CONTEMPORARY OB/GYN OCTOBER 2014, Vol. 59, No. 10

SPECIAL TECHNOLOGY SECTION ■ PROS AND CONS OF VAGINAL MESH ■ HYSTERECTOMY AND URETERAL INJURY ■ PROM

28-PAGE SECTION
SURGICAL TECHNOLOGY

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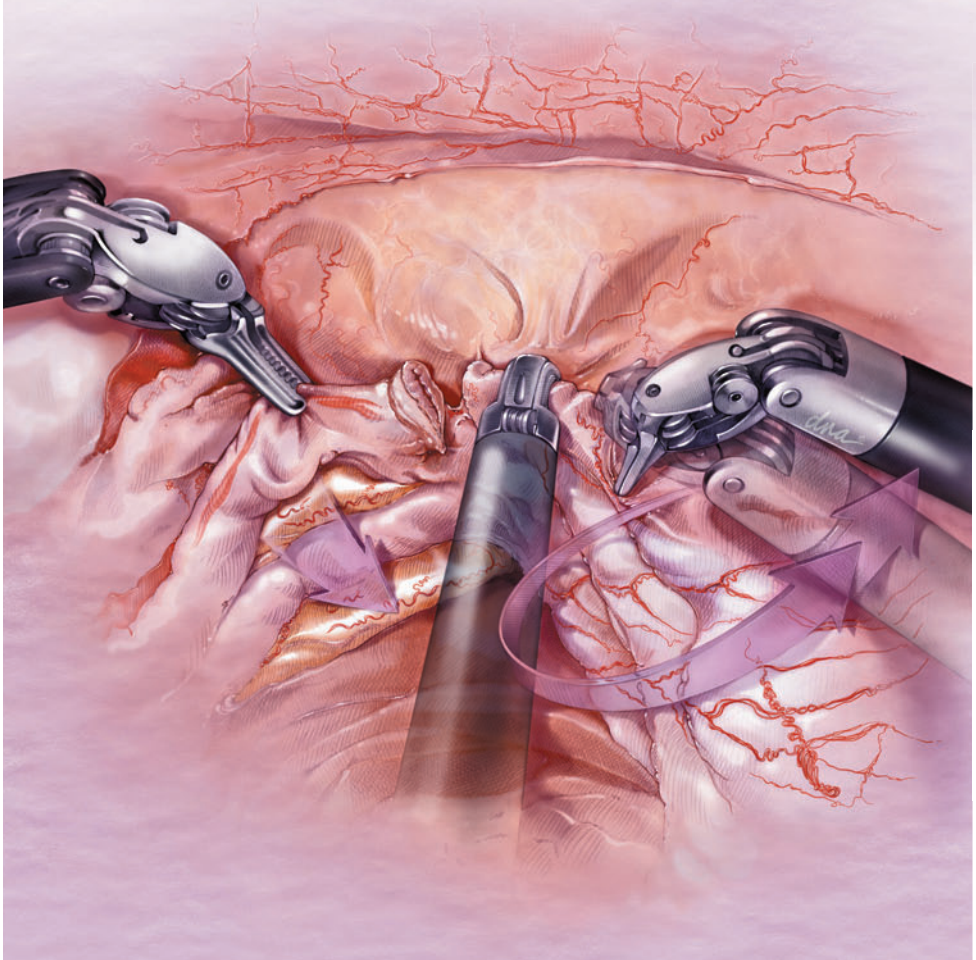
AN EXPERT APPROACH

Avoiding ureteral injury DURING HYSTERECTOMY

Javier F. Magrina, MD



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OCTOBER 2014 | VOLUME 59, NUMBER 10

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CONTEMPORARY OB/GYN OCTOBER 2014, Vol. 59, No.

Contemporary OB/GYN®

28-PAGE SECTION SURGICAL TECHNOLOGY

Expert Advice for Today's Ob/Gyn For Doctors by Doctors ContemporaryOBGYN.net

Most eligible insured patients **PAY NO MORE THAN $25*** for **Lo Loestrin® Fe** prescriptions!

Lo Loestrin Fe

is the *only* available ultra–low-dose oral contraceptive with just **10 mcg** of daily ethinyl estradiol[1]

- Unique 24/2/2 regimen may provide short, lighter periods[1,2]

Lo Loestrin® Fe

(norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets)
1 mg/10 mcg and 10 mcg

*This offer is valid only for patients with commercial prescription drug insurance and applies to prescriptions for Lo Loestrin Fe. Most eligible insured patients will pay $25 per 28-day supply for each of up to 12 prescription fills. Other eligible insured patients should check with their pharmacist for their copay discount. Maximum reimbursement limits apply; patient out-of-pocket expense may vary. Please see full terms and conditions at **actavisocsavings.com**.

INDICATION AND USAGE for Lo Loestrin® Fe

Lo Loestrin Fe is an estrogen/progestin combination oral contraceptive (COC) indicated for use by women to prevent pregnancy. The efficacy of Lo Loestrin Fe in women with a body mass index (BMI) of >35 kg/m^2 has not been evaluated.

SELECTED SAFETY INFORMATION about Lo Loestrin Fe, including Boxed Warning

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, Lo Loestrin Fe should not be used by women who are over 35 years of age and smoke.

Please see Important Safety Information and Brief Summary of Full Prescribing Information for Lo Loestrin Fe, including Boxed Warning, on adjacent pages and also available at www.loloestrin.com.

Lo Loestrin® Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets)

BRIEF SUMMARY: Consult the Package Insert for Complete 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 should not be used by women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

Lo Loestrin® Fe is indicated for use by women to prevent pregnancy.

The efficacy of Lo Loestrin Fe in women with a body mass index (BMI) of > 35 kg/m^2 has not been evaluated.

4 CONTRAINDICATIONS

Do not prescribe Lo Loestrin Fe to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning* and *Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 *[see Warnings and Precautions (5.7)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.2)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.3)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic and Other Vascular Events

Stop Lo Loestrin Fe if an arterial or deep venous thrombotic event occurs. Although use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. 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. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Lo Loestrin Fe at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Lo Loestrin Fe no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest in older (> 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Lo Loestrin Fe if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

5.2 Carcinoma of the Breast and Cervix

Women who currently have or have had breast cancer should not use Lo Loestrin Fe because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

5.9 COC Use Before or During Early Pregnancy

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Lo Loestrin Fe use should be discontinued if pregnancy is confirmed.

Administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Women with a history of depression should be carefully observed and Lo Loestrin Fe discontinued if depression recurs to a serious degree.

5.11 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid binding globulin increase with use of COCs.

5.12 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.13 Other Conditions

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

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking *[see Boxed Warning* and *Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.3)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Breast tenderness
- Nausea
- Headache

6.1 Clinical Trial Experience

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

A multicenter phase 3 clinical trial evaluated the safety and efficacy of Lo Loestrin Fe for pregnancy prevention. The study was a one year, open-label, single-arm, uncontrolled study. A total of 1,660 women aged 18 to 45 were enrolled and took at least one dose of Lo Loestrin Fe.

Common Adverse Reactions (≥ 2 percent of all Treated Subjects): The most common adverse reactions reported by at least 2 percent of the 1,660 women using Lo Loestrin Fe were the following in order of decreasing incidence: nausea/vomiting (7 percent), headache (7 percent), bleeding irregularities (including metrorrhagia, irregular menstruation, menorrhagia, vaginal hemorrhage and dysfunctional uterine bleeding) (5 percent), dysmenorrhea (4 percent), weight fluctuation (4 percent), breast tenderness (4 percent), acne (3 percent), abdominal pain (3 percent), anxiety (2 percent), and depression (2 percent).

Adverse Reactions Leading to Study Discontinuation: 10.7 percent of the women discontinued from the clinical trial due to an adverse reaction. Adverse reactions occurring in ≥1 percent of subjects leading to discontinuation of treatment were in decreasing order: menstrual irregularities (including metrorrhagia, irregular menstruation, menorrhagia and vaginal hemorrhage) (4 percent), headache/migraine (1 percent), mood disorder (including mood swings, depression, anxiety) (1 percent), and weight fluctuation (1 percent).

Serious Adverse Reactions: deep vein thrombosis, ovarian vein thrombosis, cholecystitis.

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Lo Loestrin Fe.

7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors or of non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 Increase in Plasma Levels of Ethinyl Estradiol Associated with Co-Administered Drugs

Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20 percent. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

7.3 Changes in Plasma Levels of Co-Administered Drugs

COCs containing some synthetic estrogens (for example, ethinyl estradiol) may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed should not start COCs earlier than 4 weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs 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. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

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

8.5 Geriatric Use

Lo Loestrin Fe has not been studied in postmenopausal women and are not indicated in this population.

8.6 Renal Impairment

The pharmacokinetics of Lo Loestrin Fe has not been studied in subjects with renal impairment.

8.7 Hepatic Impairment

No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of Lo Loestrin Fe. However, steroid hormones may be poorly metabolized in patients with impaired liver function. 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 *[see Contraindications (4)* and *Warnings and Precautions (5.3)]*.

8.8 Body Mass Index

The safety and efficacy of Lo Loestrin Fe in women with a body mass index (BMI) > 35 kg/m^2 has not been evaluated.

10 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.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Based on Lo Loestrin Fe Prescribing information dated 06/2012.

Manufactured By:
Warner Chilcott Company, LLC
Fajardo, PR 00738

Distributed By:
Actavis Pharma, Inc.
Parsippany, NJ 07054

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Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.3 Liver Disease
Discontinue Lo Loestrin Fe if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. 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.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases per 100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.4 High Blood Pressure
For women with well-controlled hypertension, monitor blood pressure and stop Lo Loestrin Fe if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

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.

5.5 Gallbladder Disease
Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.6 Carbohydrate and Lipid Metabolic Effects
Carefully monitor prediabetic and diabetic women who are taking Lo Loestrin Fe. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache
If a woman taking Lo Loestrin Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Lo Loestrin Fe if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.8 Bleeding Irregularities and 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 COC.

The clinical trial that evaluated the efficacy of Lo Loestrin Fe also assessed unscheduled bleeding and/or spotting. The participants in this 12-month clinical trial (N = 1,582 who had at least one post-treatment evaluation) completed over 15,000 cycles of exposure.

A total of 1,257 women (85.9 percent) experienced unscheduled bleeding and/or spotting at some time during Cycles 2 to 13 of this study. The incidence of unscheduled bleeding and/or spotting was highest during Cycle 2 (53 percent) and lowest at Cycle 13 (36 percent). Among these women, the mean number of days of unscheduled bleeding and/or spotting during a 28-day cycle ranged from 1.8 to 3.2 days.

Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over the one year study, with an average of less than 2 days per cycle.

Women who are not pregnant and use Lo Loestrin Fe may experience amenorrhea (absence of scheduled and unscheduled bleeding/spotting). In the clinical trial with Lo Loestrin Fe, the incidence of amenorrhea increased from 32 percent in Cycle 1 to 49 percent by Cycle 13. 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.

Some women may experience amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was preexistent.

INDICATION AND USAGE for Lo Loestrin® Fe

Lo Loestrin Fe is an estrogen/progestin combination oral contraceptive (COC) indicated for use by women to prevent pregnancy. The efficacy of Lo Loestrin Fe in women with a body mass index (BMI) of >35 kg/m^2 has not been evaluated.

SELECTED SAFETY INFORMATION about Lo Loestrin Fe, including Boxed Warning

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, Lo Loestrin Fe should not be used by women who are over 35 years of age and smoke.

Lo Loestrin Fe is contraindicated in pregnant patients, and those with a high risk of arterial or venous thrombotic diseases, liver tumors (benign or malignant) or liver disease, undiagnosed abnormal uterine bleeding, or breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past.

Discontinue Lo Loestrin Fe if a thrombotic event occurs, and at least 4 weeks before and through 2 weeks after major surgery. Lo Loestrin Fe should not be started any earlier than 4 weeks after delivery, in women who are not breastfeeding. If jaundice occurs, treatment should be discontinued.

Lo Loestrin Fe should not be prescribed for women with uncontrolled hypertension or hypertension with vascular disease. Women who are pre-diabetic or diabetic, should be monitored while using Lo Loestrin Fe. Alternate contraceptive methods should be considered for women with uncontrolled dyslipidemia. Patients using Lo Loestrin Fe who have a significant change in headaches or irregular bleeding or amenorrhea should be evaluated.

In the clinical trial for Lo Loestrin Fe, serious adverse reactions included deep vein thrombosis, ovarian vein thrombosis, and cholecystitis. The most common adverse reactions (incidence ≥2%) were nausea/vomiting, headache, bleeding irregularities, dysmenorrhea, weight fluctuation, breast tenderness, acne, abdominal pain, anxiety, and depression.

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

To report a Suspected Adverse Reaction from one of our products, please contact Actavis Drug Safety Department at 1-800-272-5525.

References: 1. Lo Loestrin® Fe prescribing information. Rockaway, NJ: Warner Chilcott (US), LLC; 2012. **2.** Data on file. Rockaway, NJ: Warner Chilcott (US), LLC.

Lo Loestrin® is a registered trademark of Warner Chilcott Company, LLC.

Actavis

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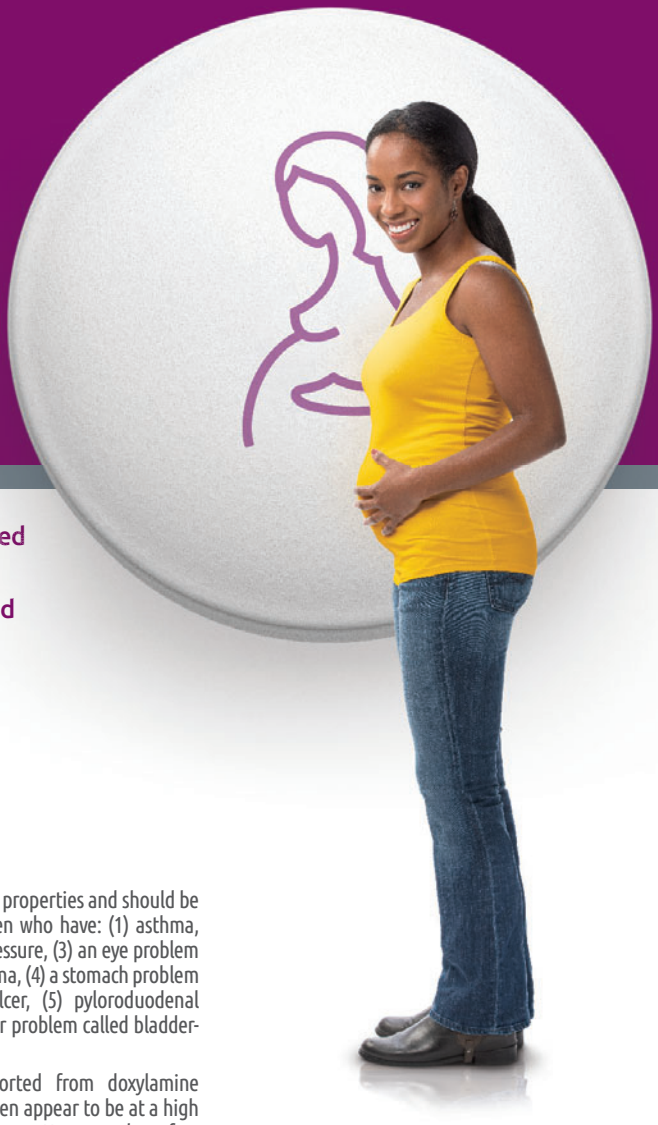
Why Not Prescribe the Only Pregnancy Category A Medication for Morning Sickness?*

…Now You Can.



Diclegis® is the only Pregnancy Category A and FDA-approved prescription treatment for morning sickness.[1]*

Pregnancy Category A means that the results of controlled studies have not shown increased risk to an unborn baby during pregnancy.[2]

Visit www.Diclegis.com for more information.

*Morning sickness is a common term for a medical condition called Nausea and Vomiting of Pregnancy.[3]

NVP | NAUSEA AND VOMITING OF PREGNANCY

Indication

Diclegis® is a fixed-dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B_6 analog, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

Diclegis has not been studied in women with hyperemesis gravidarum.

Important Safety Information

Diclegis is contraindicated in women with known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride, or any inactive ingredient in the formulation. Diclegis is also contraindicated in combination with monoamine oxidase inhibitors (MAOIs) as MAOIs intensify and prolong the adverse CNS effects of Diclegis. Use of MAOIs may also prolong and intensify the anticholinergic (drying) effects of antihistamines.

Diclegis may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using Diclegis until cleared to do so by their healthcare provider.

Use of Diclegis is not recommended if a woman is concurrently using CNS depressants, such as alcohol or sedating medications, including other antihistamines (present in some cough and cold medications), opiates, and sleep aids. The combination of Diclegis and CNS depressants could result in severe drowsiness leading to falls or other accidents.

Diclegis has anticholinergic properties and should be used with caution in women who have: (1) asthma, (2) increased intraocular pressure, (3) an eye problem called narrow angle glaucoma, (4) a stomach problem called stenosing peptic ulcer, (5) pyloroduodenal obstruction, or (6) a bladder problem called bladder-neck obstruction.

Fatalities have been reported from doxylamine overdose in children. Children appear to be at a high risk for cardiorespiratory arrest. However, the safety and effectiveness of Diclegis in children under 18 years of age have not been established.

Diclegis is a delayed-release formulation; therefore, signs and symptoms of intoxication may not be apparent immediately. Signs and symptoms of overdose may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion, and tachycardia. If you suspect an overdose or seek additional overdose information, you can contact a poison control center at 1-800-222-1222.

The FDA granted Diclegis Pregnancy Category A status, which means that the results of controlled studies have not shown increased risk to an unborn baby during pregnancy.

Women should not breast-feed while using Diclegis because the antihistamine component (doxylamine succinate) in Diclegis can pass into breast milk. Excitement, irritability, and sedation have been reported in nursing infants presumably exposed to doxylamine succinate through breast milk. Infants with apnea or other respiratory syndromes may be particularly vulnerable to the sedative effects of Diclegis resulting in worsening of their apnea or respiratory conditions.

Diclegis®

(doxylamine succinate and pyridoxine hydrochloride)
delayed-release tablets 10mg/10mg

To report suspected adverse reactions, contact Duchesnay Inc. at 1-855-722-7734 or medicalinfo@duchesnayusa.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying Brief Summary of the full Prescribing Information on adjacent page.

Tablet(s) shown are not actual size.

References: 1. Diclegis [package insert]. Bryn Mawr, PA: Duchesnay USA, Inc; 2013. **2.** US Department of Health and Human Services. Food and Drug Administration. Labeling. 21 CFR 201.57. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57. Revised April 1, 2013. Accessed August 22, 2013. **3.** ACOG Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 52, April 2004. Nausea and vomiting of pregnancy. *Obstet Gynecol.* 2004;103(4):803-815.

DUCHESNAY USA

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Rx only

DICLEGIS® (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets, for oral use.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION.
PLEASE SEE FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

DICLEGIS is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

DICLEGIS has not been studied in women with hyperemesis gravidarum.

DOSAGE AND ADMINISTRATION

Initially, take two DICLEGIS delayed-release tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, continue taking two tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, take the usual dose of two tablets at bedtime that night then take three tablets starting on Day 3 (one tablet in the morning and two tablets at bedtime). If these three tablets adequately control symptoms on Day 4, continue taking three tablets daily. Otherwise take four tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime).

The maximum recommended dose is four tablets (one in the morning, one in the mid-afternoon and two at bedtime) daily.

Take on an empty stomach with a glass of water. Swallow tablets whole. Do not crush, chew, or split DICLEGIS tablets.

Take as a daily prescription and not on an as needed basis. Reassess the woman for continued need for DICLEGIS as her pregnancy progresses.

DOSAGE FORMS AND STRENGTHS

Delayed-release tablets containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

CONTRAINDICATIONS

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

- Known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredient in the formulation
- Monoamine oxidase (MAO) inhibitors intensify and prolong the adverse central nervous system effects of DICLEGIS *(see Drug Interactions)*.

WARNINGS AND PRECAUTIONS

Activities Requiring Mental Alertness

DICLEGIS may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using DICLEGIS until cleared to do so by their healthcare provider.

DICLEGIS use is not recommended if a woman is concurrently using central nervous system (CNS) depressants including alcohol. The combination may result in severe drowsiness leading to falls or accidents *(see Drug Interactions)*.

Concomitant Medical Conditions

DICLEGIS has anticholinergic properties and, therefore, should be used with caution in women with: asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction.

Drug Interactions

Use of DICLEGIS is contraindicated in women who are taking monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic (drying) effects of antihistamines. Concurrent use of alcohol and other CNS depressants (such as hypnotic sedatives and tranquilizers) with DICLEGIS is not recommended.

Drug-Food Interactions

A food-effect study demonstrated that the delay in the onset of action of DICLEGIS may be further delayed and a reduction in absorption may occur when tablets are taken with food. Therefore, DICLEGIS should be taken on an empty stomach with a glass of water *(see Dosage and Administration)*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labelling:

- Somnolence *(see Warnings and Precautions)*
- Falls or other accidents resulting from the effect of the combined use of DICLEGIS with CNS depressants including alcohol *(see Warnings and Precautions)*

Clinical Trial Experience

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

The safety and efficacy of DICLEGIS was compared to placebo in a double-blind, randomized, multi-center trial in 261 women with nausea and vomiting of pregnancy. The mean gestational age at enrollment was 9.3 weeks, range 7 to 14 weeks gestation *(see Clinical Studies)*. Adverse reactions for DICLEGIS that occurred at an incidence ≥5 percent and exceeded the incidence for placebo are summarized in Table 1.

Table 1: Number (Percent) of Subjects with ≥ 5 Percent Adverse Reactions in a 15 Day Placebo-Controlled Study of DICLEGIS (Only Those Adverse Reactions Occurring at an Incidence ≥ 5 Percent and at a Higher Incidence with DICLEGIS than Placebo are shown)

	DICLEGIS (N = 133)	Placebo (n = 128)
Somnolence	19 (14.3%)	15 (11.7%)

To report suspected adverse reactions, contact Duchesnay Inc. at 1-855-722-7734 or medicalinfo@duchesnayusa.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Postmarketing Experience

The following adverse events, listed alphabetically, have been identified during post-approval use of the combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: dyspnea, palpitation, tachycardia
Ear and labyrinth disorders: vertigo
Eye disorders: vision blurred, visual disturbances
Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhea
General disorders and administration site conditions: chest discomfort, fatigue, irritability, malaise
Immune system disorders: hypersensitivity
Nervous system disorders: dizziness, headache, migraines, paresthesia, psychomotor hyperactivity
Psychiatric disorders: anxiety, disorientation, insomnia, nightmares
Renal and urinary disorders: dysuria, urinary retention
Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus, rash, rash maculo-papular

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category A

DICLEGIS is intended for use in pregnant women.

The combination of doxylamine succinate and pyridoxine hydrochloride has been the subject of many epidemiological studies (cohort, case control and meta-analyses) designed to detect possible teratogenicity. A meta-analysis of 16 cohort and 11 case-control studies published between 1963 and 1991 reported no increased risk for malformations from first trimester exposures to doxylamine succinate and pyridoxine hydrochloride, with or without dicyclomine hydrochloride. A second meta-analysis of 12 cohort and 5 case-control studies published between 1963 and 1985 reported no statistically significant relationships between fetal abnormalities and the first trimester use of the combination doxylamine succinate and pyridoxine hydrochloride with or without dicyclomine hydrochloride.

Nursing Mothers

Women should not breastfeed while using DICLEGIS.

The molecular weight of doxylamine succinate is low enough that passage into breast milk can be expected. Excitement, irritability and sedation have been reported in nursing infants presumably exposed to doxylamine succinate through breast milk. Infants with apnea or other respiratory syndromes may be particularly vulnerable to the sedative effects of DICLEGIS resulting in worsening of their apnea or respiratory conditions.

Pyridoxine hydrochloride is excreted into breast milk. There have been no reports of adverse events in infants presumably exposed to pyridoxine hydrochloride through breast milk.

Pediatric Use

The safety and effectiveness of DICLEGIS in children under 18 years of age have not been established.

Fatalities have been reported from doxylamine overdose in children. The overdose cases have been characterized by coma, grand mal seizures and cardiorespiratory arrest. Children appear to be at a high risk for cardiorespiratory arrest. A toxic dose for children of more than 1.8 mg/kg has been reported. A 3 year old child died 18 hours after ingesting 1,000 mg doxylamine succinate. However, there is no correlation between the amount of doxylamine ingested, the doxylamine plasma level and clinical symptomatology.

OVERDOSAGE

Signs and Symptoms of Overdose

DICLEGIS is a delayed-release formulation, therefore, signs and symptoms of intoxication may not be apparent immediately.

Signs and symptoms of overdose may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion and tachycardia.

At toxic doses, doxylamine exhibits anticholinergic effects, including seizures, rhabdomyolysis, acute renal failure and death.

Management of Overdose

If treatment is needed, it consists of gastric lavage or activated charcoal, whole bowel irrigation and symptomatic treatment. For additional information about overdose treatment, call a poison control center (**1-800-222-1222**).

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Somnolence and Severe Drowsiness

Inform women to avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using DICLEGIS until cleared to do so.

Inform women of the importance of not taking DICLEGIS with alcohol or sedating medications, including other antihistamines (present in some cough and cold medications), opiates and sleep aids because somnolence could worsen leading to falls or other accidents.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed and protect from moisture. Do not remove desiccant canister from bottle.

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CONTENT

Judith Orvos
Editorial Consultant

Susan C Olmstead
Managing Content Editor
solmstead@advanstar.com

Miranda Hester
Content Specialist
mhester@advanstar.com

Robert McGarr
Group Art Director

Nicole Davis-Slocum
Art Director

Karen Lenzen
Sr. Production Manager
218-740-6371
klenzen@media.advanstar.com

SALES & MARKETING

Georgiann DeCenzo
Executive Vice President
440-891-2778, gdecenzo@advanstar.com

Ken Sylvia
Vice President, Group Publisher
732-346-3017, ksylvia@advanstar.com

Aviva Belsky
Publisher
732-346-3044, abelsky@advanstar.com

Alison O'Connor
National Account Manager
732-346-3075, aoconnor@advanstar.com

Margie Jaxel
Dir. of Business Develpment, Healthcare Technology Sales
732-346-3003 mjaxel@advanstar.com

Patrick Carmody
Account Manager, Healthcare Technology
440-891-2621 pcarmody@advanstar.com

Joan Maley
Account Manager
Classified/Display Advertising
440-891-2722, jmaley@advanstar.com

Joanna Shippoli
Account Manager,
Recruitment Advertising
440-891-2615, jshippoli@advanstar.com

Don Berman
Business Director, eMedia
212-951-6745, dberman@advanstar.com

Meg Benson
Special Projects Director
732-346-3039, mbenson@advanstar.com

Gail Kaye
Director of Marketing & Research Services
732-346-3042, gkaye@advanstar.com

Hannah Curis
Sales Support
732-346-3055, hcuris@advanstar.com

Renee Schuster
List Account Executive
440-891-2613, rschuster@advanstar.com

Maureen Cannon
Permissions/International Licensing
440-891-2742, mcannon@advanstar.com

Reprint Services
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AUDIENCE DEVELOPMENT

Joy Puzzo
Corporate Director
jpuzzo@advanstar.com

Christine Shappell
Director
cshappell@advanstar.com

Joe Martin
Manager
jmartin@advanstar.com

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1. Sosa CG et al. *Comparison of placental alpha microglobulin-1 in vaginal fluid with intra-amniotic injection of indigo carmine for the diagnosis of rupture of membranes.* J. Perinat Med. 2014 Apr 3 [Epub ahead of print]. Study download available at www.amnisure.com.

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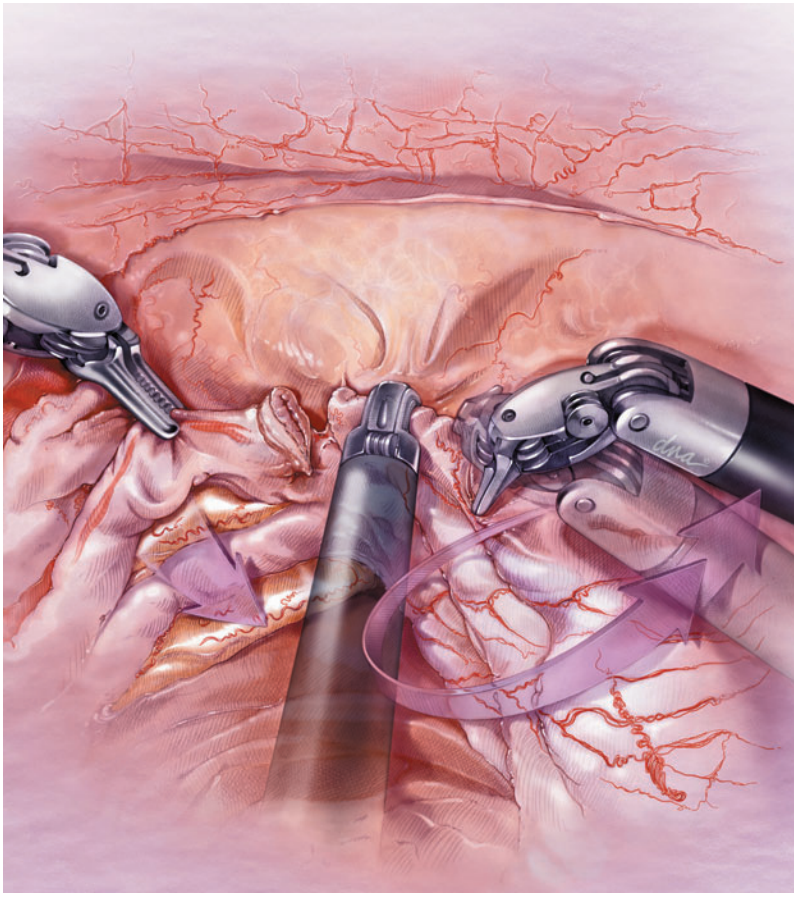

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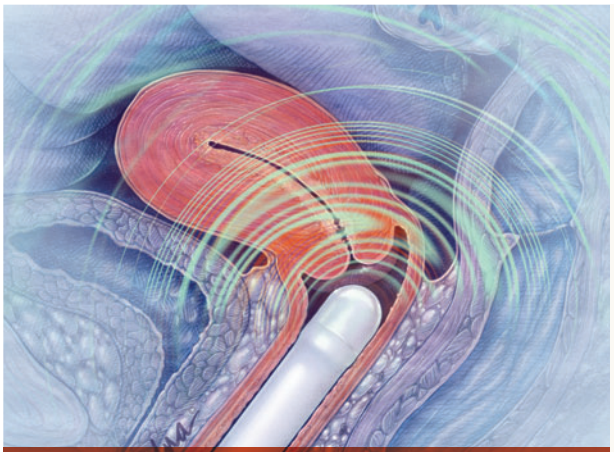

Ultrasound triage
of postmenopausal bleeding
http://bit.ly/1vrnywJ

In case you missed it: Ultrasound-based evaluation of postmenopausal bleeding is less costly than an endometrial biopsy and also allows for evaluation of the adnexa and bladder. This feature article by James M. Shwayder, MD, JD, discusses how to perform an ultrasound evaluation.

on twitter

A few recent tweets and retweets from and about ContempOBGYN

Icahn School of Med
@IcahnMountSinai
Spanning a full weekend, the #GOHO course afforded our #obgyn residents a unique opportunity http://bit.ly/1s45tqd @contempobgyn #ultrasound

Sukrant Mehta
@SukrantMehta
@yafshar @ContempOBGYN Yet another literary masterpiece from my favorite PGY-3 with some help from a future Gyn/Onc allstar! #MedEd #obgyn

Peggy Polaneczky, MD
@tbtam
Ultrasound triage of women with postmenopausal bleeding http://shar.es/1a18a0 via @ContempOBGYN Excellent state of the art review.

Joshua Copel
@jacopel
@ContempOBGYN follow #ISUOG2014 for updates from #ISUOG annual meeting in Barcelona. Over 2000 registered, largest ever!

Brian A. Levine
@DrBrianLevine
E. Bimla Schwarz "Breastfeeding can prevent 14k heart attacks / yr" #TEDMED @ContempOBGYN pic.twitter.com/vjJvWQaDPl

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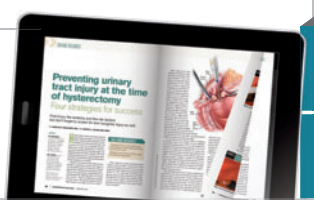

on facebook

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Contemporary OB/GYN
September 11

Our Tech Tools Editor @DrBrianLevine is tweeting live from TEDMED. Follow us and him for updates on the frontiers of medicine.

Twitter / KimAbruz: .@ ContempOBGYN @jacopel starts ...

twitter.com

Fertility takes center stage at #TEDMED Thank you Leslie Morgan Steiner for an amazing #TEDtalk pic.twitter.com/mqFeRJ2rhm

Contemporary OB/GYN
September 17

Our newest Editorial Board member, Dr. Ilana Cass, was featured in one of ExtraTV's "Life Changers" segments. Listen to her expert perspective on cervical cancer and HPV: http://www.extratv.com/videos/1-4mpspnuc/

What's Up Down There?
Dr. Ilana Cass of Cedars-Sinai Hospital in Beverly Hills answers your most intimate questions.

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LETTERS TO THE EDITOR

TO THE EDITOR:

Dr. Merida Miller's review of recurrent vulvovaginitis **["Recurrent vulvovaginitis: tips for treating a common condition," August 2014 *Contemporary OB/GYN*]** is thorough and accurately reflects the standard thinking of the care of women with these problems. I would, however, like to point out two areas of disagreement.

1. Non-culture studies of the bacterial flora of the vagina of healthy women done in the laboratory of Dr. Larry Forney do not support the primacy of the role of H_2O_2-producing *lactobacilli* in maintaining a normal bacterial environment in the vagina. Instead, lactic acid-producing bacteria seem to be the key to vaginal health. This is important, for it calls into question the Nugent criteria for the diagnosis of bacterial vaginosis.

2. The notion that a culture for yeast should only be sent to the laboratory if the diagnosis is in question reflects the microscopic expertise of Dr. Miller, but not that of the practicing physician. A number of observational studies indicate that about 42% of women who are sure they have a vaginal yeast infection have a positive culture for yeast. Many of these women have been told by their doctors that their vaginal and vulvar symptoms are due to a yeast infection.

The brutal reality for physicians is that a number of observational studies indicate that only 46% of the women diagnosed by physicians as having a vaginal yeast infection actually had a positive culture for yeast. This was reinforced years ago by the observations of Dr. Paul Nyirjesy, who noted that only one in four patients sent to him with a presumed chronic or recurrent vaginal yeast infection had a positive culture for yeast when he evaluated them.

I have had this same experience in my own referral practice. In view of this, the current standard of care should be to obtain a fungal culture in every patient suspected by the physician of having a vaginal yeast infection. It would avoid the all-too-often repeated treatments for an infection that is not present.

William J. Ledger, MD
New York, NY

IN REPLY:

I would like to thank Dr. Ledger for his well-considered points regarding the article on recurrent vaginitis. I agree with his comments and thank him for bringing them to the attention of the readers. I would like to state, however, that despite considerable research by Dr. Ledger and others, understanding of the vaginal ecosystem still remains limited. I certainly agree with his comment about the Nugent criteria, but it is not generally used clinically given the requirement for a gram stain. I rely heavily on the Amsel criteria for diagnosis as microscopy is more cost-effective, less time-consuming and results have been shown to be highly accurate.

I would also like to clarify my diagnostic strategy for yeast. If there is positive microscopy, I believe treatment can be considered. If there is any question about the diagnosis or if this is a case referred for *recurrent* yeast, then a culture is necessary. I certainly agree that there is ample evidence that yeast is misdiagnosed both by providers and patients alike. The culture can also help identify the correct strain and help tailor the treatment plan.

My thanks again to Dr. Ledger for his thoughtful comments.

Merida Miller, MD

TO THE EDITOR:

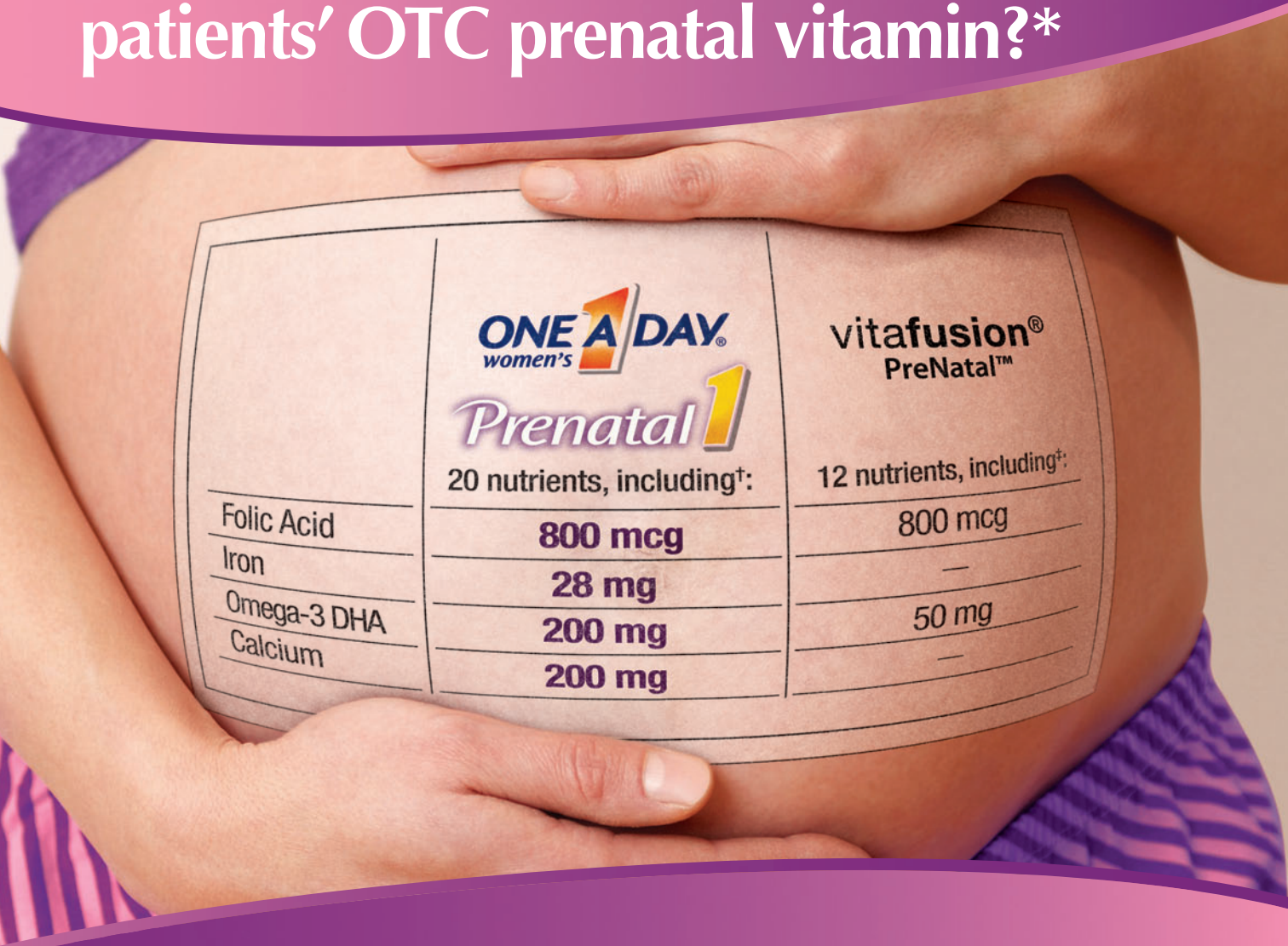
Praise to you for speaking out against the ACP Clinical Guideline against routine annual exams **["Wither the bimanual examination?" August 2014 *Contemporary OB/GYN*]**. Why are other ob/gyns not speaking out and recommending against this ridiculous statement? Daily I see women from other practices presenting for consultations regarding menopause and hear them say, "My ob/gyn said I don't need a follow up but every 2 years"!

It is ludicrous that board-certified ob/gyns have conceded to the recommendations of ACP! Is it laziness from physicians who feel seeing fewer patients is beneficial for their own good and not the good of the patient? Is it the old "it's not cost effective" statement issued by ACP and insurance companies? Well it might not be "cost effective" unless it is their mother, wife, sister, or daughter!

Thank you for bringing this to light in *Contemporary OB/GYN*. Hopefully physicians will read it and take a second look at who the authors are, heed your advice, and take a stand!

James Mirabile, MD, FACOG
Overland Park, Kansas

Which key nutrients are in your patients' OTC prenatal vitamin?*



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Reference: 1. The American College of Obstetricians and Gynecologists website. Nutrition during pregnancy: frequently asked questions. http://www.acog.org/Search?Keyword=Nutrition+During+Pregnancy+FAQs. Accessed October 14, 2013.

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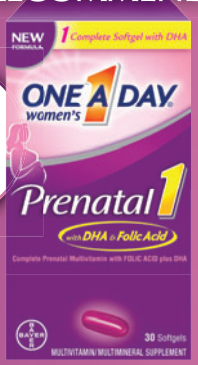

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Two cervical cancer deaths, two jury decisions

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$20.9 million award

A 37-YEAR-OLD FLORIDA WOMAN had a Pap smear in 2008, which a cytotechnologist read as normal. Two years later the patient was diagnosed with a golf-ball-sized cancerous tumor of the cervix. She died of cervical cancer in 2011.

The woman's estate sued the laboratory that analyzed the 2008 Pap smear and claimed it negligently misread the test. Her attorneys maintained that a conization biopsy and treatment at that time would have resolved the cancer.

The laboratory argued that the Pap smear interpretation was reasonable and that the cancer could not have been diagnosed in 2008. They also claimed that the patient was at fault in failing to have follow-up examinations during the next 2 years.

The verdict

The jury found the cytotechnologist 75% at fault and the patient 25% at fault and returned a $20.9 million verdict.

$2.33 million award

A NEW JERSEY WOMAN sued her gynecologist and a laboratory after she was diagnosed with advanced cervical cancer in 2009. In 2001, she had an abnormal Pap smear and was told to return in 3 months for a repeat check but she did not see that gynecologist until 2007. At that time, she had some symptoms, but her Pap smear was normal and no further testing was ordered. Two years later, the woman was diagnosed with cervical cancer and she died in 2011 at age 48. In her lawsuit, the woman's estate claimed that the second Pap smear was incorrectly interpreted. Her attorneys also claimed that further testing should have been ordered in 2001 and 2007.

The physician claimed that the patient did not return in 2001 as ordered, and when she did come to the office in 2007 her Pap smear was normal.

The verdict

The laboratory corporation entered into a confidential settlement prior to trial. The jury found negligence by the gynecologist and assessed 40% fault to her. The laboratory was assessed at 50% fault and the patient was assigned 10%. The gross verdict was for $2.33 million.

Analysis

These 2 cases have similar situations but a large disparity in the amounts of the awards. Although the verdict in the first case was reduced to $15.8 million, it is still a huge monetary award for this type of case. The first case proceeded against the laboratory corporation only, so the jury saw a big corporation in the defendant's chair. This might have had an effect, although it is never a jury's job to "punish" a corporation. Also in the first case, post-trial motions were pending claiming possible evidence that the patient had been treated by another physician in 2010. If the defense team can show that a Pap at that time was normal, the huge award may be moot.

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Bowel perforation following cesarean leads to death

IN 2010, A 37-YEAR-OLD MARYLAND WOMAN 40 4/7 weeks pregnant with her fourth child went to the hospital with ruptured membranes. The following day an ob/gyn performed a cesarean delivery of a healthy infant. The day after the delivery, the patient had an elevated white blood cell (WBC) count with a left shift. Her abdomen was tympanic but soft and she was passing flatus and belching. Her obstetrician ordered an enema. The results noted gas passed but no stool. The covering obstetrician then ordered an abdominal x-ray, which was reported to show a postoperative ileus and mild constipation.

The patient was given a second enema the next day and was noted to have watery stool with only minimal relief. She then vomited dark green emesis.

Two days later a rectal tube was placed and brown loose stools were noted. The patient vomited several times that day and had hypoactive bowel sounds. She continued to have elevated WBC counts and on her fifth postoperative day, bowel sounds were hypoactive but she tolerated clear liquids. The woman was discharged home later that day with instructions to continue on a clear liquid diet for 1 or 2 more days.

The next day she was found unresponsive at home and was taken to a hospital, but resuscitation attempts were unsuccessful. An autopsy revealed the cause of death to be sepsis.

The lawsuit that followed her death alleged negligence by those involved with her care. The claim against the obstetricians was a failure to diagnose and treat a postoperative intra-abdominal infection caused by a bowel perforation. It was argued that a surgical consult should have been obtained and that the woman was prematurely discharged from the hospital. The suit also claimed that the radiologist failed to report the presence of free air on the abdominal x-ray, which would have led to a timely diagnosis of bowel perforation.

The verdict

A $1 million settlement was reached during trial.

Vesicovaginal fistula develops after hysterectomy

IN 2009, A PATIENT was seen at a Michigan ob/gyn clinic with complaints of continuous vaginal bleeding, pain, and shortness of breath when walking. She was found to have profuse vaginal discharge, a normal cervix, and a significantly enlarged uterus. The woman was diagnosed with symptomatic uterine fibroids, failed uterine artery embolization, chronic pelvic pain, chronic endometritis, and a history of multiple abdominal surgeries.

A full abdominal hysterectomy was scheduled and performed the next month by the gynecologist with assistance from a third-year resident. The physicians encountered extensive adhesions and difficulty dissecting tissue.

After the surgery the patient was anemic and received a beta blocker for tachycardia. She received intravenous antibiotics for 48 hours after surgery and was discharged home on the third postoperative day.

A month later, the woman complained of leaking urine and was referred to a urologist, who diagnosed a vesicovaginal fistula. She underwent nephrostomy tube placement and, 4 months after that, a right ureterolysis and right ureteral reimplant.

The woman sued the gynecologist and claimed that her ureter was negligently injured during the hysterectomy.

The physician argued that ureter injury was a known risk of the procedure and that the patient had extensive adhesions, making it a difficult operation. She also claimed that the injury could have been due to the infection or a delayed effect of ischemia. Further, she claimed the patient had a repair with a good recovery and no residual injury.

The verdict

A defense verdict was returned.

You'll find expert guidance on avoiding the ureter during hysterectomy in this month's cover story, starting on page 14.

MS. COLLINS is an attorney specializing in medical malpractice in Long Beach, California. She welcomes feedback to this column via email to dawncfree@gmail.com.

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Preventing ureteral injury at hysterectomy: An expert approach

One in eight patients are at increased risk of ureteral injury during endoscopic hysterectomy due to differences in anatomy. The right tools and techniques will protect them from injury and complications.

BY **JAVIER F. MAGRINA, MD**

DR. MAGRINA is Professor of Obstetrics and Gynecology, Barbara Woodward Lipps Professor, Department of Gynecologic Surgery, Mayo Clinic Arizona.

He has no conflicts of interest to report with respect to the content of this article.

Ureteral injury can occur during many gynecologic operations, and particularly hysterectomy, regardless of the surgical approach. The pelvic ureter is the segment most commonly injured during gynecologic operations (91%), compared with 2% and 7% incidence of injuries to the upper and middle ureteral thirds, respectively.[1]

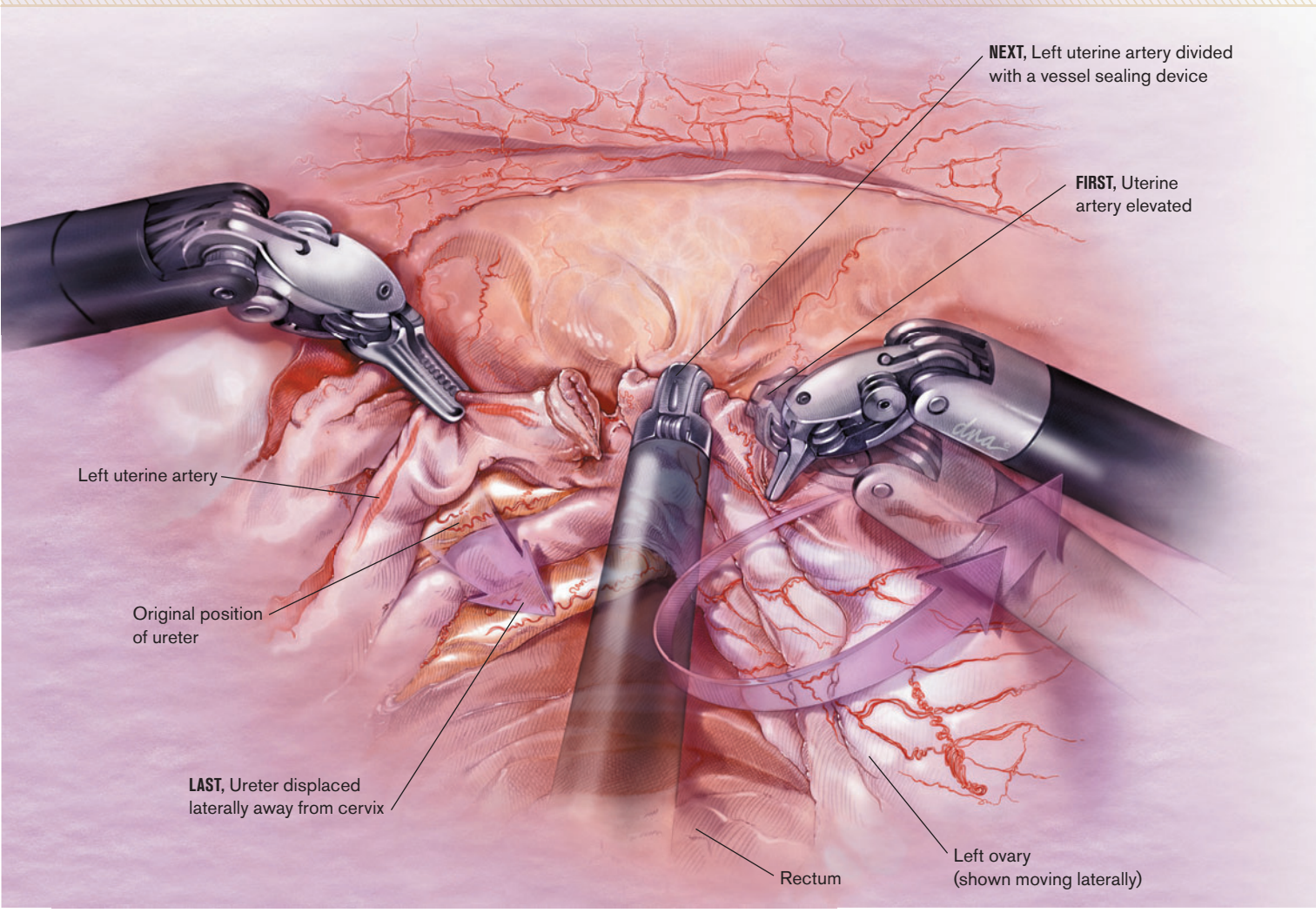
In most patients, the pelvic ureter can be easily identified in the upper pelvis at the level of the pelvic brim and also along the lateral pelvic peritoneum. The segment that is difficult to identify is the portion of the ureter between the intersection with the uterine artery and the bladder.

This article reviews how I identify and manage the course of the parametrial (paracervical) segment of the pelvic ureter in order to prevent injury to it during endoscopic, laparoscopic, or robotic hysterectomy.

Incidence of injury

Before addressing the incidence of ureteral injuries, it is important to understand that unless otherwise indicated, reports of these complications reflect postoperative detection. That incidence is always lower than for injuries detected intraoperatively as reviewed below. The rates of ureteral injury discussed in this article are postoperative, unless otherwise noted.

The risk of ureteral injury at vaginal hysterectomy is higher (0.6%) than with an open abdominal approach (0.07%), and almost all such injuries occur when the surgery is done for prolapse.[2] The main reason is the inability to see and sometimes palpate the ureter during vaginal surgery as compared to an open procedure. The introduction of laparoscopy and later robotics resulted in an increased number of urinary injuries of any type, including



Grasper is shown clipping the uterine artery as it crosses over the left ureter. This allows for moving the ureter out of harm's way while working in the area around the cervical neck. The ghosted intruments show subsequent steps in ligation: blunt dissection and gentle manipulation of the ovary with consequent drop of the ureter.

ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATIONS, INC.

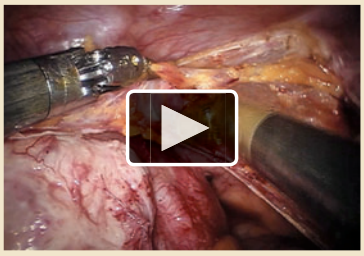
ureteral injuries. In time, the risk of ureteral injury with laparoscopy and robotics decreased surgeons' awareness of the problem grew, instrumentation improved, and experience with endoscopic procedures increased.

A collective review of 236,392 patients who underwent gynecologic operations between 1994 and 2000 reported a risk of laparoscopic injury ranging from 0.02% to 1.7%, depending on the complexity of the operation.[3] The risk of ureteral injury ranged from <1% to 2% in 2491 patients who underwent laparoscopic gynecologic surgery, based on data collected from several reports.[4] In some reports, the most common injuries were due to electrocoagulation; laparoscopic-assisted vaginal hysterectomy (LAVH) was the procedure with the highest rate of ureteral injury.[4]

However, other reports have indicated that ureteral pelvic injuries can occur with the use of any mechanical or electrocoagulation devices, laser beams, loop suturing, trocars, or staple devices.[5]

The increased risk of ureteral injuries initially associated with laparoscopic procedures extended to other surgical specialties. An increased rate was noted when comparing ureteral injuries associated with all surgical specialties from 1986–1992 to 1993–1999 and 2000–2006, resulting in a 7-fold increase.[6]

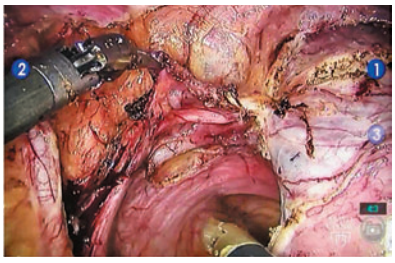
VIDEO



Visit Contemporary OB/GYN.net to see the author identifying the ureter during an endoscopic hysterectomy.
http://bit.ly/1CGf1cG

The introduction of robotic technology had a similar impact. One study documented a 2.4% rate of ureteral injury during pelvic surgeries performed before robotics, compared with 11.4% after the implementa-

FIGURE 1 **Ureter near the cervical wall**



Left ureter coursing within 5 mm of the lateral cervical wall. In spite of the cephalad displacement of the cervix, this ureter is at risk of injury during division of the uterine artery, which is seen crossing the ureter.

tion of the technology ($P = 0.05$).[7]

A 0.3% incidence of postoperatively detected ureteral injuries was reported in one series of 1300 LAVH and a 0.1% incidence was reported in another series of 7725 LAVH.[8,9] A 0.7% incidence of ureteral injury was reported in association with robotic hysterectomy performed for complex pathology.[10]

Intraoperative versus postoperative detection

The rate of ureteral injury is higher with intraoperative versus postoperative detection. The rate of intraoperative detection was 0.6% with use of cystoscopy in 3235 patients and 6 times lower (0.1%) for postoperative detection in 107,068.[11] In 2 other studies, 89% and 93.7% of ureteral injuries, respectively, were not detected intraoperatively.[11,12] Intraoperative cystoscopy identified about 90% of unrecognized ureteral injuries, 69% of which were easily managed, most by simply removing a suture.[11]

One reason for the lower rate of detection of postoperative ureteral entrapment is the lack of symptomatology following ureteral ligation. About half of intentional ureteral ligations did not result in renal symptomatology in a series of 26 inoperable patients with malignant ureteral fistulas undergoing intentional unilateral ureteral ligation.[13]

Intraoperative cystoscopy is useful to detect ureteral injuries such as entrapment and transection and facilitates immediate correction and avoidance of subsequent operations and/or permanent sequelae to the patient, and possible litigation to the surgeon. However, it is not useful for detection of ureteral injuries such as thermal damage or ischemia, which may result in subsequent ureteral sloughing.

Actually, there are no methods other than ureteral dissection and identification to prevent any type of ureteral injury.

The time to postoperative diagnosis of ureteral injury is variable and dependent upon the type and severity of the injury. That explains why in some series, a diagnosis was reported in an average of 6 days, whereas in others, it took 29 days.[4,14] Patients with ureteral transections will present with urinoma in the immediate days after surgery.

Ureteral entrapment may be asymptomatic or patients may present within 1 week with flank pain or fever due to pyelonephritis.[13] Thermal injuries may be diagnosed as long as 2 to 3 weeks after surgery.

Mechanism of injury

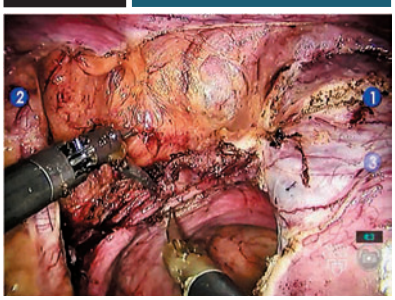
There are several types of ureteral injuries and the most common consist of entrapment, transection, or thermal damage. Entrapment results in increased renal pelvis pressure within 4 hours, distal tubular atrophy in 1 week, proximal tubular atrophy in 2 weeks, and progressive glomerulosclerosis over 4 weeks, and permanent damage unless corrected within this period of time.[13] Transection and thermal damage result in urine extravasation (urinoma) and chemical peritonitis.

Prior to endoscopic surgery, thermal ureteral injuries were almost nonexistent and they became quite common with introduction of electrical instrumentation, whether monopolar or bipolar. In the latter case, it is not the electrical current but the steam generated from the application of the electrical current, with secondary boiling of the intracellular and extracellular fluids, that results in thermal injury.

Strategies for prevention

In 12% of patients, the ureters are within 5 mm from the lateral cervical wall, unilaterally or bilaterally (Figure 1).[15] We address these ureters as "cervical ureters" because they appear to be part of the cervix instead of the cardinal ligament. Laparoscopic and robotic instruments are usually 5 and 8 mm in diameter, respectively, indicating that 1 of 8 patients is at risk of ureteral injury during endoscopic hysterectomy even when a

FIGURE 2 **Dissection of the left ureter**



The left ureter appeared lateral and safe along the left pelvic wall, until it was dissected and noted to be within 5 mm of the cervix as seen in Figure 1.

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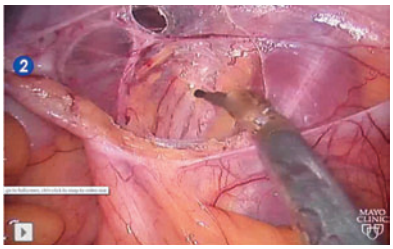
FIGURE 3 Right ureter adjacent to the external iliac artery



Identification of the ureter starts at the pelvic brim. An incision has been made lateral to the right infundibulopelvic ligament and the right ureter is seen adjacent to the external iliac artery and indicated by the robotic spatula.

proper technique is used. The risk would appear to be greater with the use of a 10-mm vessel sealing device.

The use of a uterine manipulator or similar device in the vagina with cephalad displacement of the cervix will increase the distance between the ureter and the uterine artery and increase the safety of cardinal ligament coagulation and division. However, cephalad displacement does not guarantee prevention of ureteral injury because it may not achieve sufficient displacement if the ureter is adjacent to the lateral cervical wall.

Ureteral injury at endoscopic hysterectomy can occur at many points during hysterectomy, but this discussion will be limited to potential injuries during cardinal ligament division and vaginal cuff closure.

The ureter during cardinal ligament division. Assessing the parametrial ureter's proximity to the cervix requires visualizing the intersection of the ureter and the uterine artery (Figure 1), starting with identification of the ureter upstream, cephalad to the intersection and then along the lateral pelvic peritoneum.

As a rule, ureters coursing high in the lateral pelvic wall, at a distance from the uterosacral ligament, are usually lateral to the cervix, whereas those located near the uterosacral ligament usually course close to the cervix. However, the ureters can be found at any level on the lateral pelvic wall and can be at any distance from the cervix.

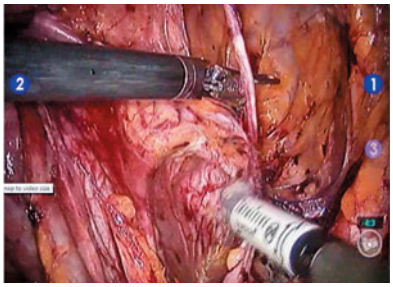
The ureter noted in Figure 1 appeared safe for cardinal ligament division because it was identified lateral to the cervix proximal to the crossing with the uterine artery (Figure 2). However, once followed to the uterine artery intersection, the ureter was noted to be adjacent to the cervix and at risk of injury (Figure 1). Whenever there is any suspicion of proximity, ureteral dissection to the crossing with the uterine artery is mandatory to prevent injury.

Laparoscopic-assisted vaginal hysterectomy (LAVH) was the procedure **with the highest rate of ureteral injury.**

How to find the intersection of the ureter with the uterine artery. The 2 surgical approaches to identifying the intersection of the ureter with the uterine artery are following the pelvic ureter or following the uterine artery.

1. Following the ureter. The level of the pelvic brim is the area in which it is easiest to identify the pelvic ureter. In that location, the ureter is superficial. Make a peritoneal incision lateral and parallel to the infundibulopelvic ligament below and above

FIGURE 4 Uterine artery medial to the takeoff of superior vesical artery



The right internal iliac artery can be seen below the scissors (R). The superior vesical artery is seen taking off anteriorly and continuing toward the bladder. The right uterine artery is seen below the grasper (L) taking off medially toward the uterus and coursing over the right ureter.

the pelvic brim to allow easy visualization of the ureter as it crosses over the common iliac artery (Figure 3).

Once identified, follow it along the lateral pelvic peritoneum until it intersects with the uterine artery.

2. Following the uterine artery. Make a peritoneal incision lateral and parallel to the infundibulopelvic ligament as indicated for the ureteral approach. Identify the external iliac artery and follow it cephalad to the common iliac artery bifurcation. Expose the internal iliac artery by simply displacing or dividing the loose areolar retroperitoneal connective tissue immediately ventral to the artery at the 12 o'clock position.

The superior vesical artery will become apparent as part of the anterior division of the internal iliac, and the uterine artery will be immediately medial to the takeoff of the superior vesical artery (Figure 4). Follow the uterine artery until it intersects with the ureter.

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FIGURES 5-9 Steps to displace the ureter at risk

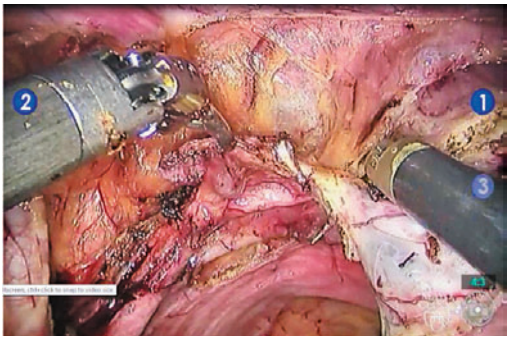

FIGURE 5 The left uterine artery is elevated and a monopolar spatula has been used to separate the artery from the left ureter.

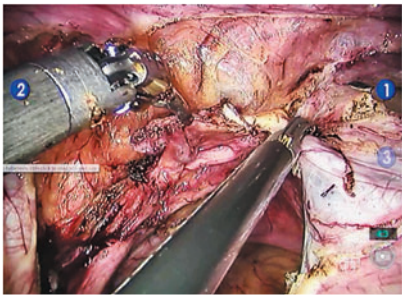

FIGURE 6 The left uterine artery is safely and selectively divided with a vessel sealing device.

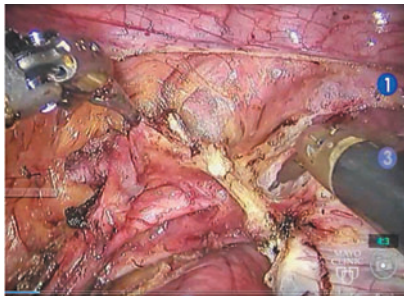

FIGURE 7 Once the uterine artery is divided the ureter is displaced laterally away from the cervix.

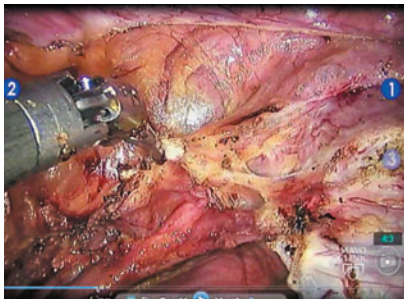

FIGURE 8 The left ureter has been "rolled away" from the cervix to allow a safe division of the left cardinal ligament. The medial segment of the transected left uterine artery is being held by a PK grasper.

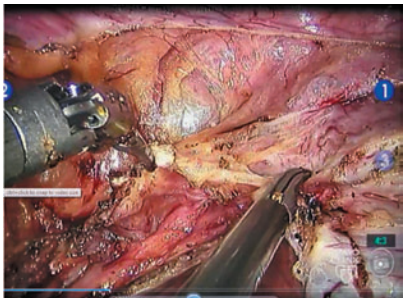

FIGURE 9 The left cardinal ligament is being divided with a vessel sealing device after transection of the left uterine artery and lateral displacement of the left ureter, preventing a ureteral injury.

Sometimes it may be difficult to identify the internal iliac or superior vesical arteries. In that case, place the lateral umbilical ligament under tension lateral to the bladder and follow it in retrograde fashion toward the origin of the superior vesical artery from the internal iliac artery. The uterine artery will be immediately medial to the origin of the superior vesical artery. Follow it as described for the uterine artery approach.

Lateral displacement of the ureter at risk. Once the intersection of the ureter and uterine artery are identified (Figure 1) and in the presence of the so-called cervical ureter, there is no need to completely dissect the parametrial portion of the ureter, known as "unroofing of the ureter," to prevent ureteral injury. The simple division of the uterine artery at its intersection with the ureter is adequate to visualize the direction of the parametrial ureter and also to laterally displace it, whenever necessary.

Elevate the uterine artery from the ureter and pass an instrument between the artery and the ureter (Figure 5). A vessel sealing device can then be safely applied to transect the uterine artery (Figure 6). Lateral displacement of the ureter (Figure 7), known as "rolling" the ureter, allows for a safe division of the cardinal ligament (Figure 8).

The cardinal ligament can now be safely divided with an electrocoagulation device (Figure 9). Use a blunt instrument to gently displace the ureter. Electrocoagulation is unnecessary unless the entire parametrial ureter needs to be dissected, which is almost never the case in a simple hysterectomy.

A variation of this approach consists of transection of the uterine artery at the level of the internal cervical os followed by lateral displacement of this pedicle. In a series of more than 1000 laparoscopic hysterectomies, no ureteral injuries were observed, according to J. Einarsson, MD (written communication, September 2014).

The ureter at vaginal cuff closure. After the uterus is removed, the relative safety that the uterine manipulator affords in cephalad displacement of the cervix and vaginal fornices no longer exists. Some ureters may then

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Please see Brief Summary of Full Prescribing Information for Lo Loestrin Fe, including Boxed Warning, on adjacent pages.

Please see Full Prescribing Information for Lo Loestrin Fe, including Boxed Warning, available at www.loloestrin.com.

References: 1. Lo Loestrin® Fe prescribing information. Rockaway, NJ: Warner Chilcott (US), LLC; 2012. **2.** Data on file. Rockaway, NJ: Warner Chilcott (US), LLC. **3.** US Food and Drug Administration. Guidance for industry: labeling for combined oral contraceptives. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075075.pdf. Published March 2004. Accessed May 21, 2014.

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Lo Loestrin® Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets)

BRIEF SUMMARY: Consult the Package Insert for Complete 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 should not be used by women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

Lo Loestrin® Fe is indicated for use by women to prevent pregnancy.

The efficacy of Lo Loestrin Fe in women with a body mass index (BMI) of > 35 kg/m^2 has not been evaluated.

4 CONTRAINDICATIONS

Do not prescribe Lo Loestrin Fe to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning* and *Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 *[see Warnings and Precautions (5.7)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.2)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.3)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic and Other Vascular Events

Stop Lo Loestrin Fe if an arterial or deep venous thrombotic event occurs. Although use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. 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. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Lo Loestrin Fe at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Lo Loestrin Fe no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest in older (> 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Lo Loestrin Fe if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

5.2 Carcinoma of the Breast and Cervix

Women who currently have or have had breast cancer should not use Lo Loestrin Fe because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.3 Liver Disease

Discontinue Lo Loestrin Fe if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. 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.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases per 100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.4 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Lo Loestrin Fe if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

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.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Lo Loestrin Fe. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking Lo Loestrin Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Lo Loestrin Fe if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.8 Bleeding Irregularities and 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 COC.

The clinical trial that evaluated the efficacy of Lo Loestrin Fe also assessed unscheduled bleeding and/or spotting. The participants in this 12-month clinical trial (N = 1,582 who had at least one post-treatment evaluation) completed over 15,000 cycles of exposure.

A total of 1,257 women (85.9 percent) experienced unscheduled bleeding and/or spotting at some time during Cycles 2 to 13 of this study. The incidence of unscheduled bleeding and/or spotting was highest during Cycle 2 (53 percent) and lowest at Cycle 13 (36 percent). Among these women, the mean number of days of unscheduled bleeding and/or spotting during a 28-day cycle ranged from 1.8 to 3.2 days.

Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over the one year study, with an average of less than 2 days per cycle.

Women who are not pregnant and use Lo Loestrin Fe may experience amenorrhea (absence of scheduled and unscheduled bleeding/spotting). In the clinical trial with Lo Loestrin Fe, the incidence of amenorrhea increased from 32 percent in Cycle 1 to 49 percent by Cycle 13. 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.

Some women may experience amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was preexistent.

5.9 COC Use Before or During Early Pregnancy

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Lo Loestrin Fe use should be discontinued if pregnancy is confirmed.

Administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Women with a history of depression should be carefully observed and Lo Loestrin Fe discontinued if depression recurs to a serious degree.

5.11 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid binding globulin increase with use of COCs.

5.12 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.13 Other Conditions

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

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking *[see Boxed Warning* and *Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.3)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

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

A multicenter phase 3 clinical trial evaluated the safety and efficacy of Lo Loestrin Fe for pregnancy prevention. The study was a one year, open-label, single-arm, uncontrolled study. A total of 1,660 women aged 18 to 45 were enrolled and took at least one dose of Lo Loestrin Fe.

Common Adverse Reactions (≥ 2 percent of all Treated Subjects): The most common adverse reactions reported by at least 2 percent of the 1,660 women using Lo Loestrin Fe were the following in order of decreasing incidence: nausea/vomiting (7 percent), headache (7 percent), bleeding irregularities (including metrorrhagia, irregular menstruation, menorrhagia, vaginal hemorrhage and dysfunctional uterine bleeding) (5 percent), dysmenorrhea (4 percent), weight fluctuation (4 percent), breast tenderness (4 percent), acne (3 percent), abdominal pain (3 percent), anxiety (2 percent), and depression (2 percent).

Adverse Reactions Leading to Study Discontinuation: 10.7 percent of the women discontinued from the clinical trial due to an adverse reaction. Adverse reactions occurring in ≥1 percent of subjects leading to discontinuation of treatment were in decreasing order: menstrual irregularities (including metrorrhagia, irregular menstruation, menorrhagia and vaginal hemorrhage) (4 percent), headache/migraine (1 percent), mood disorder (including mood swings, depression, anxiety) (1 percent), and weight fluctuation (1 percent).

Serious Adverse Reactions: deep vein thrombosis, ovarian vein thrombosis, cholecystitis.

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Lo Loestrin Fe.

7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors or of non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 Increase in Plasma Levels of Ethinyl Estradiol Associated with Co-Administered Drugs

Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20 percent. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

7.3 Changes in Plasma Levels of Co-Administered Drugs

COCs containing some synthetic estrogens (for example, ethinyl estradiol) may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed should not start COCs earlier than 4 weeks postpartum.

8.3 Nursing Mothers
When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs 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. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use
Safety and efficacy of Lo Loestrin Fe have been established in women of reproductive age. Efficacy is expected to be the same in postpubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use
Lo Loestrin Fe has not been studied in postmenopausal women and are not indicated in this population.

8.6 Renal Impairment
The pharmacokinetics of Lo Loestrin Fe has not been studied in subjects with renal impairment.

8.7 Hepatic Impairment
No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of Lo Loestrin Fe. However, steroid hormones may be poorly metabolized in patients with impaired liver function. 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 *[see Contraindications (4)* and *Warnings and Precautions (5.3)]*.

8.8 Body Mass Index
The safety and efficacy of Lo Loestrin Fe in women with a body mass index (BMI) > 35 kg/m^2 has not been evaluated.

10 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.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling.

Based on Lo Loestrin Fe Prescribing information dated 06/2012.

Manufactured By:
Warner Chilcott Company, LLC
Fajardo, PR 00738

Distributed By:
Actavis Pharma, Inc.
Parsippany, NJ 07054

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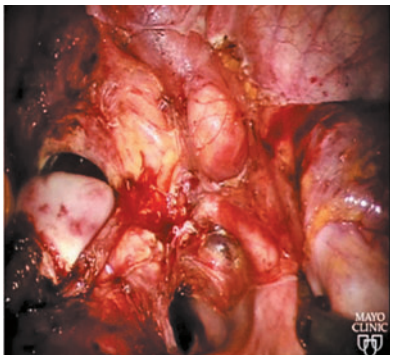
FIGURE 10 Ureter at risk of entrapment during vaginal cuff closure



The right ureter is seen taking a sharp medial course toward the right vaginal fornix. Once the uterus is removed and the cephalad displacement of the cervix is nonexistent it will become adjacent to the vaginal fornix and at risk for entrapment during cuff closure.

be close to the vaginal fornix and at risk of entrapment. They may be found lateral to the cervix and appear safe from injury, but then may take a sharp medial course toward the vaginal fornix, and be included during closure of the vaginal cuff angles (Figure 10).

The ureter in Figure 10 was lateral to the cervix and safe for cardinal ligament division. However, it was noted to have a sharp turn toward the vaginal fornix in spite of cephalad displacement of the cervix by the vaginal cup. In that situation, when the displacement is removed, the ureter may be at risk of entrapment during vaginal cuff closure. In another patient (Figure 11), the right ureter was suspected to be close to the vaginal fornix and it was dissected. It was then noted coursing within 5 mm of the vaginal cuff and could have been easily incorporated during cuff closure.

IMAGES USED WITH PERMISSION OF MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH.

Summary

In 12% of patients, the ureters are within 5 mm from the lateral cervical wall. This means that 1 out of 8 patients is at risk of ureteral injury during endoscopic hysterectomy. Cephalad displacement of the uterus with a uterine manipulator is helpful to reduce, but not to eliminate, the risk of injury. Identification of the intersection of the ureter with the uterine artery is necessary to determine the course of the ureter at risk.

Division of the uterine artery at its intersection with the ureter and lateral displacement of the ureter are necessary to prevent parametrial ureteral injury when the organ is suspected to be coursing adjacent to the cervix. The parametrial ureter is also at risk during closure of the vaginal cuff. COG

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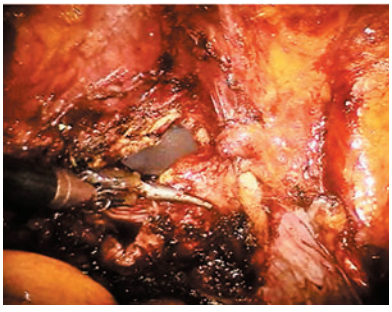
FIGURE 11 Right ureter at risk of suture entrapment during cuff closure



The uterus has been removed and an inflatable balloon is in the vagina to maintain the pneumoperitoneum. The right ureter is seen adjacent to the vaginal angle and at risk of suture entrapment unless identified.

A NOVEL TREATMENT WITH AN ALTERNATIVE TO A PROGESTIN

FOR YOUR POSTMENOPAUSAL PATIENTS WITH A UTERUS[1]

Help her put moderate to severe hot flashes as well as bone loss in their place[2]

The first and only treatment of its kind[1]

DUAVEE combines conjugated estrogens (CEs) with the SERM* bazedoxifene (BZA):

- CEs provide significant relief of **moderate to severe hot flashes due to menopause** and prevent postmenopausal osteoporosis[2]
- BZA helps protect the uterine lining from endometrial hyperplasia associated with estrogen-alone treatment[2]

Purposeful pairing of
CONJUGATED ESTROGENS

with the SERM
BAZEDOXIFENE
instead of a progestin

IMPORTANT SAFETY INFORMATION

Women taking DUAVEE should not take progestins, additional estrogens, or additional estrogen agonists/antagonists.

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. DUAVEE contains bazedoxifene, an estrogen agonist/antagonist that reduces the risk of endometrial hyperplasia that can occur with estrogens and 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.

Estrogen 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). Should either of these occur or be suspected, DUAVEE should be discontinued immediately.

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 agonists/antagonists, including bazedoxifene, and estrogens individually are known to increase the risk of venous thromboembolism (VTE).

DUAVEE™

CONJUGATED ESTROGENS/
BAZEDOXIFENE 0.45 MG/20 MG TABLETS

DUAVEE is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis.

Use DUAVEE 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.

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis, and non-estrogen medication should be carefully considered.

DUAVEE should not be used in women with undiagnosed abnormal uterine bleeding; known, suspected, or past history of breast cancer or estrogen-dependent neoplasia; active or past history of venous or arterial thromboembolism; hypersensitivity to estrogens, bazedoxifene, or any ingredients; known hepatic impairment or disease; known thrombophilic disorders. Women who are or may become pregnant and nursing mothers should not use DUAVEE.

The use of estrogen alone has been reported to result in an increase in abnormal mammograms requiring further evaluation. The effect of treatment with DUAVEE on the risk of breast and ovarian cancer is unknown.

Estrogens increase the risk of gallbladder disease. Discontinue estrogen if loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs. Monitor thyroid function in women on thyroid replacement therapy, because estrogen increases thyroid binding globulin (TBG) levels.

Adverse reactions more common in the DUAVEE treatment group in four placebo-controlled studies were muscle spasms, nausea, diarrhea, dyspepsia, abdominal pain upper, oropharyngeal pain, dizziness, and neck pain.

Please see brief summary of Full Prescribing Information, including Boxed Warning, on the following pages.

*Selective estrogen receptor modulator, also known as an estrogen agonist/antagonist. †Based on eligibility. ‡Terms and conditions apply.

References: 1. Kharode Y, Bodine PVN, Miller CP, Lyttle CR, Komm BS. The pairing of a selective estrogen receptor modulator, bazedoxifene, with conjugated estrogens as a new paradigm for the treatment of menopausal symptoms and osteoporosis prevention. *Endocrinology.* 2008;149(12):6084-6091. **2.** DUAVEE [package insert]. New York, NY: Pfizer Inc; 2013.

ORDER SAMPLES† AND SAVINGS CARDS‡ AT **DUAVEEHCP.COM**

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Pfizer U.S. Pharmaceuticals

DUAVEE™

CONJUGATED ESTROGENS/
BAZEDOXIFENE 0.45 MG/20 MG TABLETS

BRIEF SUMMARY: This is only a brief summary of prescribing information. For current Full Prescribing Information, please visit www.duaveehcp.com.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, AND PROBABLE DEMENTIA

Women taking DUAVEE should not take additional estrogens *[see Warnings and Precautions]*.

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. DUAVEE 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]*.

Estrogen therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions]*.

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]*.

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 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]*.

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 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

DUAVEE is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis.

Important Limitations of Use

Use DUAVEE 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. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medication should be carefully considered.

CONTRAINDICATIONS

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

- Undiagnosed abnormal uterine bleeding
- Known, suspected, or past history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism (PE), or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, myocardial infarction) or history of these conditions
- Hypersensitivity (for example, anaphylaxis, angioedema) to estrogens, bazedoxifene, or any ingredients
- Known hepatic impairment or disease
- Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders
- Pregnancy, women who may become pregnant, and nursing mothers. DUAVEE may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus

WARNINGS AND PRECAUTIONS

Drugs Containing Progestins, Estrogens or Estrogen Agonist/Antagonists

DUAVEE contains CE and bazedoxifene, an estrogen agonist/antagonist. Women taking DUAVEE should not take progestins, additional estrogens or additional estrogen agonist/antagonists.

Cardiovascular Disorders

Estrogen agonist/antagonists (including bazedoxifene, a component of DUAVEE) and estrogens individually are known to increase the risk of venous thromboembolism (VTE).

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should any of these occur or be suspected, DUAVEE should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or 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.

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).

Should a stroke occur or be suspected, DUAVEE should be discontinued immediately *[see Contraindications]*.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal myocardial infarction, silent myocardial infarction, or CHD death) was reported in women receiving estrogen-alone compared to placebo.

Subgroup analyses of women 50 to 59 years of age suggest 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).

Venous Thromboembolism (VTE)

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.

If feasible, DUAVEE 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. Because immobilization increases the risk for venous thromboembolic events independent of therapy, DUAVEE should be discontinued prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest) and DUAVEE therapy should be resumed only after the patient is fully ambulatory. In addition, women taking DUAVEE should be advised to move about periodically during travel involving prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women 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 increased risks of 15- to 24-fold for 5 to 10 years or more of treatment. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

DUAVEE contains an estrogen agonist/antagonist. This component reduces the risk of endometrial hyperplasia that can occur with the CE component. Endometrial hyperplasia may be a precursor to endometrial cancer. Women taking DUAVEE should not take additional estrogens as this may increase the risk of endometrial hyperplasia.

Clinical surveillance of all women taking DUAVEE 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.

Breast Cancer

The most important randomized clinical study 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 (0.625 mg)-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80).

The use of estrogen-alone has been reported to result in an increase in abnormal mammograms requiring further evaluation. The effect of treatment with DUAVEE on the risk of breast cancer is unknown.

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

In some epidemiological studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association. The effect of treatment with DUAVEE on the risk of ovarian cancer 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 *[see Use in Specific Populations]*.

Gallbladder Disease

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

Visual Abnormalities

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

Elevated Blood Pressure

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

Hypertriglyceridemia

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

Hepatic Impairment and Past History of Cholestatic Jaundice

DUAVEE has not been studied in women with impaired liver function or past history of cholestatic jaundice.

Estrogens may be poorly metabolized in women with impaired liver function.

On average, women with hepatic impairment treated with bazedoxifene alone showed a 4.3-fold increase in overall exposures compared with controls *[see Use in Specific Populations]*.

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, DUAVEE should be discontinued. Use of DUAVEE in patients with hepatic impairment is contraindicated *[see Contraindications]*.

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. Because of this, patients who have conditions that might be influenced by this factor, such as cardiac dysfunction or renal impairment, warrant careful observation when estrogens are prescribed. Use of DUAVEE in patients with renal impairment is not recommended *[see Use in Specific Populations]*.

Hypocalcemia

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

Hereditary Angioedema

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

Exacerbation of Other Conditions

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

Premenopausal Women

There is no indication for premenopausal use of DUAVEE. The efficacy and safety of DUAVEE in premenopausal women have not been established, and its use is not recommended.

Laboratory Tests

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

Drug-Laboratory Test Interactions

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

Increased thyroid-binding globulin (TBG) 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
The following adverse reactions are discussed in greater detail in other sections of the label:
- Cardiovascular Disorders *[see Warnings and Precautions]*
- Malignant Neoplasms *[see Warnings and Precautions]*
- Gallbladder Disease *[see Warnings and Precautions]*
- Hypertriglyceridemia *[see Warnings and Precautions]*

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

The safety of CE/bazedoxifene was evaluated in four Phase 3 clinical trials ranging from 12 weeks to 24 months in duration and enrolling 6,210 postmenopausal women age 40 to 75 years (mean age 55 years). A total of 1,224 patients were treated with DUAVEE and 1,069 patients received placebo. Women enrolled in Studies 1 and 2 received calcium (600-1200 mg) and vitamin D (200-400 IU) daily, while women in Studies 3 and 4 received no calcium and vitamin D supplementation as part of the protocol.

The incidence of all-cause mortality was 0.0% in the DUAVEE group and 0.2% in the placebo group. The incidence of serious adverse reactions was 3.5% in the DUAVEE group and 4.8% in the placebo group. The percentage of patients who withdrew from treatment due to adverse reactions was 7.5% in the DUAVEE group and 10.0% in the placebo group. The most common adverse reactions leading to discontinuation were hot flush, abdominal pain upper, and nausea.

The most commonly observed adverse reactions (incidence ≥ 5%) more frequently reported in women treated with DUAVEE than placebo are summarized in the following table.

ADVERSE REACTIONS (INCIDENCE ≥ 5%) MORE COMMON IN THE DUAVEE TREATMENT GROUP IN PLACEBO-CONTROLLED TRIALS

	DUAVEE (N=1224) n (%)	Placebo (N=1069) n (%)
Gastrointestinal disorders		
Nausea	100 (8)	58 (5)
Diarrhea	96 (8)	57 (5)
Dyspepsia	84 (7)	59 (6)
Abdominal pain upper	81 (7)	58 (5)
Musculoskeletal and connective tissue disorders		
Muscle spasms	110 (9)	63 (6)
Neck pain	62 (5)	46 (4)
Nervous system disorders		
Dizziness	65 (5)	37 (3)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	80 (7)	61 (6)

Venous thromboembolism: In the clinical studies with DUAVEE, the reporting rates for venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) were low in all treatment groups. Adverse reactions of venous thromboembolism were reported in 0.0% of patients treated with DUAVEE and 0.1% of patients treated with placebo. Due to the low rate of events in both groups, it is not possible to conclude that the risk of venous thromboembolism with DUAVEE is different from that seen with other estrogen therapies *[see Warnings and Precautions]*.

DRUG INTERACTIONS
No drug interaction studies were conducted with DUAVEE. Results from *in vitro* and *in vivo* studies and clinical studies conducted with the CE or bazedoxifene components of DUAVEE are noted below:

Cytochrome P450 (CYP)
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 the exposure of CE resulting in an increased risk of endometrial hyperplasia. Therefore, for chronically administered CYP3A4 inhibitors (>30 days) concurrently administered with DUAVEE, adequate diagnostic measures, including directed or random endometrial sampling when indicated by signs and symptoms of endometrial hyperplasia, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Bazedoxifene undergoes little or no cytochrome P450 (CYP)-mediated metabolism. Bazedoxifene does not induce or inhibit the activities of major CYP isoenzymes. *In vitro* data suggest that bazedoxifene is unlikely to interact with co-administered drugs via CYP-mediated metabolism.

Uridine Diphosphate Glucuronosyltransferase (UGT)
Bazedoxifene undergoes metabolism by UGT enzymes in the intestinal tract and liver. The metabolism of bazedoxifene may be increased by concomitant use of substances known to induce UGTs, such as rifampin, phenobarbital, carbamazepine, and phenytoin. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. 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.

Atorvastatin
Concomitant administration of bazedoxifene (40 mg daily) and atorvastatin (20 mg, single-dose) to healthy postmenopausal women did not affect the pharmacokinetics of bazedoxifene, atorvastatin or its active metabolites.

USE IN SPECIFIC POPULATIONS
Pregnancy Pregnancy Category X *[see Contraindications]*

DUAVEE must not be used in women who are or may become pregnant.

No studies were performed on animals to evaluate the effects on reproduction with CE/bazedoxifene.

Administration of bazedoxifene to rats at maternally toxic dosages ≥ 1 mg/kg/day (≥ 0.3 times the human area under the curve (AUC) at the 20 mg dose) resulted in reduced numbers of live fetuses and/or reductions in fetal body weights. No fetal developmental anomalies were observed. In studies conducted with pregnant rabbits treated with bazedoxifene, abortion and an increased incidence of heart (ventricular septal defect) and skeletal system (ossification delays, misshapen or misaligned bones, primarily of the spine and skull) anomalies in the fetuses were present at maternally toxic dosages of ≥ 0.5 mg/kg/day (2 times the human AUC at the 20 mg dose).

Nursing Mothers
DUAVEE should not be used by lactating women *[see Contraindications]*. It is not known whether this drug is excreted in human milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving CE. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

Pediatric Use
DUAVEE is not indicated for use in children *[see Indications and Usage]*.

Geriatric Use
DUAVEE is not recommended for use in women greater than 75 years of age.

Of the total number of women in phase 3 clinical studies who received DUAVEE, 4.60% (n=224) were 65 years and over. DUAVEE was not studied in women aged 75 and over. No overall differences in safety or effectiveness were observed between women 65-74 years of age and younger women, and other reported clinical experience has not identified differences in responses between the elderly and younger women, but greater sensitivity of some older women cannot be ruled out.

An increased risk of probable dementia in women over 65 years of age was reported in the WHIMS ancillary studies of the WHI using daily CE (0.625 mg).

Renal Impairment
DUAVEE is not recommended for use in patients with renal impairment.

The pharmacokinetics, safety, and efficacy of DUAVEE have not been evaluated in women with renal impairment.

Hepatic Impairment
DUAVEE is contraindicated in patients with hepatic impairment *[see Contraindications]*.

The pharmacokinetics, safety, and efficacy of DUAVEE have not been evaluated in women with hepatic impairment. In a pharmacokinetics study of bazedoxifene 20 mg alone, the Cmax and AUC of bazedoxifene increased 67% and 143%, respectively, in women with mild hepatic impairment (Child Pugh Class A), compared to healthy women. The Cmax and AUC of bazedoxifene increased 32% and 109%, respectively, in women with moderate hepatic impairment (Child Pugh Class B). The Cmax and AUC of bazedoxifene increased 20% and 268%, respectively, in women with severe hepatic impairment (Child Pugh Class C).

No pharmacokinetic studies with CE were conducted in women with hepatic impairment.

Use in Women with Body Mass Index (BMI) > 27 kg/m^2
A 17% reduction in bazedoxifene exposure was predicted in women with BMI > 27 kg/m^2 (N=144) compared to those with BMI ≤ 27 kg/m^2 (N=93) after administration of DUAVEE, based on a population pharmacokinetic model using data from four Phase 1 studies. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. Regardless of BMI, 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.

PATIENT COUNSELING INFORMATION See FDA-approved patient labeling (Patient Information).
Venous Thromboembolic Events
Advise patients to immediately report to their physician any signs or symptoms related to venous thrombosis and thromboembolic events *[see Warnings and Precautions]*.

Abnormal Vaginal Bleeding
Inform postmenopausal women of the importance of reporting abnormal vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions]*.

Possible Serious Adverse Reactions with Estrogen Therapy
Inform postmenopausal women of possible serious adverse reactions of estrogen therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions]*.

Possible Less Serious Adverse Reactions with DUAVEE
Inform postmenopausal women of possible less serious but common adverse reactions of DUAVEE therapy such as muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, throat pain, dizziness and neck pain.

Calcium and Vitamin D Intake
Advise patients to add supplemental calcium and/or vitamin D to the diet if daily intake is inadequate.

This brief summary is based on the DUAVEE full prescribing information LAB-0582-1.0, October 2013.

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NEW REPORT: Teen birth rates continue to decline

Birth rates for adolescents in the United States continue their dramatic drop, although they are still far higher than in most developed countries, according to a National Center for Health Statistics (NCHS) report.

Last year, adolescent girls aged 15 to 19 years had a birth rate of 26.6 per 1000, according to preliminary data, which was less than half the 1991 rate of 61.8 and less than one-third the 1957 rate of 96.3.

The decline has been almost continuous for 5 decades except for small upturns and a 23% increase from 1986 to 1991. The 2013 total number of adolescent births, at 274,641, was below 300,000 for only the second time since 1940. It was 280,997 in 1945 and peaked at 644,708 in 1970.

However, the United States, which long had the highest teenaged birth rate of all developed countries, still has one of the highest. Switzerland had a recent rate of 3.4 and the Netherlands had a rate of 4.8. Of 31 selected countries including Japan, Canada, Israel, and many European nations, only 7 had rates above 20 in reports from 2009 to 2012.

The vast majority of adolescent births in the United States are to mothers aged 18 or 19 years. In 2013, that group had 199,407 births, while girls aged 15 to 17 years had 75,234 and those aged 10 to 14 years had 3108.

Although almost all states have seen impressive reductions in the last 20 years, specifically in the 5 years ending in 2012—the last year state data were available—states still vary greatly in both their adolescent birth rates and the rates of decline. In 2012, Vermont had a birth rate of 16.3 per 1000 for teenagers aged 15 to 19 years and New Hampshire's rate was 13.8. On the other end of the scale, New Mexico's rate was 47.5 and Oklahoma's was 47.3.

Colorado has received media attention for its rapid reduction, which state officials attribute to the Colorado Family Planning Initiative.

The states with rates of 36 or higher per 1000 were Alabama, Arizona, Arkansas, District of Columbia, Kentucky, Louisiana, Mississippi, New Mexico, Oklahoma, South Carolina, Tennessee, Texas, and West Virginia.

The lowest teenaged birth rates, 13.8 to 22.9, were in Connecticut, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Rhode Island, Vermont, Virginia, and Wisconsin.

The NCHS says the drop in the adolescent birth rate during 2007–2012 ranged from 18% in Montana to 39% in Colorado.

Colorado has received media attention for its rapid reduction, which state officials attribute to the Colorado Family Planning Initiative that has provided 30,000 LARCs free or inexpensively to low-income women at 68 family planning clinics since 2009.

The NCHS notes that data on teenaged pregnancy, including abortion and fetal loss, are not as current as those on birth. However, from 1991 to 2009 the abortion rate among teenagers fell 56% to 16.3 per 1000.

It also said an analysis of 2 cycles of the National Survey of Family Growth, also done by the NCHS, "concluded that improved contraceptive use may have been the key factor behind the declines in [teenaged] birth rates."

The National Survey of Family Growth, which is done by interviewing subjects, also found that from the time the survey was done in 1988 to the survey cycle of 2006–2010 there had been a gradual reduction in the percentage of both male and female teenagers who had had sex.

Over those 2 decades, the rate for girls who had had intercourse dropped from 51% to 43%. For boys, it dropped from 60% to 42%. CDG

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KATHY HUANG, MD; JOHN F. STEEGE, MD

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JAMES A. GREENBERG, MD, & MOBOLAJI OLUWASEUN AJAO, MD

PRO CON

Should I use mesh?

VINCENT LUCENTE, MD, MBA, & CARLOS ROBERTS, MD; ANDREW I. SOKOL, MD, & LADIN YUTERI-KAPLAN, MD

DR. EINARSSON ON TECHNOLOGY & THE OB/GYN | PLUS AAGL Preview

Technology and the ob/gyn

Advances in technology and medicine are closely intertwined. In the last few decades, we have witnessed a complete transformation of the way we practice medicine and this evolution continues at a rapid pace, in large part due to technological advances. The introduction of novel devices into surgical practice entails an intricate balance between ensuring patient safety and expeditiously bringing enabling technology into the operating room.

The Food and Drug Administration (FDA) classifies surgical devices into 3 categories. Class I devices do not require premarket approval or clearance (dental floss is an example), Class II devices are cleared using the Premarket Notification (510K) process (eg, laparoscopic morcellators), and Class III devices (eg, implantable pacemakers) are approved by the Premarket Approval (PMA) process, which is the most stringent type of medical device application and requires clinical trials and rigorous documentation.

Most medical devices go through the 510K process, which has come under some scrutiny.[1] The contentious issue is that the 510K process enables companies to market a device if it is considered "substantially equivalent" to a device already on the market (ie, a predicate device). This process is significantly faster and less expensive than the PMA process and, therefore, encourages the rapid introduction of new technology. However, there is minimal or no clinical testing required in the 510K process, and this may lead to unforeseen complications, such as happened with use of vaginal mesh for pelvic organ prolapse and more recently, with the use of electromechanical morcellation for tissue extraction in patients undergoing laparoscopic surgery for symptomatic uterine fibroids.

Introducing **novel devices into surgical practice** requires balancing patient safety and expeditiousness.

Cost is another important factor in introducing new technology to the market. In the current environment, with its emphasis on cost containment, novel technology should ideally be not only enabling and safe, but also cost effective. Unfortunately, cost effectiveness can be problematic to prove for 2 reasons. Cost can be difficult to ascertain because surgical billing is complicated. Also, the main variable in surgical trials (ie, the surgeon) introduces significant bias. Most surgeons are not equally adept at performing 2 different surgical modalities, such as conventional laparoscopy and robotically assisted laparoscopy.

In this special section on surgical technology, respected authors explore some of these points. Point/Counterpoint debates explore the role of robotics in gynecology (page T3) and the use of vaginal mesh in surgical treatment of pelvic organ prolapse (page T12). Also inside (on page T10) you will find information on the AAGL conference coming up in November in Vancouver, British Columbia. Finally, enabling technologies for laparoscopic contained tissue extraction (CTE) are described beginning on page T22. This rapidly evolving surgical strategy may offer a safe alternative to uncontained electromechanical morcellation. CDG

DR. EINARSSON, Deputy Editor of *Contemporary OB/GYN*, is Associate Professor of Obstetrics and Gynecology at Harvard Medical School, Boston, Massachusetts, and Director of the Division of Minimally Invasive Gynecologic Surgery at Brigham and Women's Hospital, Boston.
This is his second year serving as editor of the special section on surgical technology.

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Indication

Essure is indicated for women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes.

Important Safety Information

Who should not use Essure

- Essure is contraindicated in patients who are uncertain about ending fertility, can have only one insert placed (including contralateral proximal tubal occlusion or suspected unicornuate uterus), have previously undergone a tubal ligation, are pregnant or suspect pregnancy, delivered or terminated a pregnancy less than 6 weeks prior to the Essure procedure, have an active or recent upper or lower pelvic infection, or have a known allergy to contrast media.
- Patients undergoing immunosuppressive therapy (e.g. systemic corticosteroids or chemotherapy) are discouraged from undergoing the Essure procedure.
- Uterine or fallopian tube anomalies may make it difficult to place Essure inserts.

Please see additional Important Safety Information about Essure on next page.

essure®
permanent birth control

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Important Safety Information continued

Prescription Only

Caution: Federal law restricts this device to sale by or on the order of a physician. Device to be used only by physicians who are knowledgeable hysteroscopists; have read and understood the Instructions for Use and Physician Training manual; and have successfully completed the Essure training program, including preceptoring in placement until competency is established, typically 5 cases.

Pregnancy Considerations
- The Essure procedure should be considered irreversible. Patients should not rely on Essure inserts for contraception until an Essure Confirmation Test [modified hysterosalpingogram (HSG)] demonstrates bilateral tubal occlusion and satisfactory location of inserts.
- Effectiveness rates for the Essure procedure are based on patients who had bilateral placement. If Essure inserts cannot be placed bilaterally, then the patient should not rely on Essure inserts for contraception.
- Effects, including risks, of Essure inserts on in vitro fertilization (IVF) have not been evaluated.
- Pregnancies (including ectopic pregnancies) have been reported among women with Essure inserts in place. Some of these pregnancies were due to patient non-compliance or incorrect clinician interpretation of the Essure Confirmation Test (modified HSG).

Procedural Considerations
- Perform the Essure procedure during early proliferative phase of the menstrual cycle. Terminate procedure if distension fluid deficit exceeds 1500cc or hysteroscopic time exceeds 20 minutes as it may signal uterine or tubal perforation. Never attempt to advance Essure insert(s) against excessive resistance. If tubal or uterine perforation occurs or is suspected, discontinue procedure and work-up patient for possible complications related to perforation, including hypervolemia. Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity due to risk of fractured insert, fallopian tube perforation or other injury.
- DO NOT perform the Essure procedure concomitantly with endometrial ablation. Avoid electrosurgery on uterine cornua and proximal fallopian tubes without visualizing inserts.

Nickel Allergy
Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.

MRI Information
The Essure insert was determined to be MR-conditional according to the terminology specified in the American Society for Testing and Materials (ASTM) International, Designation: F2503-05.

Clinical Trial Experience
- Safety and effectiveness of Essure is not established in patients under 21 or over 45 years old, nor in patients who delivered or terminated a pregnancy less than 8-12 weeks before procedure. Women undergoing sterilization at a younger age are at greater risk of regretting their decision.
- The most common (≥10%) adverse events resulting from the placement procedure were cramping, pain, and nausea/vomiting. The most common adverse events (≥3%) in the first year of reliance were back pain, abdominal pain, and dyspareunia.

This product does not protect against HIV infection or other sexually transmitted diseases.

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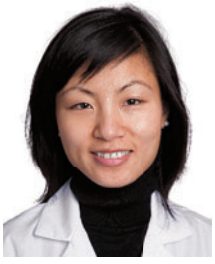
TWO EXPERT OPINIONS

DOES THE ROBOT HURT OR HELP?

Using the robot for gynecologic surgery makes sense

BY **KATHY HUANG, MD**



DR. HUANG is Director, Gynecologic Robotic Surgery, and Assistant Professor, New York University School of Medicine, New York. She reports receiving consulting fees from Intuitive Surgical.

Robotic-assisted (RA) laparoscopic surgery is one of the newest innovations in minimally invasive gynecologic surgery (MIGS). The technology was first used in 1999 to perform a tubal anastomosis, and applications have since expanded to many benign gynecologic procedures, including but not limited to hysterectomy, myomectomy, sacrocolpopexy, and treatment of endometriosis.[1,2] In 2005, the da Vinci surgical system was approved by the US Food and Drug Administration to be used in gynecology. It provides 3-D visualization of the operative field, 7 degrees of freedom of motion, ergonomic benefits, and elimination of surgeons' tremors.[2,3] It has decreased the percentage of gynecologic cases performed via laparotomy incision by overcoming some of the challenges associated with traditional laparoscopy.[4]

The robotic platform also has been shown to have a shorter learning curve than conventional laparoscopy.[5-7] Many studies have demonstrated the safety and feasibility of robotic surgery in gynecology, but the definitive role of the robot within the realm of MIGS has yet to be established. Here I summarize the evidence regarding the role of the robotic platform in benign gynecologic surgery.

Hysterectomy

Hysterectomy is the most common surgery performed by gynecologists in the United States. In 2003, 538,722 benign hysterectomies were performed; 66.1% abdominally, 21.8% vaginally, and 11.8% laparoscopically.[8] In 2002, Diaz-Arrastia et al demonstrated the safety and feasibility of robotic-assisted hysterectomy (RAH), which has been reaffirmed in multiple studies.[9,10] From 2007 to 2010, benign laparoscopic hysterectomy increased from 24.3% to 30.5% as documented in a cohort of 264,758 women; RAH increased from 0.5% to 9.5%.[11] Between 1998 and 2010, the number of inpatient hysterectomies performed in the United States decreased by more than 40%, which suggests that more hysterectomies are being performed using a minimally invasive approach.[12]

The trend toward more minimally invasive procedures continues amidst debate about which minimally invasive approach is optimal. In a recent report on a randomized controlled trial comparing conventional laparoscopic hysterectomy to RAH, 56 women underwent

hysterectomy for benign indications and the operative time for RAH was significantly longer, with a mean difference of 77 minutes.[13] There were no differences in estimated blood loss or length of stay and no statistically significant differences in complications or postoperative pain. However, this group of 5 skilled laparoscopic surgeons performed 26 RAH in the span of study enrollment. Therefore, they were still in the early part of their learning curve in adoption of robotics, making it difficult to draw valid conclusions from this study.

In another trial, 100 patients with benign indications were randomized to robotic or laparoscopic hysterectomy.[14] No statistically significant differences were seen in length of hospital stay, time to return to activity, time to return to work, or analgesic use, nor were there differences in intraoperative complications such as blood loss and conversion rates. However, there was a significant difference in mean operating times. Given that both traditional laparoscopy and RAH have been shown in multiple studies to have similar outcomes, the optimal approach should be individualized depending on a patient's clinical scenario and a surgeon's expertise.

Martino et al reported on a comparison of quality outcome measures in patients undergoing hysterectomy.[15] In their large, retrospective cohort study, 2554 patients underwent hysterectomy for benign disease in an academic community hospital over 4 years. They found that patients who underwent robotic hysterectomy for benign disease had less blood loss, a shorter hospital stay, fewer readmissions <30 days, and reported cost savings related to these readmissions when compared to the laparoscopic, abdominal, and vaginal cohorts. The total readmission cost was $32,946 for robotic procedures, $50,290 for laparoscopic procedures, $328,230 for abdominal procedures, and $51,264 for vaginal hysterectomies. The robotic cohort had the lowest rate of readmission <30 days.

Myomectomy

Myomectomy is an option for women with fibroids who want uterine-sparing surgery. Laparotomy has historically been the most widely used approach, despite its associated increased morbidity; however, minimally invasive myomectomies have gradually been increasing over the past decade largely due to the use of a robot-assisted approach.[16]

> The optimal approach **should be individualized** depending on a patient's clinical scenario and a surgeon's expertise.

Since publication of the first case series of robot-assisted laparoscopic myomectomies that demonstrated the safety and feasibility of the procedure, multiple studies have demonstrated the benefits of robotic myomectomy versus abdominal myomectomy.[17] In fact, the robot may allow patients with larger myomas to have a minimally invasive procedure.[18] This may be attributable to the robotic platform's ability to overcome the technical challenges of laparoscopic myomectomies, specifically multilayer closures.

In a comparison of short-term outcomes between robot-assisted and abdominal myomectomies, the former approach was associated with lower estimated blood loss (195 mL vs 365 mL) and shorter length of hospital stay (1.48 days vs 3.62 days).[19] However, it was also associated with longer operative times (231 ±85 minutes vs 154 ±43 minutes) and higher costs ($30,084.20 ±$6689.29 vs $13,400.62 ±$7747.26). Two larger retrospective studies have demonstrated similar results.[18,20] No differences in short-term outcomes and complication rates were found in a comparison of robotic laparoscopic myomectomies but the operative time and estimated blood loss were found to be significantly greater in the robotic cohort.[21] However, these differences may be attributable to the use of barbed sutures in the laparoscopic cohort only.

Because myomectomies are considered a fertility-sparing surgery, pregnancy outcomes are also an important factor when considering techniques. In a retrospective study of 107 women who conceived resulting in 127 pregnancies and 92 deliveries, results were similar to prior published studies looking at laparoscopic myomectomy outcomes.[22] Obstetrical outcomes were also similar and included only 1 uterine rupture and 1 uterine dehiscence, which resulted in no adverse outcomes. Robot-assisted myomectomy is a safe option for women desiring future fertility.

Sacrocolpopexy

Abdominal sacrocolpopexy is a common procedure primarily performed by pelvic surgeons to correct apical pelvic organ prolapse with long-term success rates ranging from 78% to 100%.[23] Its proven efficacy makes it an ideal procedure; however the abdominal approach is often associated with significant morbidity and post-

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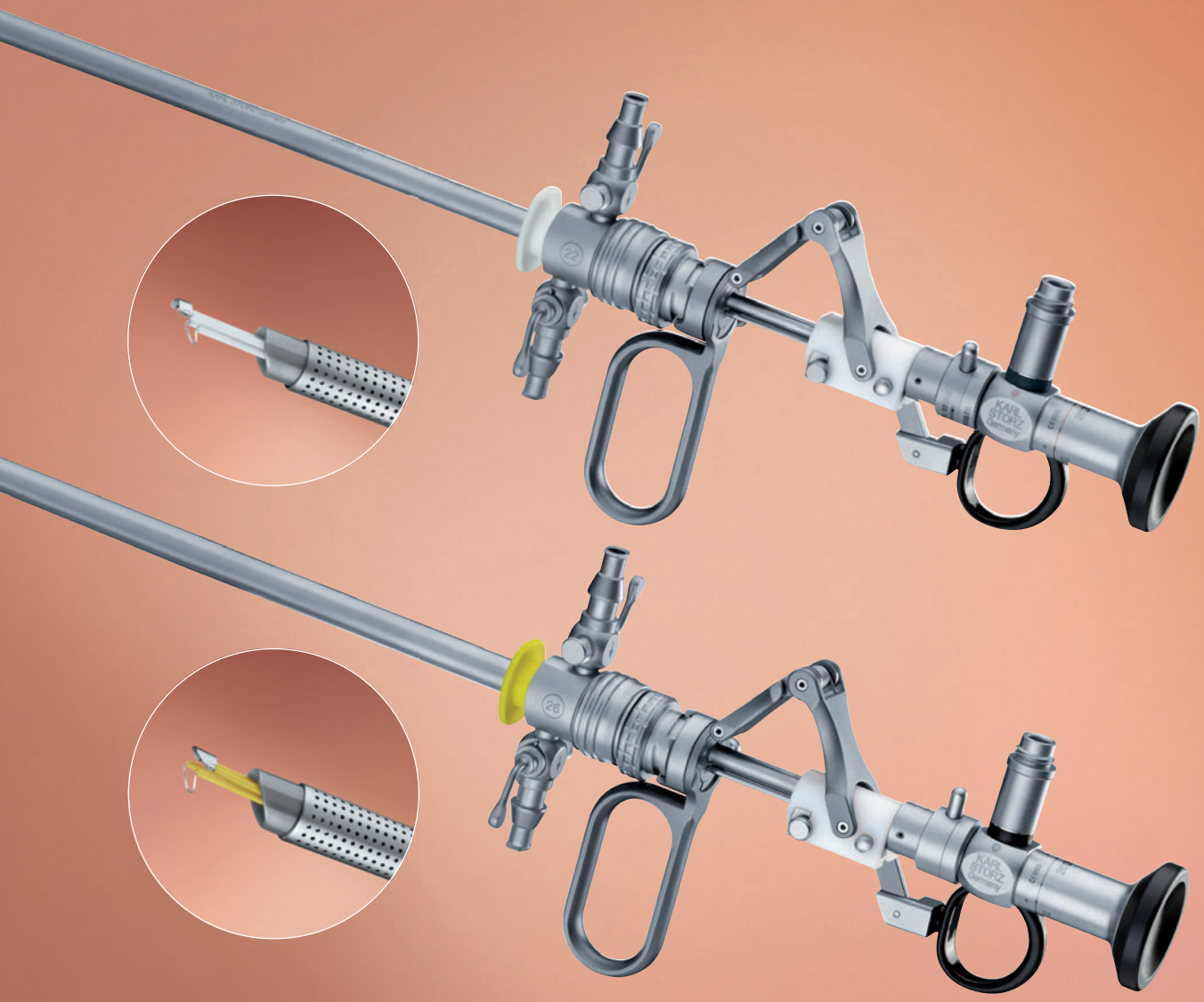

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operative recovery time.

Minimally invasive sacrocolpopexy has been steadily increasing over the past decade. Robotic surgery results in similar long-term outcomes and has been shown to decrease morbidity as it relates to estimated blood loss and length of hospital stay when compared to abdominal sacrocolpopexy.[24] Sustained efficacy over 44 months after robotic sacrocolpopexy also has been demonstrated, results similar to abdominal sacrocolpopexy.[25] In a randomized controlled trial, robotic sacrocolpopexy was associated with longer operating times, increased cost, and increased pain up to 3 to 5 weeks postoperatively as compared to the laparoscopic procedure.[23] As with other robotic procedures, the operative times and increased costs are likely surgeon-dependent, and increased skill will result in a decrease in both parameters.

Endometriosis

In a retrospective cohort study, a comparison of robotic and standard laparoscopy for treatment of endometriosis found significantly decreased operative time with laparoscopy. No differences were reported in estimated blood loss or intraoperative/postoperative complications.[27] That study demonstrated the feasibility of using the robot for endometriosis, however, there was no proven benefit to using it rather than laparoscopy. Most patients in both groups had stage I or II endometriosis. There was no comparison between abdominal endometriosis surgeries and robotic laparoscopic surgeries, but the authors suggest that the advantages of the robot would likely be noted in cases of severe endometriosis in which a surgeon may convert an abdominal approach to a robotic one.

The largest series on robot-assisted treatment of deep infiltrating endometriosis included 164 women with stage IV endometriosis who underwent robot-assisted laparoscopic treatment of endometriosis in 8 international clinics. The average operative time was 180 minutes. With a mean follow-up period of 10.2 months, 86.7% of the patients experienced a full recovery. Twenty-eight of the 42 patients desiring pregnancy were able to conceive postoperatively. No increases in surgical time, blood loss, intra- or postoperative complications were observed. The authors concluded that robotic surgery seems to be a promising platform for treatment of deeply infiltrating endometriosis.[28]

> Once a surgeon and team have surpassed their learning curve, robotic procedures **may take less time** than laparoscopic ones.

Cost

Many studies have demonstrated the increased costs associated with robotic-assisted surgery as compared to open or laparoscopic surgery. In one study, the average cost of a RAH was €4067 compared to €2151 for traditional laparoscopic hysterectomy.[29] In another study, mean hospital charges ($30,084.20 ±$6689.29 vs $13,400.62 ±$7747.26) also were reportedly higher for robotic myomectomies, but professional reimbursement was not statistically significant between the 2 groups.[19] Similar findings have been reported for robotic sacrocolpopexy.[23] In almost all of these studies, the robotic operative time was significantly longer. However, recent research revealed that once a surgeon and team have surpassed their learning curve, a robotic procedure may take less time than its laparoscopic counterparts.[30]

In a comprehensive financial review at a high-volume robotics program, profitability was achieved by increased robotic volume and operative efficiency.[31] This pattern has spanned surgical fields utilizing the robot. For example, a reduction in case time for sacrocolpopexy to 179 minutes allowed for profitability. Factors that made this feasible include having a coordinated nursing and surgical technician team, appropriate surgical instrumentation, and skilled surgeons. As surgical teams gain experience with the robotic surgical system and surgeons surpass the learning curve, overall costs can be expected to gradually decrease.

In our unpublished data, procedural time is significantly shorter in the RAH group when compared to laparoscopic hysterectomies (120 min vs 181 min, $P=0.001$). Since the primary contributor to cost is operating room time, the significant decrease in the procedural time leads to decreased cost for our robotic cohort when compared to the laparoscopic cohort ($9505 vs $7349). Our experience suggests that operative time is directly related to experience. Surgeons who are proficient on the robot can minimize costs by decreasing operating room time. Rather than focusing solely on the cost of performing the surgery, it is important to account for throughput and volume. The decreased operative time of 1 hr associated with RAH

has allowed our group to perform 3 to 4 RAH per day instead of 2 laparoscopic hysterectomies per day, effectively increasing throughput by at least 50%. This increased throughput is highly meaningful in the current economic climate. Cost and revenue aside, increasing throughput safely and effectively enables practitioners to care for more patients.

Summary

Robot-assisted surgery is an additional tool that surgeons can use to decrease the overall morbidity associated with many gynecologic procedures. Most studies cite increased operative time and cost as major limitations, but these factors are largely due to limited surgeon experience with the robotic platform. With increased surgeon knowledge, experience, and skill, robotic surgery will likely prove to be more advantageous for patients and surgeons and will eventually surpass traditional laparoscopic surgery. Finally, the role of the robotic platform is to maximize a patient's chance of having a minimally invasive procedure. The robotic platform has enabled many to reduce the number of open surgeries performed for benign gynecologic indications. COG

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TWO EXPERT OPINIONS The robot does not improve outcomes

BY **JOHN F. STEEGE, MD**

DR. STEEGE is a Professor in the Department of Obstetrics and Gynecology and former Director, Division of Advanced Laparoscopy and Pelvic Pain, University of North Carolina, Chapel Hill.

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Ideally, innovations in medicine that are wildly popular when first introduced later settle into an appropriate clinical niche as data accumulate about clinical outcomes and cost. Medical care would be well served if the use of the robot in gynecologic surgery were to follow this classic pattern.

Opposing this evolution, however, are the powerful forces of heavy marketing of robotics to the public and to surgeons. Hospitals join in and market their robotics programs to show the public that they're up to date.[1] In this marketing, which often uses text and images lifted directly from the robot manufacturer's website, the robot is described as having improved perioperative outcomes, making it superior to "conventional surgery." This leaves the reader to figure out whether the comparison is to conventional laparoscopy or to laparotomy. Members of the public who are naïve often assume that the comparison is to conventional laparoscopy.

Any form of laparoscopy is superior to laparotomy in terms of outcomes, including comfort, morbidity, and cost, but comparisons between conventional laparoscopy and the robot-assisted approach have completely failed to support the claims of superiority for the robot in gynecologic surgery. In addition, extensive analysis has shown the robot to be more expensive.[2]

But why quibble? Hasn't robotics "enabled" surgeons to do laparoscopy? Perhaps that is true in some instances, but it introduces another set of questions:

1 How can a gynecologist get good (or better) at minimally invasive gynecologic surgery (MIGS)?

In my view, there are 3 ways to get good at laparoscopic surgery: 1) Teach yourself, expanding your skills gradually over time (this is how most of the surgeons of my vintage learned it); 2) Get trained in a residency that does a high volume of laparoscopic surgery; or 3) Do a fellowship in MIGS. Many practicing ob/gyns did not have a laparoscopy-heavy residency and don't have a fellowship available to them. The robot appeals to them because they are left with option 1 only, and the robot enthusiasts would suggest that it can accelerate learning.

The robot appeals to 3 types of surgeons: 1) good, experienced laparoscopists who just happen to like to use it; 2) those whose training was not adequate in conventional laparoscopy; and 3) those who wish to take advantage of the marketing in building their surgical practices. I suggest that many gynecologic laparoscopists fit both categories 1 and 3.

The ones who fit categories 2 and 3, however, are the most dangerous. They are most likely to depend on the robot, to use it for most or all of their cases (even diagnostic laparoscopy: Really?!), and to explain it to their patients in a way that allows persistence of the fiction that the robot is inherently superior. In some instances, a clinician's desire to build an image of surgical competence seems to lead them to spend more time in the retroperitoneal spaces than they have been trained to do, and to tackle ever larger uteri without sufficient training or experience.

Having marketed themselves as better because they use the robot, these surgeons create their own trap: Even if the robot does help them learn, can they then go back to "straight sticks" without endangering their practices? Ironically, they then become robot-dependent,

leaving them in a tough spot when the robot is not available or breaks down. The path of least resistance is overwhelmingly attractive: Just keep telling patients they do it better with the robot.

But wait: There's another path that the specialty has not taken: better training of people already out in practice. Using a carefully structured and relatively inexpensive program of didactics and proctoring, Kaiser (Southern California Permanente Medical Group) was able to increase the percentage of hysterectomies done laparoscopically in their system from 38% to 78% over a 5-year span. More than 300 gynecologists took the course across 12 medical centers. None of these procedures was done robotically. The instructional materials for this process are available for use by other programs.[3]

2 What is the minimum annual surgical volume for maintaining competence?

If every practicing gynecologist did 60 to 80 major surgeries annually, then maybe this wouldn't be such an issue. But national data suggest that the annual volume is closer to 10 to 15 cases at most. Over the past 3 decades, the number of practicing gynecologists has increased 2.5-fold, while the number of hysterectomies has declined.[4]

Indeed, for the last several years, I've asked resident candidates while interviewing them, "How many surgeries do you think the average gynecologist does in a year?" Answers have ranged from 100 to 800! Our young ob/gyns-to-be seem to have little idea of what they're getting into. In contrast, each of my fellows does between 200 and 300 cases in each year of their 2-year fellowship. That is equivalent to an entire career of surgery for the average gynecologic surgeon in the country.

Even those who do graduate from laparoscopy-heavy residencies face a problem. In order to establish their practices in the community, they need to present themselves as competent surgeons. If their surgical volumes are not sufficient, they risk a declining reputation as well as true deterioration of their skills. The robotics marketing may serve their needs, as well as the competitive needs of the hospitals in which they practice.

There is much discussion currently about the number of robotic cases a surgeon should be required to do annually to maintain privileges in that area of MIGS. With the low case volume per surgeon described above, almost any specific number might only serve to inappropriately encourage surgeons to do cases robotically, when, in the vast majority of instances, they could be readily done with conventional laparoscopic techniques. Given recent publications documenting the increased cost of robotics, this has implications for the medical care system in general.

3 What should the patient be told about the surgeon's training and experience?

Many patients are becoming more informed consumers, and are asking their providers about their surgical volumes, complication rates, etc. Many others, wanting to trust, don't ask. Surgeons with low volumes are then in a difficult position regarding what they say on this topic. Is a surgeon really going to say, "I use the robot because it helps overcome the problem of my volume being low"? More likely, the patient will be left with the impression that because the robot is employed, the surgery will be done better.

Summary

Where does this leave us? Feeling that this is just the beginning of a much longer debate, I offer the following thoughts for consideration:

1) The true additive role of the robot may be limited to certain niches of gynecologic surgery (and even these are debated), such as sacral colpopexy and lymph node dissection.
2) The other role of the robot may be as a training tool, the "training wheels" of gynecologic surgery.
3) The healthcare system as a whole needs to carefully review the appropriate use of multiple technologies in general, and robotics in particular.
4) Current marketing practices that present misleading information to the public are unacceptable.
5) The public needs to be made more aware that robotics does not lead to better outcomes. The surgeon does the surgery, not the robot.
6) Surgeons need to be completely honest with their patients about why they use the robot, if they do. COG

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Hands-on surgery takes center stage at 43rd Congress

The 43rd annual AAGL Global Congress on minimally invasive gynecology takes place November 17–21, 2014, in Vancouver, British Columbia, Canada.

In recognition of recent issues and controversies in gynecologic surgery (ie, the use of robotics, electromechanical morcellation), the theme of this year's scientific program is "setting new standards in minimally invasive gynecologic surgery through knowledge and innovation." The scientific program chair is Arnold P. Advincula, MD.

A live interactive cadaveric demonstration called "Tackling Controversies and Optimizing Tissue Extraction in Minimally Invasive Gynecologic Surgery with Best Practice Techniques" will be held on Tuesday from 4:45 to 6 pm. The session will be an overview of the concerns about open power morcellation and an introduction to alternative tissue extraction techniques.

The Women Surgeons' Breakfast, scheduled for 6:30 to 7:45 on Wednesday morning and open to all attendees for a fee of $50, is called "Have You Got That Inner Glow?" It will be hosted by Dr. Quyen Nguyen, who will discuss how a molecular marker can make tumors light up, showing surgeons exactly where to cut.

A new feature of this year's conference is "Stainless Steel Surgeon," AAGL's version of the television show "Iron Chef." Three master surgeons will present their techniques for a secret procedure that will not be announced until the day of the event. The surgeons will have 30 minutes to perform portions of their procedures on cadavers in an operating theater (aka the "Surgical Stadium") set up in the convention center. Judges will decide who used the best, most effective approach (whether laparoscopic, robotic, or vaginal) and name the winner the Stainless Steel Surgeon. The face-off will take place on Thursday from 7:50 to 9:30 am.

The Vancouver Convention Centre West, site of the 2014 Global Congress

L to R: Ceana H. Nezhat, MD, FACOG, FACS, AAGL President; Linda Michaels, AAGL Executive Director; and Arnold P. Advincula, MD, FACOG, FACS, 2014 Scientific Program Chair and AAGL Vice President

"The theme of AAGL's 43rd Global Congress is 'Setting New Standards in Minimally Invasive Gynecologic Surgery through Knowledge and Innovation'" said Dr. Advincula.

"Many new elements have been incorporated into this year's meeting to both educate and inspire attendees with an impressive roster of esteemed faculty from all over the world. A common thread throughout all of these courses will be an emphasis on the fundamentals of minimally invasive surgery."

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Chief of Gynecology, Sloane Hospital for Women
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A case for and against mesh use

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THE CASE FOR MESH USE

By Vincent Lucente, MD, MBA, and Carlos Roberts, MD

In more than 25 years of experience as a pelvic reconstructive surgeon, I (Dr. Lucente) have practiced, published, evolved, and gained perspective. After completing a prospective randomized controlled trial (RCT) that favored the abdominal route of pelvic reconstruction[1] and listening to colleagues review and critique my paper, the fact that the abdominal group received a mesh augmentation sank in. Through my experience with the transvaginal tape (TVT) procedure,[2] which began in 1998, I had become confident in the transvaginal placement of mesh via a trocar-based delivery system. The innovation of transvaginal mesh (TVM) for pelvic organ prolapse (POP) expanded on the surgical principles of TVT. TVM for POP is an attractive surgical alternative without the technical challenges of traditional laparoscopy or the significant cost associated with robotically performed abdominal sacral colpopexy (ASC).

Surgeons' skills vary widely and teaching newer techniques is challenging. It is crucial to master new surgical techniques to optimally and safely execute TVM procedures.

In 1997 Sackett defined evidence-based medicine as the use of clinical expertise *combined* with current best evidence to make decisions about patient care.[3] But when we hear the term "evidence-based" we often ignore the component of clinical expertise. In 2009, Vintzileos elegantly discussed reality-based medicine versus evidence-based medicine. He also described the components of evidence-based medicine, highlighting the variation of clinical expertise among providers.[4] The opinion expressed in this commentary is grounded in reality-based medicine with careful consideration of evidence-based medicine.

The routine use of mesh in repair of abdominal wall fascial defects for hernia repair is based on the well established superior success rates when compared to suture-based repairs. If suture-based repair of dense regular connective tissue on the ventral, non-dependent surface of our upright abdominal-pelvic cavity requires mesh augmentation, there is no doubt that surgical repair of the pelvic floor, which

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THE CASE FOR MESH USE CONTINUED

is composed of mostly loose regular and irregular connective tissue, necessitates the use of mesh to achieve durable high success rates.

Beyond the differences in the connective tissue matrix and the force loads experienced by the abdominal wall and the female pelvic floor, one must also consider the degenerative effects of aging with loss of spinal curvature and decreasing neuromuscular function of the levator ani group.[5] Biomechanical and physical challenges to the pelvic organ support system experienced by older patients today exceed those experienced by women of a similar age in the past.[6] Obesity, physically demanding occupations, and recreational physical activity are just a few demographic and environmental factors that challenge the long-term durability of suture-based native tissue repairs.

Properties that facilitate host tissue integration while minimizing inflammation include the chemical composite of mesh filaments, mesh structure, pore size, rigidity, elasticity, burst strength, thickness, and overall density.[7,8] Although some believe that too small a pore size (<10mm) poses an absolute barrier for the "entry" of the neutrophils or macrophages to properly survey the mesh construct where bacteria (<1mm) could survive unchallenged, recent 3-D scanning electron microscopy casts doubt on this.[9] This may help explain why postoperative surgical site infections are relatively uncommon after TVM procedures.

The importance of deterioration in the host tissue in response to the effect of stress shielding created by the increased stiffness of the implant has been well described.[10] Although new lighter-weight synthetic polypropylene implants appear to be promising, a prosthesis that meets all the criteria of the ideal transvaginal implant does not yet exist. Level I evidence supporting the improved success rate of TVM compared to suture-based native tissue is not yet robust, although it is growing.

A 2008 Cochrane review of demonstrated that the placement of graft "inlays" or TVM significantly reduced the risk of recurrent prolapse.[11] Several studies since 2008 have also supported the success of mesh-augmented transvaginal reconstruction over suture-based repair of native tissue.

From the evidence-based literature and the experience of surgeons who have safely performed TVM for several years (yet have not had the resources or opportunity to publish their results) it is obvious and not surprising that mesh-augmented repairs provide durable anatomical benefit. The concern remains, however, that this benefit may not be worth the inherent risk associated with TVM use. The only truly unique risk associated with TVM surgery is that of mesh exposure or extrusion. Fortunately this adverse event is often only mildly symptomatic or asymptomatic and eventually curable in 95% of patients.[12]

Postoperative de novo dyspareunia has been reported as a result of all pelvic reconstructive surgeries although the rates widely vary. Among surgeons skilled in TVM surgery, de novo dyspareunia rates are similar to both native tissue repairs and ASC.

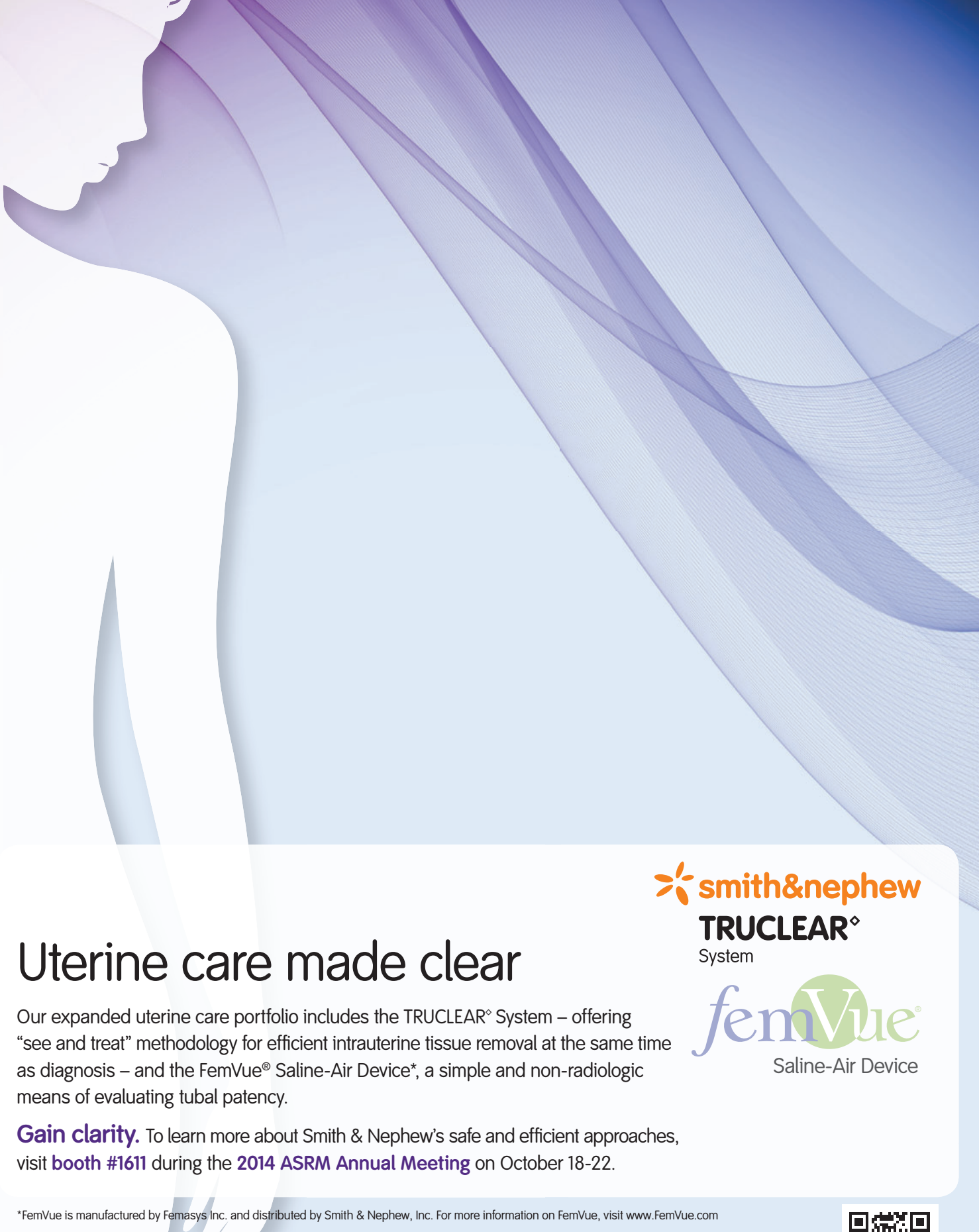
In one study, when patients who developed dyspareunia after TVM were surveyed, 94.7% responded that overall the TVM surgery had improved the quality of their lives, and they would have it done again.[13] So perhaps the real question is whether we can truly minimize complications associated with TVM-augmented repairs.

Minimizing exposures and de novo dyspareunia

Variation in surgical skill levels when performing TVM is a much greater determinant of patient outcomes than are mesh properties or delivery systems. Several studies have highlighted this fact.[14-17] In one multicenter RCT comparing trocar-guided mesh based repair to conventional repair involving 22 surgeons, the exposure rate ranged from 0% to 100%.[14] The same mesh and delivery system was used throughout the study. The obvious conclusion is that the wide variation in exposure rate is more of a function of variation in surgeon expertise.

I often hear the argument that because surgeons are "experienced" the reported suboptimal results can't be related to insufficient skills. But in the case of more innovative procedures that require expertise in new and different techniques, we must discard the notion that experience equals expertise. For TVM procedures this expertise includes full-thickness vaginal wall dissection, careful and proper sizing, safe and accurate trocar placement, and proper mesh tensioning or setting.

Although there is one comparative trial reporting TVM exposure rates similar to ASC rates,[18] overall the reported TVM exposure rates are indeed higher than ASC. If the same mesh is being placed in exactly the same anatomical space as for an ASC performed at the same setting as a hysterectomy (both involving vaginal incisions), the question is, why? Correct placement of the mesh into the true vesicovaginal space is technically



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THE CASE FOR MESH USE CONTINUED

easier with a transabdominal route than with a transvaginal approach.

Surgeons are very familiar with the proper planes of dissection from the abdominal route to enter the vesicovaginal space and have the visual guidance to help avoid bladder injury. Transvaginal entrance requires that the surgeon dissect completely through the full thickness of the vaginal wall. If the surgeon uses a "splitting" dissection technique instead of achieving a full thickness dissection, the mesh exposure rate will be higher.

Several authors have recognized suboptimal dissection during surgical trials, noticing that exposure rates decreased over time (despite the use of the same material), implying that the learning curve of the surgeon is a key factor.[14]

Critical in our development of proper surgical dissection of the vaginal wall was routine utilization of precise hydro-dissection into the true vesicovaginal space. We have found that use of a Tuohy needle, commonly employed for the placement of epidural anesthesia, is helpful with placement of the dissection fluid. The periscope shape of the needle tip provides tactile feedback. The 10-mm silver/black hash marks provide visual reference. The surgical steps of sharp and blunt dissection "follow" the space created by hydro-dissection.[19]

During sharp dissection it is imperative that gross visible fat or adipose tissue be seen and "followed." The presence of this adipose tissue is the only absolute confirmation of entrance into the true vesicovaginal space. By using this technique we have reduced our postoperative vaginal mesh exposure rate to 2%–3%.[20] Over the past 2 years, we have continued the same dissection technique but have utilized even lower-density meshes (18–21 g/m^2) and our exposure is now <1%. Small exposures are often asymptomatic and resolvable in the office setting.[12]

The most clinically challenging adverse event, and most troublesome to the patient, is the onset of dyspareunia. Fortunately, many patients experience an overall improvement in sexual health after undergoing TVM surgery for POP.[13,21] The surgeon's experience in performing TVM has also been shown to correlate with the incidence of dyspareunia.[16]

There are several factors that can contribute to the development of postoperative dyspareunia. Setting of the mesh itself is perhaps most important. The mesh must be properly sized to the patient's anatomical dimensions. It should be delivered to attachment sites that are relatively void of muscle volume (ligaments, fascia, or tendinous insertions).

Lastly, there should be no tension within the mesh. We have found it beneficial to simulate vaginal inward displacement, as with coital penetration, while adjusting the mesh setting to minimize the risk of any restriction of the mesh setting onto the vagina itself.

If dyspareunia develops, directed therapies to resolve the pain should be employed as soon as possible. If there is no palpable mesh banding or bulking (which may require surgical revision or resection), tender or hypersensitive scar areas can be injected with a combination of steroids and an intermediate-acting anesthetic.

If the pain is relieved but keeps recurring, careful injection into the scar with a neurolytic solution of 5% NaCl can be performed. For patients whose mesh was implanted under tension, or was folded, bunched, or otherwise sub-optimally placed, creating a palpable mass or ridge, resection/removal is necessary.

We have also found transvaginal suppositories containing muscle relaxants (diazepam) to be helpful in alleviating pelvic muscle spasm.

> Unfortunately, suture repair of native tissue carries a **high failure rate approaching nearly 40%** even when performed by experts.

Summary

Both the literature and our experience clearly establish the need for a long-term durable surgical treatment for POP. The success criteria for our pelvic reconstructive surgeries must be stringent, both anatomically and functionally. Unfortunately, suture repair of native tissue carries a high failure rate approaching nearly 40% even when performed by experts.[22] Reconstructive surgery using mesh augmentation has been clearly demonstrated to offer patients a higher success rate for defects involving both anterior or anterior/apical compartments.

Transvaginal placement offers a

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THE CASE AGAINST MESH USE

By Andrew I. Sokol, MD, and Ladin Yurteri-Kaplan, MD

The past decade has been a tumultuous time in the field of pelvic medicine and reconstructive surgery. Much attention has focused on the use of vaginal mesh for pelvic organ prolapse (POP) repair. The issue has been hotly debated in both the lay and medical literature. With approximately 240,000–290,000 transvaginal POP surgeries performed annually in the United States, this debate is anything but trivial. Vaginal mesh "kit" procedures were developed with the intent of improving anatomical cure rates for native tissue vaginal prolapse repairs. At the heart of the idea was the notion that failure and reoperation are common after POP repair, with an oft-quoted reoperation rate of 29.2%.[1] However, this is likely an overestimation, since the reoperation rate in that commonly cited study was for *both* incontinence and prolapse, and 21% of initial surgeries were hysterectomies alone done for uterovaginal prolapse. Hysterectomy alone is inadequate for the treatment of uterovaginal prolapse.[2,3]

Initial case series of transvaginal mesh showed promising results, with high reported cure rates (>90%) and low complication rates.[4] The kits were marketed aggressively, and adoption of the technology was rapid.[5] According to 2010 data from the US Food and Drug Administration (FDA), 25% of all POP surgeries in that year used transvaginal mesh.[6] Many of the early adopters became paid preceptors for the manufacturers of the devices, holding weekend training courses to "certify" surgeons in the performance of these techniques. Some of these physicians made handsome profits teaching the techniques, consulting with the companies, and participating in speaker's bureaus. In fact, a recent *Wall Street Journal* article reported that some of the biggest proponents of vaginal mesh kits made hundreds of thousands of dollars working with the device manufacturers.[7] Investigators with industry relationships performed many of these early studies, potentially leading to bias in outcomes. A study evaluating the effect of blinding on outcome assessors in pelvic reconstructive surgery trials found that, on average, unblinded examiners (usually the surgeons themselves) report a 15% higher rate of success than their blinded counterparts.[8]

> Evidence shows a **higher overall reoperation rate with transvaginal mesh** versus native tissue repair when used for multi-compartment prolapse . . .

The rapid growth of the use of vaginal mesh for POP repair was paralleled by increasing reports of mesh-related complications. The FDA's Manufacturer and User Facility Device Experience database tracked increasing reports of transvaginal mesh complications (eg, erosion, pain, and visceral injury), malfunction, and death,[6] resulting in the release of a public health notification in 2008. In response to a 5-fold increase in adverse event reports during the next 3 years, the FDA released a Safety Communication in 2011. In April 2014, the FDA proposed orders to reclassify surgical mesh for transvaginal POP from a moderate-risk device (Class II) to a high-risk device (Class III), an order that will require rigorous testing of new mesh products against native tissue repairs prior to release.[9]

Over the same time period, randomized controlled trial (RCT) data began to emerge. One RCT comparing native tissue to vaginal mesh repairs performed at 3 high-volume centers with fellowship-trained, "certified" surgeons was stopped early after a predetermined erosion threshold of 15% was exceeded in the mesh arm of the trial.[10] To date, vaginal mesh has shown benefit only in the anterior compartment, without proven benefit in apical or posterior compartment prolapse.[11] According to the Cochrane review, traditional anterior repair is associated with higher rate of anatomic recurrence (RR 3.15, 95% CI 2.50–3.96) compared to polypropylene mesh repairs.[11] However, studies show no difference in total reoperation rates for prolapse. To the contrary, evidence shows a higher overall reoperation rate with transvaginal mesh versus native tissue repair when used for multi-compartment prolapse—mostly due to mesh-related complications.[12,13] In a

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review of complications and reoperation after apical repairs, vaginal mesh had a higher reoperation rate (8.5%) compared to native tissue vaginal repairs (3.2%).[13] This was similarly noted in the Cochrane review for multicompartment treatment of prolapse. The reoperation rate after transvaginal polypropylene mesh repair (11%) was higher than after native tissue repair (3.7%) (RR 3.1, 95% CI 1.3–7.3).[11]

Moreover, no studies show quality-of-life differences between mesh and native tissue repairs, and quality of life may be the most important factor from a patient's perspective. Patient-centered outcomes research shows that anatomical outcomes correlate poorly with patients' perception of success after POP surgery, and that the absence of a sensation of vaginal bulge, rather than anatomic "success" alone, impacts overall patient perception of improvement. The NIH Pelvic Floor Disorders Network now recommends that subjective outcomes be included in the definition of success for surgery.[14]

Proponents of vaginal mesh often use the argument that the high complication and failure rates associated with mesh-based repairs in randomized trials are related to surgeon inexperience. This same argument could be made for currently published data regarding cure rates after native tissue repairs; that is, surgical cure rates may be tied to surgeon experience. However, if only a select few around the world can achieve very high success and very low complication rates, is this technology generalizable to practicing pelvic surgeons? Even the inventors of this technology reported high long-term complication rates for mesh exposure (16%) and dyspareunia (10%).[15] This led them to recommend lower-weight mesh and RCTs before widespread clinical use.

Native tissue POP repairs can also result in complications. However, it is the sometimes-intractable nature of the complications of mesh-based vaginal POP repairs that is most problematic. Those treating mesh complications have seen these patients—women with pain, vaginal stenosis, and loss of sexual function. In one large multicenter review, vaginal mesh complications were typically described as severe and were usually managed surgically, with 60% requiring multiple interventions.[16]

To responsibly serve our patients, the benefit of adding a permanent synthetic mesh must be significantly greater than the risk. Unfortunately, current data are limited and have not yet defined the role of vaginal mesh in the treatment of POP. Until robust data are available, vaginal mesh should be used mainly in well-designed randomized trials or FDA-mandated post-market surveillance studies ("522 trials") so that outcomes can be adequately tracked. The Pelvic Floor Disorders Registry was created by the American Urogynecologic Society to track these outcomes and will launch in 2015. This registry collects information about composite (subjective and anatomic) outcomes, patient-reported outcomes, and complications associated with prolapse repair surgery. Ultimately, this will allow physicians to determine what role vaginal mesh will play in the future of pelvic reconstructive surgery. COG

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DR. SOKOL is Associate Director, Minimally Invasive Surgery, Section of Female Pelvic Medicine and Reconstructive Surgery, MedStar Washington Hospital Center, Associate Professor of Ob/Gyn and Urology, Georgetown University School of Medicine, Washington, DC.

He has no conflict of interest to report with respect to the content of this article.

DR. YURTERI-KAPLAN is Co-Director of Female Pelvic Medicine and Reconstructive Surgery, MedStar Franklin Square Medical Center, Baltimore, Maryland.
She has no conflict of interest to report with respect to the content of this article.

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minimally invasive and more cost-effective approach than transperitoneal, especially when compared to robotically performed ASC. True expertise in TVM procedures is paramount to achieving a very low complication rate. Likewise, one must be knowledgeable and skillful at administering interventions to bring adverse events to resolution. COG

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DR. LUCENTE is Medical Director, Institute for Female Pelvic Medicine and Reconstructive Surgery, Pennsylvania; Chief of Gynecology, St. Luke's University Health Network, Bethlehem, Pennsylvania; and Clinical Professor, Obstetrics and Gynecology, Temple University Hospital, Philadelphia, Pennsylvania.
He reports receiving consulting fees from AMS, Coloplast, and Medtronics, receiving fees for promotional services from Astellas and Shionogi, and performing contracted research for Allergan, AMS, and Coloplast.

DR. ROBERTS is Vice-Chairman, Department of Obstetrics & Gynecology, York Hospital, York, Pennsylvania.
He has no conflicts of interest to report with respect to the content of this article.

Technologies for laparoscopic contained tissue extraction

BY **JAMES GREENBERG, MD,** AND **MOBOLAJI OLUWASEUN AJAO, MD**

DR. GREENBERG is Chief, Division of Gynecology, Brigham & Women's Faukner Hospital, Harvard Medical School, Boston, Massachusetts.
He reports receiving intellectual property rights/ holding a patent related to the design of a tissue extraction bag.

DR. AJAO is a Fellow in Minimally Invasive Gynecologic Surgery, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts.
He has no conflicts of interest to report with respect to the content of this article.

Morcellation technologies were developed to facilitate the removal of large amounts of tissue through small laparoscopic incisions. These techniques have been notably useful in surgeries involving the uterus with a particular focus on procedures for fibroids (leiomyomas). The advantages of using laparoscopic approaches compared to laparotomy to treat uterine fibroids include a lower risk of infection, less blood loss, less postoperative pain, and more rapid return to full activities.[1] However, recent data have demonstrated that intracorporeal morcellation of tumor tissue without the use of a containment system may have a greater potential to spread tumor tissue throughout the peritoneal cavity than previously recognized.[2]

While the absolute risk of encountering an unanticipated uterine malignancy is small (1:350 to 1:1000),[3-5] newer surgical techniques to facilitate the extraction of uterine tumors in a containment system (contained tissue extraction or CTE) have sufficiently advanced to make this small risk even lower.

Here we focus on a few of the newer techniques and technologies in this niche. This is a rapidly evolving space that may be dramatically different in a short period of time.

Insufflated contained tissue extraction

The core of the techniques discussed here was first described by Shibley et al in 2012.[6] Common features include the following steps:

- Introduction of a specimen bag into the abdomen
- Placement of the surgical specimen inside the bag
- Exteriorization of the neck of the bag through one of the incisions
- Intracorporeal insufflation of the bag with concomitant desufflation of the surrounding abdomen.
- Introduction of a laparoscopic camera and power tissue morcellator into the insufflated bag
- Power tissue extraction of the specimen entirely within the confines of the bag
- Removal of the bag from the abdomen

In general terms, the most significant variation with insufflated contained tissue extraction (iCTE) methods is single-site incision versus a multiport technique. With the single-site technique, the single-site port is uncapped, the specimen bag is introduced through the single site port, and the port is recapped. Next the specimen is placed into the bag using traditional laparoscopic single-site techniques. The port is

then uncapped and the neck of the bag is exteriorized through the port. The port is recapped with the bag's edges enclosed within its rim and the bag is insufflated intracorporeally while the abdomen outside of the bag is desufflated. A power morcellator and a laparoscope can then be introduced through the single-site port and the specimen can be extracted, with the entire process fully contained. With the specimen extracted, the bag is removed and the procedure is completed as per routine.

With the multi-port technique, the specimen bag is introduced through a 12- or 15-mm port or directly through the largest incision already in the abdomen. The specimen is then placed into the bag and the neck of the bag is exteriorized through the largest incision. The 12- or 15-mm trocar is introduced into the bag through the neck and the bag is insufflated intracorporeally while the abdomen outside of the bag is desufflated. With the bag insufflated inside the abdomen, a 5-mm trocar is used to puncture the bag near the top to provide an access port for visualization and insufflation. Once the secondary port in secured inside the bag, the trocar in the neck is removed and replaced with a power morcellator and the specimen can be extracted. The entire process is contained. With the specimen extracted, the bag is removed and the procedure is completed as per routine.

Technologies to facilitate iCTE

Containment bags

At the core of all the variations of iCTE is the extraction bag. In his original description of his technique, Shibley reported using a Lahey bag.

Lahey bags

Lahey bags or "isolation bags" are large, sterile, transparent PVC bags initially designed to cover limbs during sterile surgical procedures. These bags are produced by several manufacturers (eg, 3M Steri-Drape Isolation bag 1003, the Iso/Drape Isolation bag). Typically they measure about 50 x 50 cm with a drawstring at the neck. Although the Lahey bag can accommodate virtually any size specimen, it can be unwieldy within the confines of the closed abdomen. Also the material is not overly robust and can easily tear if pulled too hard with laparoscopic instruments—especially during the process of introducing the bag into the abdomen.

Rip-stop nylon

Given the limited strength of the Lahey bags and the ease with which they can tear with manipulation, many surgeons have turned to rip-stop nylon bags. However, not all rip-stop nylon products are the same. Because the manufacturing of these products requires stitching or welding of sheets of material, the seams are further treated (usually with polyurethane) to prevent leakage when they are subjected to the higher pressure of insufflation. Given these parameters, 2 products are often used: the LapSac and the Eco Sac.

LapSac – Cook Medical's LapSac is the only specimen retrieval product on the market today that carries an FDA-approved indication for tissue morcellation.[7] Manufactured from 2 sheets of rip-stop nylon with polyurethane coating over the seams and a drawstring at the neck, the LapSac comes in several sizes, the largest measuring 8 x 10 cm (1500 mL). Although the LapSac performs admirably with smaller specimens and when used to manually morcellate tissue through a mini-laparotomy, its small size makes it of limited use for iCTE.

FIGURE 1 **The EcoSac 230**

Image courtesy Espiner Medical Ltd.

Eco Sac – Like the LapSac, the Eco Sac (Figure 1) is constructed from stitched rip-stop nylon coated with polyurethane, but it has several features that make it easier to use with iCTE techniques. First, it comes in much larger sizes, with the largest Eco Sac 230 accommodating 3100 cc. While the larger size increases the amount of material taking up visual space within the limited confines of the pelvis, when insufflated, the 3100-cc bag is perfect for most procedures. Second, the EcoSac has 4 loops secured to the edges that make introducing and manipulating the bag much easier.

Trocars

With a multiport iCTE technique, a lateral puncture into the bag is necessary to provide a port for visualization and insufflation. Any standard 5-mm trocar can be used, but the Kii advanced fixation (balloon) shielded bladed trocar in the 5 x 150-mm configuration is ideal for this application (Figure 2). The balloon at the end minimizes the risk of spill-

FIGURE 2 **The 5mm Kii Advanced Fixation Trocar**

Image courtesy Applied Medical.

age and helps pull the walls of the bag closer to the abdominal wall. The shielded bladed tip facilitates penetrating the bag—even a rip-stop nylon bag. The added length of the 150-mm configuration allows for more flexibility in accessing the bag's interior when using smaller bags or more lateral ports.

Minilaparotomy contained tissue extraction

As compared with the Shibley-style iCTE, the steps involved with minilaparotomy contained tissue extraction (mlCTE) are identical except that there is no insufflation of the bags and manual morcellation is employed rather than power morcellation. (*Power morcellators should never be used when the tip of the morcellator blade cannot be fully visualized.*)

After the specimen is placed into the bag, the neck of the bag is exteriorized and the tissue within the bag is morcellated into smaller pieces with either a knife or scissors and extracted. This technique may be somewhat easier for some surgeons to quickly adopt, but morcellating the tissue without cutting the walls of the bag can be challenging—especially through small incisions.

Technology to facilitate mlCTE

As with iCTE, the choice of bag is important. With mlCTE, however, smaller bags can be used because insufflation is not involved. Surgeons' options include a myriad of traditional plunger-style deployable endoscopic tissue removal bags manufactured from either PVC or rip-stop nylon, although these bags do not exceed 1850 cc in capacity.

Many companies make PVC plunger-style deployable endoscopic tissue removal bags. In rip-stop nylon, the most popular plunger-style deployable endoscopic tissue removal bags are produced by Anchor Surgical in their Tissue Removal System. Importantly, the seams on these bags are RF-welded rather than stitched, making them less likely to leak than noncoated, stitched rip-stop nylon bags.

Other products that can be useful for mlCTE are surgical wound retractors such as the Alexis O wound retractor/protector, Mobius mini, and the SurgiSleeve. For larger specimens which require a large mini-laparotomy incision (4–5 cm), the rings can be deployed inside the neck of the exteriorized bags to minimize the risk of inadvertently cutting the bag.

For smaller specimens just marginally too large for an incision, the Schellpfeffer Forceps are a clever means of extracting a contained specimen without morcellation (Figure 3). In a manner similar to obstetric forceps, the Schellpfeffer blades are placed around a bagged specimen and the whole contained package is delivered through the incision.

Summary

Few innovative techniques have evolved in a purely linear trajectory. Rather, most involve a few steps forward balanced by a few steps back. The most recent controversy involving morcellation should serve as a reminder to surgeons that complacency is the enemy. We must constantly seek to improve our techniques to ensure the best outcomes for our patients. CDG

FIGURE 3 **The Schellpfeffer Forceps**

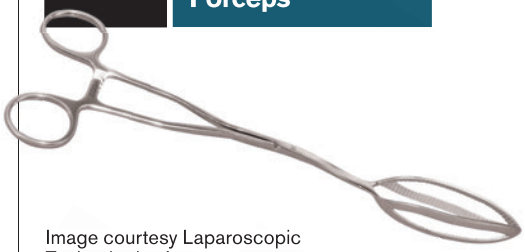

Image courtesy Laparoscopic Technologies Inc.

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Jon I. Einarsson, MD, PhD, MPH

Wednesday, November 19th at 2:30pm

Dr. Einarsson is Associate Professor of Obstetrics and Gynecology, Harvard Medical School, and Director, Division of Minimally Invasive Gynecologic Surgery, Brigham and Women's Hospital, Boston, Massachusetts. He is the editor of our Special Section on Surgical Technology.

James Greenberg, MD

Wednesday, November 19th at 2:30pm

Dr. Greenberg is Chief, Division of Gynecology, Brigham & Women's Faulkner Hospital, and Associate Professor, Harvard Medical School, Boston, Massachusetts. He personally tests all of the surgical tools reviewed in his column.

Committee on Practice Bulletins—Obstetrics
ACOG Practice Bulletin No. 139: *Premature Rupture of Membranes,* October 2013 *Obstet Gynecol* 2013;122;918-30.
Full text of ACOG Practice Bulletin available to ACOG members at http://www.acog.org/Resources_And_Publications/Practice_Bulletins/Committee_on_Practice_Bulletins_--_Obstetrics/Premature_Rupture_of_Membranes

Premature Rupture of Membranes

Preterm delivery occurs in approximately 12% of all births in the United States and is a major factor that contributes to perinatal morbidity and mortality (1,2). Preterm premature rupture of membranes (PROM) complicates approximately 3% of all pregnancies in the United States (3). The optimal approach to clinical assessment and treatment of women with term and preterm PROM remains controversial. Management hinges on knowledge of gestational age and evaluation of the relative risks of delivery versus the risks of expectant management (eg, infection, abruptio placentae, and umbilical cord accident). The purpose of this document is to review the current understanding of this condition and to provide management guidelines that have been validated by appropriately conducted outcome-based research when available. Additional guidelines on the basis of consensus and expert opinion also are presented.

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COMMENTARY

PROM: What have we learned since 2007?

By **Sarah J. Kilpatrick, MD, PhD**

Dr. Kilpatrick is the Helping Hand Endowed Chair, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, California, and a member of the *Contemporary OB/GYN* Editorial Board.

Practice Bulletin Number 139 replaced a 2007 Practice Bulletin and a 2011 Committee Opinion.[1] Not much has changed regarding the incidence or diagnosis of PROM, so what prompted this new document? Six new questions or recommendations were addressed:

- Should expectant management of preterm premature rupture of membranes (PPROM) continue after 34 weeks' gestation?
- Should a cerclage be removed after PPROM?
- Should women with PPROM receive antenatal steroids between 32 and 34 weeks' gestation just like those with other risks for imminently delivering preterm?
- Should women with PPROM receive a rescue course of antenatal steroids?
- Should antenatal magnesium sulfate for neuroprotection be recommended for women with PPROM?
- What should be offered to women with a history of PPROM in their subsequent pregnancy?

The standard recommendation—that women with PPROM and no other indications for delivery should be delivered at 34 weeks—stemmed from retrospective studies suggesting that risk of infection to mother and neonate outweighed the prematurity risks by 34 weeks. Recent studies have questioned this principle and suggest that expectant management between 34 and 37 weeks' gestation was not associated with a significant increase in neonatal infection.[2,3] However, the same studies reported a significant increase in chorioamnionitis in the expectant group.

Based on these results, the American College of Obstetricians and Gynecologists (ACOG) reaffirmed its position to recommend induction at 34 weeks' gestation in women with PPROM.

Cerclage after PPROM

How to manage a cerclage after PPROM is a difficult issue because data are insufficient to recommend either retention or removal, which is exactly what the current Practice Bulletin concludes. That conclusion is similar to the 2007 Practice Bulletin. However, the results of a randomized trial published this year provide little additional guid-

ance because it was stopped before it reached its intended power.[4] No significant difference in latency to delivery was found between women with cerclage retention and those with cerclage removal (mean 9 vs 13 days, respectively). Chorioamnionitis occurred in 42% of the women with retained cerclage versus 25% of those in whom a cerclage was removed. Although that difference was not significant, there is always the possibility of a type 2 error (ie, accepting a null hypothesis that is false).

Likewise, there was no difference in neonatal composite morbidity with incidences of 56% and 50%, respectively, in neonates born to women with retained cerclages versus removed cerclages. I have always removed cerclages in women with PPROM based on the earlier data regarding a possible association with increase in neonatal death and infection,[5,6] and this new randomized trial supports this approach.[4-6]

Antenatal steroids and magnesium sulfate

Just as for any woman at risk of imminent preterm delivery, a course of antenatal steroids was recommended for women with PPROM 24 0/7 – 34 0/7 weeks' gestation. That is a change from the 2011 Committee Opinion, which recommended antenatal steroids only for women with PPROM before 32 weeks' gestation, based on lack of efficacy data between 32 and 34 weeks in PPROM.

The new guidance, of course, makes the general antenatal steroid recommendation much simpler: Treat all women likely to deliver imminently before 34 weeks with antenatal steroids to improve neonatal outcome. Data are insufficient to make a recommendation as to whether women with PPROM should receive a rescue course.

The concept that antenatal magnesium sulfate is associated with a reduced risk of cerebral palsy (CP) is also new since the last Practice Bulletin on PROM. The largest randomized trial, reporting a significant reduction in CP in the children of mothers who received antenatal magnesium sulfate, included a large proportion of women with PPROM.[7] Therefore, ACOG recommended (Level A) that women with PPROM likely to deliver before 32 0/7 weeks' gestation, just like women at risk of imminent preterm delivery without ruptured membranes, should be candidates for magnesium sulfate for neuroprotection.

Like women with prior spontaneous preterm delivery, those with a history of prior PPROM are at increased risk of subsequent preterm delivery. Women with a history of PPROM were included in the randomized trials of progesterone for reduction of subsequent preterm delivery and they are candidates for progesterone treatment beginning at 16 to 24 weeks' gestation in a subsequent pregnancy.[8]

Obstetric principles

Interesting affirmations of basic obstetric principles also appear in this Practice Bulletin. We are reminded to allow sufficient time (12-18 hours) for latent labor to progress before proceeding with a failed induction in women induced at term with PPROM.

This is a timely reminder, given our national efforts to decrease the rate of nulliparous term singleton vertex cesarean delivery. We are reminded to avoid digital exams in women with PPROM who are not in labor. And, we are reminded that there is no consensus or reasonable data to direct the frequency of fetal assessment or assessment for infection in women with viable PPROM.

So, in this time of medicine moving toward value-based care, perhaps we should minimize if not eliminate any routine laboratory evaluation of women with asymptomatic PPROM?

This Practice Bulletin recommends proceeding with induction because in randomized trials and meta-analysis, induction was associated with reduced time to delivery and reduced chorioamnionitis.[9,10] However, the Practice Bulletin states that expectant management may be appropriate if a patient declines induction, and she is informed of the potential increased risks of delayed delivery.

There continues to be recommendation for delivery at 34 weeks' gestation in women with PPROM. However, the Practice Bulletin goes on to state that if expectant management is undertaken after 34 weeks, then the risk:benefit balance should be considered and discussed with the patient, and delivery should not be delayed past 37 weeks. COG

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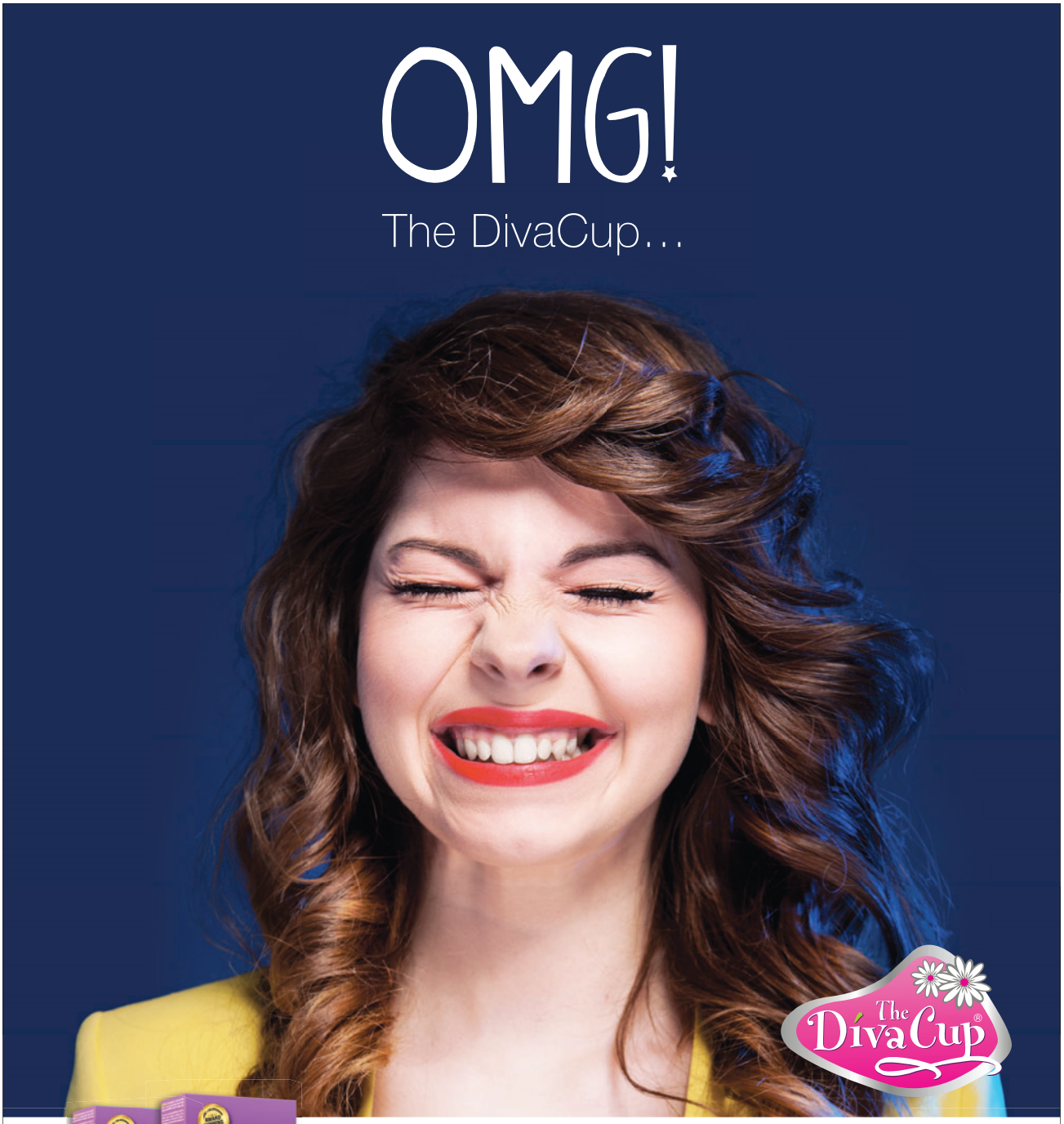

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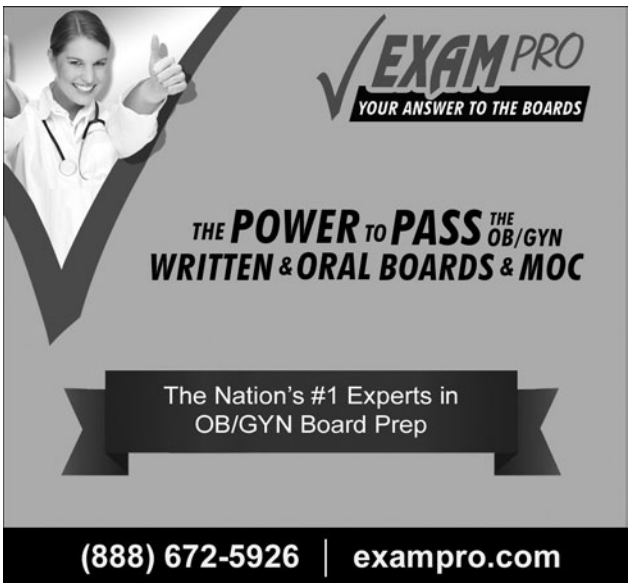

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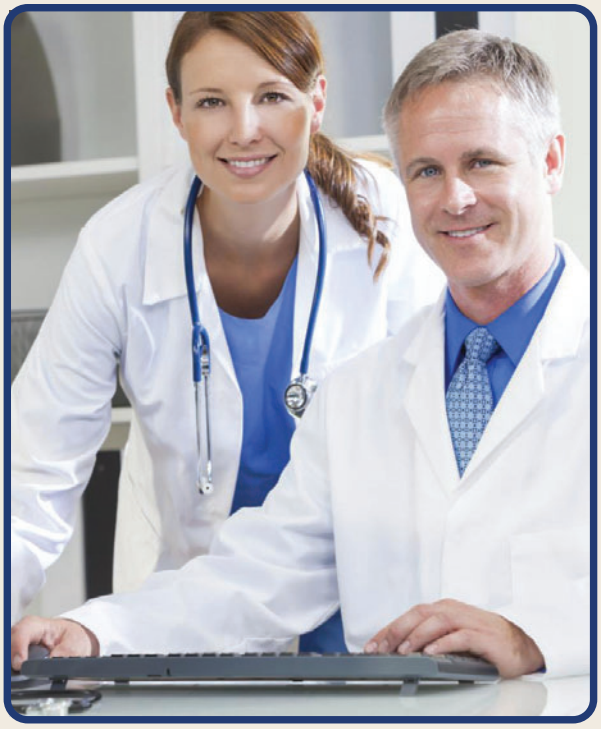

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PAULA J. ADAMS HILLARD, MD
SECTION EDITOR

RACIAL DISPARITIES AND SUPPORT FOR BREASTFEEDING

A new report from the Centers for Disease Control and Prevention (CDC) and the first of its kind based on national data shows that racial composition in the area of a maternity facility may impact its practices in support of breastfeeding.

Facilities in zip codes with a population that was >12.2% black were less likely than those in zip codes where the population was ≤12.2% black to meet 5 of 10 indicators from CDC's 2011 **Maternity Practices in Infant Nutrition and Care (mPINC)** survey.

Women in areas with a higher percentage of blacks thus may have less access to breastfeeding services and need additional support from their ob/gyns so their infants can have the benefits of breastfeeding.

Procedures followed by the **HIGHEST PERCENTAGE** of hospitals

Prenatal breastfeeding education

Breastfeeding education is included as a routine element of prenatal classes.

92.7%

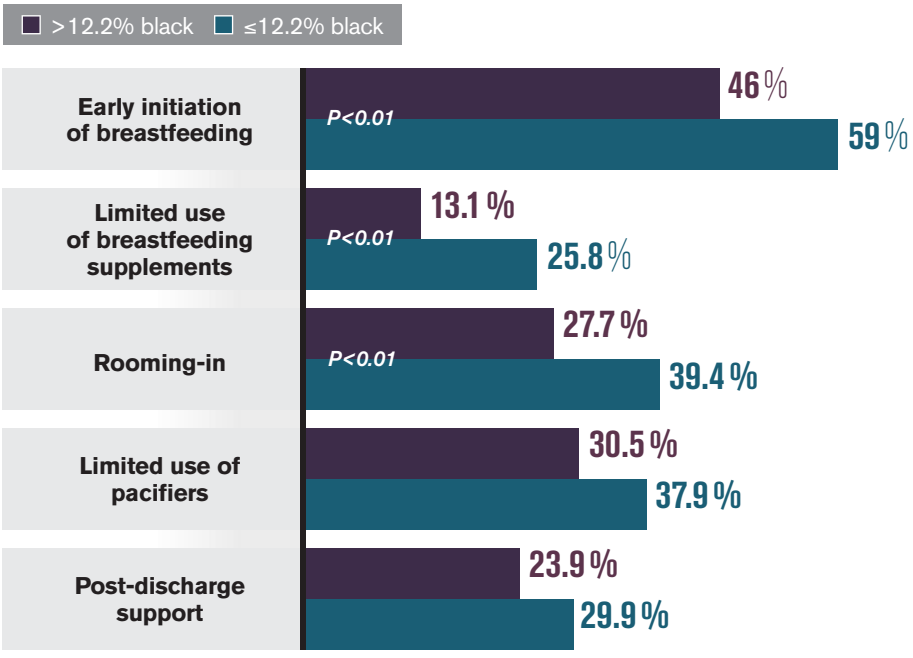
Procedures followed by the **LOWEST PERCENTAGE** of hospitals

Model breastfeeding policy

Written breastfeeding policy includes 10 model policy elements.

18.9%

Prevalence of Facilities Meeting mPINC Indicators



mPINC indicators met by >75% of 2,643 facilities surveyed

Providing prenatal breastfeeding education

92.7%

Teaching breastfeeding techniques

90.7%

Teaching mothers how to recognize and respond to infant feeding cues

84.7%

Source: Lind JN, Perrine CG, Li R, et al. Racial disparities in access to maternity care practices that support breastfeeding – United States, 2011. *MMWR*. 2014;63(33):725-728.

Important Safety Information continued

Prescription Only

Caution: Federal law restricts this device to sale by or on the order of a physician. Device to be used only by physicians who are knowledgeable hysteroscopists; have read and understood the Instructions for Use and Physician Training manual; and have successfully completed the Essure training program, including preceptoring in placement until competency is established, typically 5 cases.

Pregnancy Considerations
- The Essure procedure should be considered irreversible. Patients should not rely on Essure inserts for contraception until an Essure Confirmation Test [modified hysterosalpingogram (HSG)] demonstrates bilateral tubal occlusion and satisfactory location of inserts.
- Effectiveness rates for the Essure procedure are based on patients who had bilateral placement. If Essure inserts cannot be placed bilaterally, then the patient should not rely on Essure inserts for contraception.
- Effects, including risks, of Essure inserts on in vitro fertilization (IVF) have not been evaluated.
- Pregnancies (including ectopic pregnancies) have been reported among women with Essure inserts in place. Some of these pregnancies were due to patient non-compliance or incorrect clinician interpretation of the Essure Confirmation Test (modified HSG).

Procedural Considerations
- Perform the Essure procedure during early proliferative phase of the menstrual cycle. Terminate procedure if distension fluid deficit exceeds 1500cc or hysteroscopic time exceeds 20 minutes as it may signal uterine or tubal perforation. Never attempt to advance Essure insert(s) against excessive resistance. If tubal or uterine perforation occurs or is suspected, discontinue procedure and work-up patient for possible complications related to perforation, including hypervolemia. Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity due to risk of fractured insert, fallopian tube perforation or other injury.
- DO NOT perform the Essure procedure concomitantly with endometrial ablation. Avoid electrosurgery on uterine cornua and proximal fallopian tubes without visualizing inserts.

Nickel Allergy
Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.

MRI Information
The Essure insert was determined to be MR-conditional according to the terminology specified in the American Society for Testing and Materials (ASTM) International, Designation: F2503-05.

Clinical Trial Experience
- Safety and effectiveness of Essure is not established in patients under 21 or over 45 years old, nor in patients who delivered or terminated a pregnancy less than 8-12 weeks before procedure. Women undergoing sterilization at a younger age are at greater risk of regretting their decision.
- The most common (≥10%) adverse events resulting from the placement procedure were cramping, pain, and nausea/vomiting. The most common adverse events (≥3%) in the first year of reliance were back pain, abdominal pain, and dyspareunia.

This product does not protect against HIV infection or other sexually transmitted diseases.

References: 1. World Health Organization Department of Reproductive Health and Research (WHO/RHR) and Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP) INFO project. Family Planning: A Global Handbook for Providers 2011. Baltimore and Geneva: CCP and WHO;165. **2.** Arjona JE, et al. Satisfaction and tolerance with office hysteroscopic tubal sterilization. *Fertil Steril*. 2008;90(4):1182-1186. **3.** Cooper JM. Microinsert nonincisional hysteroscopic sterilization. *Obstet Gynecol*. 2003;102(1):59-67. **4.** Essure ESS305: Instructions for use. 03/2012:1-6. **5.** US Department of Health and Human Services. Women's preventive services guidelines: required health plan coverage guidelines. Health Resources and Services Administration website. http://www.hrsa.gov/womensguidelines/. Accessed September 6, 2013.

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Indication

Essure is indicated for women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes.

Important Safety Information

Who should not use Essure

- Essure is contraindicated in patients who are uncertain about ending fertility, can have only one insert placed (including contralateral proximal tubal occlusion or suspected unicornuate uterus), have previously undergone a tubal ligation, are pregnant or suspect pregnancy, delivered or terminated a pregnancy less than 6 weeks prior to the Essure procedure, have an active or recent upper or lower pelvic infection, or have a known allergy to contrast media.
- Patients undergoing immunosuppressive therapy (e.g. systemic corticosteroids or chemotherapy) are discouraged from undergoing the Essure procedure.
- Uterine or fallopian tube anomalies may make it difficult to place Essure inserts.

Please see additional Important Safety Information about Essure on next page.

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