form, is ideal for women desiring permanent contraception but who have a

contraindication to laparoscopic surgery, or for women who can access an office procedure in their community but lack access to a hospital-based procedure. For a pharmaceutical company, that smaller market may not be enough. However, the technology itself is still vital, and future development should focus on what we have learned; the ideal product should be immediately effective, not require a follow-up confirmation test, and not leave permanent foreign body within the uterus or tube. ●

References

1. Lawrie TA, Kulier R, Nardin JM. Techniques for the interruption of tubal patency for female sterilisation. Cochrane Database Syst Rev. 2016(8):CD003034. doi:10.1002/14651858.CD003034.pub3.
2. Daniels K, Daugherty J, Jones J, et al. Current contraceptive use and variation by selected characteristics among women aged 15-44: United States, 2011-2013. Natl Health Stat Report. 2015(86):1–14.
3. Kavanaugh ML, Jerman J. Contraceptive method use in the United States: trends and characteristics between 2008, 2012 and 2014. Contraception. 2018;97(1):14–21.
4. Chan LM, Westhoff CL. Tubal sterilization trends in the United States. Fertil Steril. 2010;94(1):1–6.
5. Summary of safety and effectiveness data. FDA website. https://www.accessdata.fda.gov/cdrh_docs/pdf2/P020014b.pdf. Accessed August 2, 2018.
6. Shah V, Panay N, Williamson R, Hemingway A. Hysterosalpingogram: an essential examination following Essure hysteroscopic sterilisation. Br J Radiol. 2011;84(1005):805–812.
7. What is Essure? Bayer website. http://www.essure.com/what-is-essure. Accessed July 6, 2018.
8. Stuart GS, Ramesh SS. Interval female sterilization. Obstet Gynecol. 2018;131(1):117–124.
9. Essure permanent birth control: instructions for use. Bayer website. http://labeling.bayerhealthcare.com/html/products/pi/essure_ifu.pdf. Accessed July 16, 2018.
10. Espey E, Hofler LG. Evaluating the long-term safety of hysteroscopic sterilization. JAMA. 2018;319(4). doi:10.1001/jama.2017.21268.
11. American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 133: benefits and risks of sterilization. Obstet Gynecol. 2013;121(2 pt 1):392–404.
12. Cabezas-Palacios MN, Jiménez-Caraballo A, Tato-Varela S, et al. Safety and patients' satisfaction after hysteroscopic sterilisation. J Obstet Gynaecol. 2018;38(3):377–381.
13. Antoun L, Smith P, Gupta JK, et al. The feasibility, safety, and effectiveness of hysteroscopic sterilization compared with laparoscopic sterilization. Am J Obstet Gynecol. 2017;217(5):570.e571–570.e576.
14. Franchini M, Zizolfi B, Coppola C, et al. Essure permanent birth control, effectiveness and safety: an Italian 11-year survey. J Minim Invasive Gynecol. 2017;24(4):640–645.
15. Vleugels M, Cheng RF, Goldstein J, et al. Algorithm of transvaginal ultrasound and/or hysterosalpingogram for confirmation testing at 3 months after Essure placement. J Minim Invasive Gynecol. 2017;24(7):1128–1135.
16. Essure confirmation test: Essure confirmation test overview. Bayer website. https://www.hcp.essure-us.com/essure-confirmation-test/. Accessed July 16, 2018.
17. Casey J, Cedo-Cintron L, Pearce J, et al. Current techniques and outcomes in hysteroscopic sterilization: current evidence, considerations, and complications with hysteroscopic sterilization micro inserts. Curr Opin Obstet Gynecol. 2017;29(4):218–224.
18. Jeirath N, Basinski CM, Hammond MA. Hysteroscopic sterilization device follow-up rate: hysterosalpingogram versus transvaginal ultrasound. J Minim Invasive Gynecol. 2018;25(5):836–841.
19. US Department of Health and Human Services, US Food & Drug Administration. FDA Activities: Essure. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/ucm452254.htm. Accessed July 6, 2018.
20. Horwell DH. End of the road for Essure? J Fam Plann Reprod Health Care. 2017;43(3):240–241.
21. Mackenzie J. Sterilisation implant withdrawn from non-US sale. BBC News Health. https://www.bbc.com/news/health-41331963. Accessed July 14, 2018.
22. Federal Agency for Medicines and Health Products. ESSURE sterilisation device permanently withdrawn from the market in the European Union. Federal Agency for Medicines and Health Products. https://www.famhp.be/en/news/essure_sterilisation_device_permanently_withdrawn_from_the_market_in_the_european_union. Accessed July 9, 2018.
23. Statement from FDA Commissioner Scott Gottlieb, MD, on manufacturer announcement to halt Essure sales in the US; agency's continued commitment to postmarket review of Essure and keeping women informed [press release]. Silver Spring, MD; US Food and Drug Administration. July 20, 2018.
24. Gariepy AM, Creinin MD, Smith KJ, et al. Probability of pregnancy after sterilization: a comparison of hysteroscopic versus laparoscopic sterilization. Contraception. 2014;90(2):174–181.
25. Gariepy AM, Creinin MD, Schwarz EB, et al. Reliability of laparoscopic compared with hysteroscopic sterilization at 1 year: a decision analysis. Obstet Gynecol. 2011;118(2 pt 1):273–279.
26. Bouillon K, Bertrand M, Bader G, et al. Association of hysteroscopic vs laparoscopic sterilization with procedural, gynecological, and medical outcomes. JAMA. 2018;319(4):375–387.
27. Mosher WD, Martinez GM, Chandra A, et al. Use of contraception and use of family planning services in the United States: 1982–2002. Adv Data. 2004(350):1–36.
28. Mosher WD, Jones J. Use of contraception in the United States: 1982–2008. Vital Health Stat 23. 2010(29):1–44.
29. Falconer H, Yin L, Grönberg H, et al. Ovarian cancer risk after salpingectomy: a nationwide population-based study. J Natl Cancer Inst. 2015;107(2). pii: dju410.doi:10.1093/jnci/dju410.
30. Madsen C, Baandrup L, Dehlendorff C, et al. Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: a nationwide case-control study. Acta Obstet Gynecol Scand. 2015;94(1):86–94.
31. Committee on Gynecologic Practice. Committee opinion no. 620: salpingectomy for ovarian cancer prevention. Obstet Gynecol. 2015;125(1):279–281.
32. Erickson BK, Conner MG, Landen CN. The role of the fallopian tube in the origin of ovarian cancer. Am J Obstet Gynecol. 2013;209(5):409–414.
33. Powell CB, Alabaster A, Simmons S, et al. Salpingectomy for sterilization: change in practice in a large integrated health care system, 2011–2016. Obstet Gynecol. 2017;130(5):961–967.
34. Daniels K, Daugherty J, Jones J. Current contraceptive status among women aged 15–44: United States, 2011–2013. NCHS Data Brief. 2014(173):1–8.
35. Stoddard A, McNicholas C, Peipert JF. Efficacy and safety of long-acting reversible contraception. Drugs. 2011;71(8):969–980.
36. Darney P, Patel A, Rosen K, et al. Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertil Steril. 2009;91(5):1646–1653.
37. Long-term reversible contraception. Twelve years of experience with the TCu380A and TCu220C. Contraception. 1997;56(6):341–352.



Energy-based devices used to treat various gynecologic conditions are distinct technologies. Radiofrequency devices deliver energy to the deeper connective tissue of the vaginal wall architecture, while laser devices deliver energy to the vaginal wall, creating sequential micro traumas that subsequently undergo a healing reaction, altering the underlying tissue architecture.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

The techno vagina: The laser and radiofrequency device boom in gynecology

Michael Krychman, MD

Energy-based devices are being used to treat vaginal, vulvar, and sexual symptoms, but we need more clinical evidence of efficacy and safety and standardized patient selection criteria before we incorporate these high-tech therapies into the treatment paradigm

In recent years, an increasing number of laser and radiofrequency device outpatient treatments have been heralded as safe and effective interventions for various gynecologic conditions. Laser devices and radiofrequency technology rapidly have been incorporated into certain clinical settings, including medical practices specializing in dermatology, plastic surgery, and gynecology. While this developing technology has excellent promise, many clinical and research questions remain unanswered.

Concerns about energy-based vaginal treatments

Although marketing material often suggests otherwise, most laser and radiofrequency devices are cleared by the US Food and Drug Administration (FDA) only for nonspecific gynecologic and hematologic interventions. However, both laser and radiofrequency device treatments, performed as outpatient procedures, have been touted as appropriate interventions for many conditions, including female sexual dysfunction, arousal and orgasmic concerns, vaginal laxity, vaginismus, lichen sclerosus, urinary incontinence, and vulvar vestibulitis.

Well-designed studies are needed. Prospective, randomized sham-controlled trials of energy-based devices are rare, and most data in the public domain are derived from case series. Many studies are of short duration with limited follow-up. Randomized controlled trials therefore are warranted and should have stringent inclusion and exclusion criteria. Body dysmorphic syndrome, for example, should be a trial exclusion. Study design for research should include the use of standardized, validated scales and long-term follow-up of participants.

Which specialists have the expertise to offer treatment? Important ethical and medical concerns regarding the technology need to be addressed. A prime concern is determining which health care professional specialist is best qualified to assess and treat underlying gynecologic conditions. It is not uncommon to see internists, emergency medicine providers, family physicians, plastic surgeons, psychiatrists, and dermatologists self-proclaiming their gynecologic "vaginal rejuvenation" expertise.

In my experience, some ObGyns have

Dr. Krychman is Executive Director, Southern California Center for Sexual Health and Survivorship Medicine, Newport Beach, California.

Dr. Krychman reports that he is a consultant and speaker for Viveve Medical. He has a Viveve radiofrequency device in his private clinical office.

IN THIS ARTICLE

voiced concern about the diverse medical specialties involved in performing these procedures. Currently, no standard level of training is required to perform them. In addition, those providers lack the training needed to adequately and accurately assess the potential for confounding, underlying gynecologic pathology, and they are inadequately trained to offer patients the full gamut of therapeutic interventions. Many may be unfamiliar with female pelvic anatomy and sexual function and a multidisciplinary treatment paradigm.

We need established standards. A common vernacular, nosology, classification, and decision-tree assessment paradigm for genitopelvic laxity (related to the condition of the pelvic floor and not simply a loose feeling in the vagina) is lacking, which may make research and peer-to-peer discussions difficult.

Which patients are appropriate candidates? Proper patient selection criteria for energy-based vaginal treatment have not been standardized, yet this remains a paramount need. A comprehensive patient evaluation should be performed and include a discussion on the difference between an aesthetic complaint and a functional medical problem. Assessment should include the patient's level of concern or distress and the impact of her symptoms on her overall quality of life. Patients should be evaluated for body dysmorphic syndrome and relationship discord. A complete physical examination, including a detailed pelvic assessment, often is indicated. A treatment algorithm that incorporates conservative therapies coupled with medical, technologic, and psychologic interventions also should be developed.

FAST TRACK

Radiofrequency and laser device technologies are separate and distinct technologies with similar and differing proposed utilizations

Various energy-based devices are available for outpatient procedures

Although the number of procedures performed (such as vaginal rejuvenation, labiaplasty, vulvar liposculpturing, hymenoplasty, G-spot amplification, and O-Shot treatment) for both cosmetic and functional problems has increased, the published scientific data on the procedures' short- and long-term efficacy and safety are limited. The American College of Obstetricians and Gynecologists (ACOG) published a committee opinion stating that many of these procedures, including "vaginal rejuvenation," may not be considered medically indicated and may lack scientific merit or ample supportive data to confirm their efficacy and safety.[1] ObGyns should proceed with caution before incorporating these technologic treatments into their medical practice.

Much diversity exists within the device-technology space. The underpinnings of each device vary regarding their proposed mechanism of action and theoretical therapeutic and tissue effect. In device marketing materials, many devices have been claimed to have effects on multiple tissue types (for example, both vaginal mucosa and vulvar tissue), whereas others are said to have more focal and localized effects (that is, targeted behind the hymenal ring). Some are marketed as a one-time treatment, while others require multiple repeated treatments over an extended period. When it comes to published data, adverse effect reporting remains limited and follow-up data often are short term.

Radiofrequency and laser devices are separate and very distinct technologies with similar and differing proposed utilizations. Combining radiofrequency and laser treatments in tandem or sequentially may have clinical utility, but long-term safety may be a concern for lasers.

Radiofrequency-based devices

Typically, radiofrequency device treatments:

- are used for outpatient procedures
- do not require topical anesthesia
- are constructed to emit focused electromagnetic waves
- are applied to vaginal, vulvar, or vaginal introital or vestibular tissue
- deliver energy to the deeper connective tissue of the vaginal wall architecture.

Radiofrequency device energy can be monopolar, unipolar, bipolar, or multipolar depending on design. Design also dictates

current and the number of electrodes that pass from the device to the grounding pad. Monopolar is the only type of radiofrequency that has a grounding pad; bipolar and multipolar energy returns to the treatment tip.

Radiofrequency devices typically are FDA 510(k)-cleared devices for nonspecific electrocoagulation and hemostasis for surgical procedures. None are currently FDA cleared in the United States for the treatment of vaginal or vulvar laxity or genitourinary syndrome of menopause (GSM). These energy-based devices aim to induce collagen contraction, neocollagenesis, vascularization, and growth factor infiltration to restore the elasticity and moisture of the underlying vaginal mucosa. Heat shock protein activation and inflammation activation are thought to be the underlying mechanisms of action.[2–5]

Treatment outcomes with 2 radiofrequency devices

Multiple prospective small case series studies have reported outcomes of women treated with the ThermiVa (ThermiAesthetics LLC) radiofrequency system.[3,4] Typically, 3 treatments (with a between-treatment interval of 4 to 6 weeks) were applied. The clinical end point temperature had a range of 40°C to 45°C, which was maintained for 3 to 5 minutes per treated zone during 30 minutes' total treatment time.

Some participants self-reported improvement in vaginal laxity symptoms with the 3 treatments. In addition, women reported subjective improvements in both vaginal atrophy symptoms and sexual function, including positive effect in multiple domains. No serious adverse events were reported in these case series. However, there was no placebo-controlled arm, and validated questionnaires were not used in much of this research.[3,4]

In another trial, the ThermiVa system was studied in a cohort of 25 sexually active women with self-reported anorgasmia or increased latency to orgasmic response.[6] Participants received 3 treatments 4 weeks apart. Approximately three-quarters of the participants reported improved orgasmic responsivity, vaginal lubrication, and clitoral sensitivity. Notably, this research did not use validated questionnaires or a placebo or sham-controlled design. The authors suggested sustained treatment benefits at 9 to 12 months. While repeat treatment was advocated, data were lacking to support the optimal time for repeat treatment efficacy.[6]

A cryogen-cooled monopolar radiofrequency device, the Viveve system (Viveve Medical, Inc) differs from other radiofrequency procedures because it systematically cryogen cools and protects the surface of the vaginal mucosal tissue while heating the underlying structures.

The Viveve system was evaluated in 2 small pilot studies (24 and 30 participants) and in a large, randomized, sham-controlled, prospective trial that included 108 participants (VIVEVE I trial).[5,7,8] Results from both preliminary small studies indicated that participants experienced significant improvement in overall sexual function at 6 months. In one of the small studies (in Japanese women), sustained efficacy at 12 months posttreatment was reported.[7] Neither small study included a placebo-control arm, but they did include the use of validated questionnaires.

In the VIVEVE I trial (a multicenter international study), treatment in the active group consisted of a single, 30-minute outpatient procedure that delivered 90 J/cm^2 of radiofrequency energy at the level just behind the hymenal ring behind the vaginal introitus. The sham-treated group received ≤1 J/cm^2 of energy with a similar machine tip.[8]

Statistically significant improvements were reported in the arousal and orgasm domains of the validated Female Sexual Function Index (FSFI) for the active-treatment group compared with the sham-treated group. In addition, there were statistically significant differences in the FSFI and the Female Sexual Distress Scale–Revised total scores in favor of active treatment. Participants in the active-treatment arm reported statistically significant improvement in overall sexual satisfaction coupled with lowered overall sexual distress.[8]

FAST TRACK

Radiofrequency devices aim to induce collagen contraction, neocollagenesis, vascularization, and growth factor infiltration to restore the elasticity and moisture of the underlying vaginal mucosa

CONTINUED ON PAGE 44

CONTINUED FROM PAGE 43

These data are provocative, since the Viveve treatment demonstrated superior efficacy compared with the sham treatment, and prior evidence demonstrated that medical device trials employing a sham arm often demonstrate particularly large placebo/sham effects.[9] A confirmatory randomized, sham-controlled multicenter US-based trial is currently underway. At present, the VIVEVE I trial remains the only published, large-scale, randomized, sham-controlled, blinded study of a radiofrequency-based treatment.

New emerging data support the efficacy and safety of this specific radiofrequency treatment in patients with mild to moderate urinary stress incontinence; further studies confirming these outcomes are anticipated. The Viveve system is approved in many countries for various conditions, including urinary incontinence (1 country), sexual function (17 countries), vaginal laxity (41 countries), and electrocoagulation and hemostasis (4 countries, including the United States).

FAST TRACK

Laser technology is promising for the treatment of GSM symptoms by virtue of its superficial mechanism of action; several trials have shown efficacy and safety in breast cancer patients

Laser technology devices

Laser (Light Amplification by Stimulated Emission of Radiation) therapy, which uses a carbon dioxide (CO2), argon, YAG, or erbium energy source, also is currently marketed as a method to improve various gynecologic conditions, including genital pelvic relaxation syndrome, vaginal laxity, GSM, lichen sclerosus, and sexual problems such as dyspareunia and arousal or orgasmic disorders.

The CO2 laser therapy device, such as the MonaLisa Touch (DEKA Laser), appears to be very popular and widely available. It delivers fractional CO2 laser energy to the vaginal wall, creating sequential micro traumas that subsequently undergo a healing reaction; the newly healed area has an improved underlying tissue architecture (but at a superficial level). The laser's proposed mechanism of action is that it ablates only a minute fraction of the superficial lamina propria; it acts primarily to stimulate rapid healing of the tissue, creating new collagen and elastic fibers. There is no evidence of scarring.[10]

Treatment outcomes with laser device therapy

Authors of a 2017 study series of CO2 laser treatments in women with moderate to severe GSM found that 84% of participants experienced significant improvement in sexual function, dyspareunia, and otherwise unspecified sexual issues from pretreatment to 12 to 24 months posttreatment.[11] These findings are consistent with several other case series and provide supportive evidence for the efficacy and safety of CO2 laser therapy. This technology may be appropriate for the treatment of GSM.

Laser technology shows excellent promise for the treatment of GSM symptoms by virtue of its superficial mechanism of action. In addition, several trials have demonstrated efficacy and safety in breast cancer patient populations.[12] This is particularly interesting since breast cancer treatments, such as aromatase inhibitors (considered a mainstay of cancer treatment), can cause severe atrophic vaginitis. Breast cancer survivors often avoid minimally absorbed local vaginal hormonal products, and over-the-counter products (moisturizers and lubricants) are not widely accepted. Hence, a nonhormonal treatment for distressing GSM symptoms is welcomed in this population.

Pagano and colleagues recently studied 82 breast cancer survivors in whom treatment with vaginal moisturizers and lubricants failed.[12] Participants underwent 3 laser treatment cycles approximately 30 to 40 days apart; they demonstrated improvements in vaginal dryness, vaginal itchiness, stinging, dyspareunia, and reduced sensitivity.

Microablative fractional CO2 laser may help reestablish a normative vaginal microbiome by altering the prevalence of lactobacillus species and reestablishing a normative postmenopausal vaginal flora.[13]

The tracking and reporting of adverse events associated with laser procedures has been less than optimal. In my personal clinical experience, consequences from both short- and long-term laser treatments have included vaginal canal agglutination, worsening dyspareunia, and constricture causing vaginal hemorrhage.

Cruz and colleagues recently conducted a randomized, double-blind, placebo-controlled clinical trial designed to evaluate the efficacy of fractional CO2 laser compared with topical estriol and laser plus estriol for the treatment of vaginal atrophy in 45 postmenopausal women.[14] They found statistically significant differences in dyspareunia, dryness, and burning compared with baseline levels in all 3 treatment groups. Results with the fractional CO2 laser treatment were deemed to be similar to those of the topical estriol and the combined therapy.[14]

By contrast, an erbium (Er):YAG laser, such as the IntimaLase (Fotona, LLC) laser, functions by heating the pelvic tissue and collagen within the introitus and vaginal canal.[15,16] When the underlying collagen is heated, the fibers are thought to thicken and shorten, which may result in immediate contracture of the treated tissue. Additionally, this process stimulates the existing collagen to undergo remodeling and it also may cause neocollagen deposition.[15] In a general review of gynecologic procedures, after 1 to 4 treatment sessions (depending on the study), most patients reported improved sexual satisfaction or vaginal tightness.[15]

Although trials have included small numbers of patients, early evidence suggests some lasers with reportedly deeper penetration may be useful for treatment of vaginal laxity, but further studies are needed. In smaller studies, the Er:YAG laser has shown efficacy and safety in the treatment of stress urinary incontinence and improved lower urinary tract symptoms, quality of life, and sexual function.[16,17]

Insurance does not cover energy-based treatment costs

Currently, both laser and radiofrequency device treatments are considered fee-for-service interventions. Radiofrequency and laser treatments for gynecologic conditions are not covered by health insurance, and treatment costs can be prohibitive for many patients. In addition, the long-term safety of these treatments remains to be studied further, and the optimal time for a repeat procedure has yet to be elucidated.

Medications are still the principle treatment for dyspareunia

Despite recent technologic advancements and applications in gynecologic care, minimally absorbed local vaginal hormonal products (creams, rings, intravaginal tablets) and estrogen agonists/antagonists remain the mainstay and frontline treatment for moderate to severe dyspareunia, a symptom of vulvovaginal atrophy due to menopause. Newer medications, such as intravaginal steroids[1] and the recently approved bioidentical estradiol nonapplicator vaginal inserts,[2] also offer excellent efficacy and safety in the treatment of this condition. These medications now are included under expanded insurance coverage, and they offer safe, simple, and cost-effective treatments for this underdiagnosed condition.

References
1. Intrarosa [package insert]. Waltham, MA: AMAG Pharmaceuticals Inc; February 2018.
2. Imvexxy [package insert]. Boca Raton, FL: TherapeuticsMD; 2018.

The FDA cautions against energy-based procedures

In July 2018, the FDA released a statement of concern reiterating the need for research and randomized clinical trials before energy-based device treatments can be widely accepted, and that they are currently cleared only for general gynecologic indications and not for disorders and symptoms related to menopause, urinary incontinence, or sexual function.[18]

The FDA stated that "we have not cleared or approved for marketing any energy-based devices to treat these symptoms or conditions [vaginal laxity; vaginal atrophy, dryness, or itching; pain during sexual intercourse; pain during urination; decreased sexual sensation], or any symptoms related to menopause, urinary incontinence, or sexual function." The FDA noted that serious complications have been reported, including vaginal burns, scarring, pain during sexual intercourse, and recurring, chronic pain. The FDA issued letters to 7 companies regarding concerns about the marketing of their devices for off-label use and promotion.

Several societies have responded. ACOG reaffirmed its 2016 position statement on fractional laser treatment of vulvovaginal atrophy.[19] JoAnn Pinkerton, MD, Executive Director of The North American Menopause

FAST TRACK

Energy-based device treatments are FDA cleared only for general gynecologic indications—not for symptoms related to menopause, urinary incontinence, or sexual function

Society (NAMS), and Sheryl Kingsberg, PhD, President of NAMS, alerted their members that both health care professionals and consumers should tread cautiously, and they encouraged scrutiny of existing evidence as all energy-based treatments are not created equal.[20] They noted that some research does exist and cited 2 randomized, sham-controlled clinical trials that have been published.

Looking forward

Various novel technologic therapies are entering the gynecologic market. ObGyns must critically evaluate these emerging technologies with a keen understanding of their underlying mechanism of action, the level of scientific evidence, and the treatment's proposed therapeutic value.

Radiofrequency energy devices appear to be better positioned to treat urinary incontinence and vaginal relaxation syndrome because of their capability for deep tissue penetration. Current data show that laser technology has excellent promise for the treatment and management of GSM. Both technologies warrant further investigation in long-term randomized, sham-controlled trials that assess efficacy and safety with validated instruments over an extended period. In addition, should these technologies prove useful in the overall treatment armamentarium for gynecologic conditions, the question of affordability and insurance coverage needs to be addressed.

ObGyns must advocate for female sexual wellness and encourage a comprehensive multidisciplinary team approach for offering various therapies. Ultimately, responsible use of evidence-based innovative technology should be incorporated into the treatment paradigm. ●

FAST TRACK

Both radiofrequency and laser technologies warrant further investigation in long-term randomized, sham-controlled trials to assess efficacy and safety with validated instruments

References

1. ACOG Committee on Gynecologic Practice. ACOG Committee Opinion No. 378: Vaginal "rejuvenation" and cosmetic vaginal procedures. Obstet Gynecol. 2007;110(3):737–738.
2. Dunbar SW, Goldberg DJ. Radiofrequency in cosmetic dermatology: an update. J Drugs Dermatol. 2015;14(11):1229–1238.
3. Leibaschoff G, Izasa PG, Cardona JL, Miklos JR, Moore RD. Transcutaneous temperature-controlled radiofrequency (TTCRF) for the treatment of menopausal vaginal /genitourinary symptoms. Surg Technol Int. 2016;29:149–159.
4. Alinsod RM. Temperature controlled radiofrequency for vulvovaginal laxity. Prime J. July 23, 2015. https://www.prime-journal.com/temperature-controlled-radiofrequency-for-vulvovaginal-laxity/. Accessed August 15, 2018.
5. Millheiser LS, Pauls RN, Herbst SJ, Chen BH. Radiofrequency treatment of vaginal laxity after vaginal delivery: nonsurgical vaginal tightening. J Sex Med. 2010;7(9):3088–3095.
6. Alinsod RM. Transcutaneous temperature controlled radiofrequency for orgasmic dysfunction. Lasers Surg Med. 2016;48(7):641–645.
7. Sekiguchi Y, Utsugisawa Y, Azekosi Y, et al. Laxity of the vaginal introitus after childbirth: nonsurgical outpatient procedure for vaginal tissue restoration and improved sexual satisfaction using low-energy radiofrequency thermal therapy. J Womens Health (Larchmt). 2013;22 (9):775–781 .
8. Krychman M, Rowan CG, Allan BB, et al. Effect of single-treatment, surface-cooled radiofrequency therapy on vaginal laxity and female sexual function: the VIVEVE I randomized controlled trial. J Sex Med. 2017;14(2):215–225.
9. Kaptchuk TJ, Goldman P, Stone DA, Statson WB. Do medical devices have enhanced placebo effects? J Clin Epidemiol. 2000;53(8): 786–792.
10. Gotkin RH, Sarnoff SD, Cannarozzo G, Sadick NS, Alexiades-Armenakas M. Ablative skin resurfacing with a novel microablative CO2 laser. J Drugs Dermatol. 2009;8(2):138–144.
11. Behnia-Willison F, Sarraf S, Miller J, et al. Safety and long-term efficacy of fractional CO2 laser treatment in women suffering from genitourinary syndrome of menopause. Eur J Obstet Gynecol Reprod Biol. 2017;213:39–44.
12. Pagano T, De Rosa P, Vallone R, et al. Fractional microablative CO2 laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments, a retrospective study. Menopause. 2018;25(6):657–662.
13. Anthanasiou S, Pitsouni E, Antonopoulou S, et al. The effect of microablative fractional CO2 laser on vaginal flora of postmenopausal women. Climateric. 2016;19(5):512–518.
14. Cruz VL, Steiner ML, Pompei LM, et al. Randomized, double-blind placebo-controlled clinical trial for evaluating the efficacy of fractional CO2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. Menopause. 2018;25(1): 21–28.
15. Vizintin Z, Rivera M, Fistonic I, et al. Novel minimally invasive VSP Er:YAG laser treatments in gynecology. J Laser Health Acad. 2012;2012(1):46–58.
16. Tien YM, Hsio SM, Lee CN, Lin HH. Effects of laser procedure for female urodynamic stress incontinence on pad weight, urodynamics, and sexual function. Int Urogynecol J. 2017;28 (3):469–476.
17. Oginc UB, Sencar S, Lenasi H. Novel minimally invasive laser treatment of urinary incontinence in women. Laser Surg Med. 2015;47(9):689-697.
18. US Food and Drug Administration. FDA warns against use of energy based devices to perform vaginal 'rejuvenation' or vaginal cosmetic procedures: FDA safety communication. July 30, 2018. https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm615013.htm. Accessed August 16, 2018.
19. The American College of Obstetricians and Gynecologists. Fractional laser treatment of vulvovaginal atrophy and US Food and Drug Administration clearance: position statement. May 2016. https://www.acog.org/Clinical-Guidance-and-Publications/Position-Statements/Fractional-Laser-Treatment-of-Vulvovaginal-Atrophy-and-US-Food-and-Drug-Administration-Clearance. Accessed August 16, 2018.
20. The North American Menopause Society. FDA mandating vaginal laser manufacturers present valid data before marketing. August 1, 2018. https://www.menopause.org/docs/default-source/default-document-library/nams-responds-to-fda-mandate-on-vaginal-laser-manufacturers-08-01-2018.pdf. Accessed August 16, 2018.

JOIN YOUR COLLEAGUES AT THESE
CME/CE COURSES

Global Academy for Medical Education

PAIN CARE/PRIMARY CARE

PAINCARE FOR PRIMARYCARE

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

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

PCPC-cme.com

DERMATOLOGY

SKIN DISEASE EDUCATION FOUNDATION PRESENTS
19TH ANNUAL
Las Vegas Dermatology Seminar®
FEATURING THE 15TH ANNUAL PSORIASIS FORUM

NOVEMBER 1-3, 2018
Caesars Palace | Las Vegas, Nevada

17.5 CME/CE Credits Available

GlobalAcademyCME.com/SDEFLasVegasDerm

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

MENTAL HEALTH

Current Psychiatry | AACP American Academy of Clinical Psychiatrists
PRESENT
ENCORE!
PSYCHIATRY UPDATE 2018
SOLVING CLINICAL CHALLENGES, IMPROVING PATIENT CARE

DECEMBER 2-4, 2018
Encore at Wynn Las Vegas

22 CME Credits Available

CPAACP-cme.com/site/encore

EMERGENCY MEDICINE

Created especially for primary care physicians, NPs, and PAs

Created Especially for PAs, NPs & Primary Care Physicians!
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.

Delayed diagnosis of breast cancer: $15M award

A WOMAN IN HER MID-50S had been seen by a breast surgeon for 16 years for regular mammograms and sonograms. In May 2009, the breast surgeon misinterpreted a mammogram as negative, as did a radiologist who re-read the mammogram weeks later. In December 2010, the patient returned to the breast surgeon with nipple discharge. No further testing was conducted. In October 2011, the patient was found to have Stage IIIA breast cancer involving 4 lymph nodes. She underwent left radical mastectomy, chemotherapy, radiation therapy, and breast reconstruction. At time of trial, the cancer had invaded her vertebrae, was Stage IV, and most likely incurable.

PATIENT'S CLAIM: Although the surgeon admittedly did not possess the qualifications required under the Mammography Quality Standards Act, he interpreted about 5,000 mammograms per year in his office. In this case, he failed to detect a small breast tumor in May 2009. He also failed to perform testing when the patient reported nipple discharge. A more timely diagnosis of breast cancer at Stage I would have provided a 90% chance of long-term survival.

DEFENDANTS' DEFENSE: The defense held the radiologist fully liable because the surgeon was not a qualified interpreter of mammography, therefore relying on the radiologist's interpretation. The radiologist was legally responsible for the missed diagnosis.

VERDICT: A $15M New York verdict was reached, finding the breast surgeon 75% at fault and the radiologist 25%. The radiologist settled before the trial (the jury was not informed of this). The breast surgeon was responsible for $11.25M. The defense indicated intent to appeal.

Alleged failure to evacuate uterus after cesarean delivery

A 37-YEAR-OLD WOMAN underwent cesarean delivery (CD) performed by 2 ObGyns. After delivery, she began to hemorrhage and the uterus became atonic. Hysterectomy was performed but the bleeding did not stop. The ObGyns called in 3 other ObGyns. During exploratory laparotomy, the bleeding was halted.

PATIENT'S CLAIM: She and her husband had hoped to have more children but the hysterectomy precluded that. She sued all 5 ObGyns, alleging that the delivering ObGyns failed to properly perform the CD and that each physician failed to properly perform the laparotomy, causing a large scar. The claim was discontinued against the 3 surgical ObGyns; trial addressed the 2 delivering ObGyns.

The patient's expert ObGyn remarked that the hemorrhage was caused by a small placental remnant that remained in the uterus as a result of inadequate evacuation following delivery. The presence of the remnant was indicated by the uterine atony and should have prompted immediate investigation. The physicians' notes did not document exploration of the uterus prior to closure.

PHYSICIANS' DEFENSE: The defense's expert contended that atony would not be a result of a small remnant of placenta. The patient's uterus was properly evacuated, the hemorrhage was an unforeseeable complication, and the ObGyns properly addressed the hemorrhage.

VERDICT: A New York defense verdict was returned.

Alleged bowel injury during hysterectomy

TWO DAYS AFTER a woman underwent a hysterectomy performed by her ObGyn, she went to the emergency department with increasing pain. Her ObGyn admitted her to the hospital. A general surgeon performed an exploratory laparotomy the next day that revealed an abscess; a 1-cm perforation of the patient's bowel was surgically repaired. The patient had a difficult recovery. She developed pneumonia and respiratory failure. She underwent multiple repair surgeries for recurrent abscesses and fistulas because the wound was slow to heal.

PATIENT'S CLAIM: The ObGyn's surgical technique was negligent. He injured the bowel when inserting a trocar and did not identify the injury in a timely manner. The expert witness commented that such an injury can sometimes be a surgical complication, but not in this case: the ObGyn rushed the procedure because he had another patient waiting for CD at another hospital.

PHYSICIAN'S DEFENSE: The ObGyn denied negligence and contended that the trocar used in surgery was too blunt to have caused a perforation. It would have been obvious to the ObGyn during surgery if a perforation had occurred. The perforation developed days after surgery within an abscess.

VERDICT: A Mississippi defense verdict was returned. ●

These cases were selected by the editors of OBG MANAGEMENT *from* Medical Malpractice Verdicts, Settlements, & Experts, *with permission of the editor, Lewis Laska (www.verdictslaska.com). The information available to the editors about the cases presented here is sometimes incomplete. Moreover, the cases may or may not have merit. Nevertheless, these cases represent the types of clinical situations that typically result in litigation and are meant to illustrate nationwide variation in jury verdicts and awards.*

PRODUCT Update

SURGICAL SITE WOUND THERAPY

PICO NPWT is a negative-pressure wound therapy device to treat surgical site infection (SSI). According to **Smith & Nephew,** a new meta-analysis demonstrates that the prophylactic application of **PICO** with AIRLOCK™ Technology significantly reduces surgical site complications by 58%, the rate of dehiscence by 26%, and length of stay by one-half day when compared with standard care.

The PICO System is canister-free and disposable. Patients can be discharged safely with PICO in place. Seven days of therapy are provided in each kit, with 1 pump, 2 dressings, and fixation strips to allow for a dressing change.

PICO uses a 4-layer multifunction dressing design in which the layers work together to ensure that negative pressure is delivered to the wound bed and exudate is removed through absorption and evaporation. Approximately 20% of fluid still remains in the dressing. The top film layer has a high-moisture vapor transmission rate to transpire as much as 80% of the exudate, says **Smith & Nephew.**

FOR MORE INFORMATION, VISIT:
http://www.smith-nephew.com/

SHIELDED LAPAROSCOPIC INSTRUMENTS PREVENT BURNS

Encision's patented **Active Electrode Monitoring (AEM®) Shielded Laparoscopic Instruments** eliminate patient burns and the associated complications.

Every 90 minutes in the United States, a patient is severely injured from a stray energy burn during laparoscopic surgery, according to **Encision**. The **AEM® Shielded Instruments** are designed to eliminate burns caused by monopolar energy insulation failure and capacitive coupling, reducing complications and readmissions.

In addition to helping health care professionals improve patient safety in line with a recent FDA safety communication, **Active Electrode Monitoring** is a recommended practice of AORN and AAGL.

Encision offers a complete line of premium laparoscopic monopolar surgical instruments with integrated **AEM®** technology as well as complimentary products to improve clinical effectiveness and patient safety, including bipolar and cold instrumentation.

FOR MORE INFORMATION, VISIT: https://www.encision.com/

iSORT: 7-DAY BLUETOOTH PILLBOX

TimerCap has a new Bluetooth-enabled 7-day pill box called the **iSort** that sends reminders to take medication to a patient's phone using a free TimerCap App found at the AppStore and Android Market.

The **iSort** automatically records and stores the times when each door/slot is opened and closed. It knows which door has been used and seamlessly updates the TimerCap App. The app will notify the patient and, if designated, a caregiver, whenever a dose is due or missed using pictures to show what and how many meds are scheduled. More than one **iSort** box can be used with the app.

iSort provides reminders that help improve adherence to medication dosing instructions and eliminates annoying false alarms, double entries, and unnecessary reminders when pills already have been taken. The portable **iSort** uses 2 AA batteries that need to be changed about once per year.

FOR MORE INFORMATION, VISIT:
https://www.timercap.com/isort

PLATFORM TO COORDINATE HEALTH AND TECHNOLOGY

The **American Medical Association** (AMA)recently has established a new initiative that introduces a solution to improve, organize, and share health care information. The **Integrated Health Model Initiative (IHMI)** is a platform that coordinates the health and technology sectors around a common data model. **IHMI** fills the national imperative to pioneer a shared framework for organizing health data, emphasizing patient-centric information, and refining data elements to those most predictive of better outcomes. The **AMA** says that evolving available health data to depict a complete picture of a patient's journey from wellness to illness to treatment and beyond allows health care delivery to fully focus on patient outcomes, goals, and wellness. Participation in **IHMI** is open to all health care and technology stakeholders.

FOR MORE INFORMATION, VISIT: www.ama-assn.org/ihmi

CONTINUED FROM PAGE 31

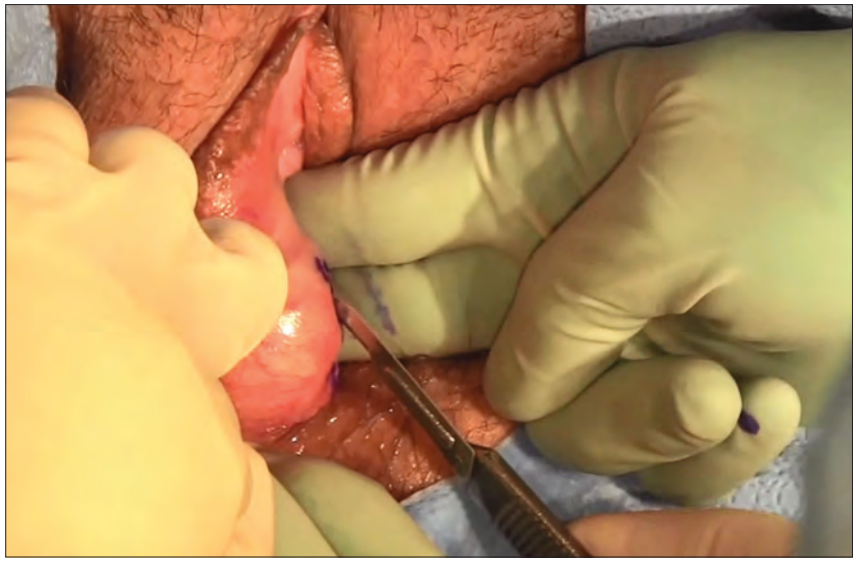
15. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002;359:1877–1890.
16. Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: lessons learned from recent trials. Am J Obstet Gynecol. 2004;190:1520–1526.
17. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016;374:1311–1320.
18. Publications Committee, Society for Maternal-Fetal Medicine, Sibai BM. Evaluation and management of severe preeclampsia before 34 weeks' gestation. Am J Obstet Gynecol. 2011;205:191–198.
19. Norwitz E, Funai E. Expectant management of severe preeclampsia remote from term: hope for the best, but expect the worst. Am J Obstet Gynecol. 2008;199:209–212.
20. Gordon R, Magee LA, Payne B, et al. Magnesium sulphate for the management of preeclampsia and eclampsia in low and middle income countries: a systematic review of tested dosing regimens. J Obstet Gynaecol Can. 2014;36(2):154–163.
21. Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstet Gynecol. 2005;105(2):402–410.
22. Liu S, Joseph KS, Liston, RM, et al; Maternal Health Study Group of Canadian Perinatal Surveillance System (Public Health Agency of Canada). Incidence, risk factors, and associated complications of eclampsia. Obstet Gynecol. 2011;118(5):987–994.
23. Yancey LM, Withers E, Bakes K, Abbot J. Postpartum preeclampsia: emergency department presentation and management. J Emerg Med. 2011;40:380–384.
24. Sibai BM. Etiology and management of postpartum hypertension-preeclampsia. Am J Obstet Gynecol. 2012;206:470–475.
25. You WB, Wolf MS, Bailey SC, Grobman WA. Improving patient understanding of preeclampsia: a randomized controlled trial. Am J Obstet Gynecol. 2012;206:431.e1–e5.
26. Henderson JT, Whitlock EP, O'Connor E, et al. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the US Preventive Services Task Force. Ann Intern Med. 2014;160:695–703.
27. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol. 2017;216(2):110–120.e6.
28. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335:974–986.
29. McDonald SD, Malinowski A, Zhou Q, et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156:918–930.

INDEX OF ADVERTISERS

Excision of a Bartholin gland cyst

Anatomy and pathologies review followed by surgical technique

Lisa R. Gabor, MD; Patricia J. Mattingly, MD; and Jin Hee Kim, MD



To view the video
Visit Arnold Advincula's Surgical Techniques Video Channel in the Multimedia Library at **mdedge.com/obgmanagement** or use the QR code

Bartholin gland cysts comprise up to 2% of all outpatient gynecology visits each year[1] and are a common consult for trainees in obstetrics and gynecology. Although excision of a Bartholin gland cyst is a procedure performed infrequently, knowledge of its anatomy and physiology is important for ObGyn trainees and practicing gynecologists, especially when attempts at conservative management have been exhausted.

Before proceeding with surgical excision, it is important to understand the basics of Bartholin gland anatomy, pathologies, and treatment options. This video demonstrates the excisional technique for a 46-year-old woman with a recurrent, symptomatic Bartholin gland cyst who failed prior conservative management. I hope that you will find this video from my colleagues beneficial to your clinical practice. ●

Reference

1. Marzano DA, Haefner HK. The bartholin gland cyst: past, present, and future. J Low Genit Tract Dis. 2004;8(3):195–204.

Dr. Gabor is PGY-4 Resident, Columbia University Medical Center, New York, New York.

Dr. Mattingly is from Novant Health Pelvic Health & Surgery, Winston-Salem, North Carolina.

Dr. Kim is Assistant Clinical Professor of Obstetrics and Gynecology at Columbia University College of Physicians and Surgeons in the Division of Gynecologic Surgical Services.

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

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

Operative Hysteroscopy
~~capital cost and complexity~~

LiNA **OperåScope™**
Single-Use Operative Hysteroscopy System

Introducing LiNA OperåScope™, the first and only fully disposable, operative hysteroscopy system. Developed specifically for the office, the convenient single-use design is ready for use out of the box without the cost and complexity of traditional hysteroscopy. Turn every exam room into an operative hysteroscopy suite with the complete system for operative hysteroscopy, LiNA OperåScope™.

LiNA Medical
Formervangen 5, 2600 Glostrup, Denmark | Tel: (855) 546-2633 | www.linamed.com