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MORCELLATION DEBATE

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

Generess® Fe (norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets)

BRIEF SUMMARY: Consult the respective Package Inserts 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/Generess® Fe is indicated for use by women to prevent pregnancy. The efficacy of Lo Loestrin Fe/Generess 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/Generess 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)* and *Use in Specific Populations (8.7)]*
- 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/Generess Fe if an arterial or deep venous thrombotic event (VTE) 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/Generess 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/Generess 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/Generess 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/Generess 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/Generess 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/Generess 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/Generess 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/Generess Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Lo Loestrin Fe/Generess 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 for Lo Loestrin® Fe
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.

5.8 Bleeding Irregularities for Generess® Fe
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.

Patient diaries from the clinical trial of Generess Fe showed that on the first cycle of use, 37% of subjects taking Generess Fe had unscheduled bleeding and/or spotting. From Cycle 2-13, the percent of women with unscheduled bleeding/spotting ranged from 21-31% per cycle. For those women with unscheduled bleeding/spotting, the mean number of days of unscheduled bleeding/spotting was 5.2 in the first cycle of use and ranged from 3.6 – 4.2 in cycles 2-13. A total of 15 subjects out of 1,677 (0.9%) discontinued the study prematurely due to metrorrhagia or irregular menstruation.

Women who are not pregnant and use Generess Fe may not have scheduled (withdrawal) bleeding every cycle or may experience amenorrhea (absence of any bleeding and spotting). The incidence of amenorrhea in the clinical trial increased from 8.1% of the subjects in Cycle 2 to 18.4% by Cycle 13. For those women who had scheduled (withdrawal) bleeding, the average duration of bleeding per cycle in Cycles 2-13 was 3.7 days.

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 encounter amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

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/Generess 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/Generess 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 for Lo Loestrin® Fe

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.

6.1 Clinical Trial Experience for Generess® Fe

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.

A phase 3 clinical trial evaluated the safety and efficacy of Generess Fe for pregnancy prevention. The study was a multicenter, non-comparative, open-label study with a treatment duration of 12 months (thirteen 28-day cycles). A total of 1,677 women aged 18-46 were enrolled and took at least one dose of Generess Fe.

Adverse Reactions Leading to Study Discontinuation: 8.5% of the women discontinued from the clinical trial due to an adverse reaction. The most common adverse reactions leading to discontinuation were nausea (1.0%), weight increase (0.8%), acne (0.8%), metrorrhagia (0.7%), altered mood (0.4%), hypertension (0.4%), irritability (0.3%), migraine (0.3%), decreased libido (0.3%) and mood swings (0.3%).

Common Adverse Reactions (≥ 2% of all treated subjects): nausea/vomiting (8.8%), headaches/migraine (7.5%), depression/mood complaints (4.1%), dysmenorrhea (3.9%), acne (3.2%), anxiety symptoms (2.4%), breast pain/tenderness (2.4%), and increased weight (2.3%).

Serious Adverse Reactions: Hypertension, depression, cholecystitis, and deep vein thrombosis.

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Lo Loestrin Fe/Generess 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/Generess 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/Generess Fe have not been studied in postmenopausal women and are not indicated in this population.

8.6 Renal Impairment
The pharmacokinetics of Lo Loestrin Fe/Generess Fe have 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/Generess 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/Generess Fe in women with a body mass index (BMI) > 35 kg/m^2 have 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 and Generess Fe Prescribing Information dated 03/2012.

Lo Loestrin Fe/Generess Fe Manufactured By:
Warner Chilcott Company, LLC
Fajardo, PR 00738

Lo Loestrin Fe/Generess Fe Distributed By:
Actavis Pharma, Inc
Parsippany, NJ 07054

Minastrin® 24 Fe (norethindrone acetate and ethinyl estradiol chewable tablets and ferrous fumarate tablets), for oral use

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
Minastrin® 24 Fe is indicated for use by females of reproductive age to prevent pregnancy. The efficacy of Minastrin 24 Fe in women with a body mass index (BMI) of more than 35 kg/m^2 has not been evaluated.

4 CONTRAINDICATIONS
Do not prescribe Minastrin 24 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 (5.3)]*
- Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.5)]*
- Have headaches with focal neurological symptoms or have migraine headaches with aura
  - All women over age 35 with migraine headache *[see Warnings and Precautions (5.6)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.7)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.8)* and *Use in Specific Populations (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.10)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Minastrin 24 Fe if an arterial or deep venous thrombotic event (VTE) occurs. Stop Minastrin 24 Fe if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

If feasible, stop Minastrin 24 Fe at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE.

Start Minastrin 24 Fe no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use of a COC. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest in older (greater than 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with underlying risk factors.

Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

Do not use Minastrin 24 Fe in women with acute viral hepatitis or severe (decompensated) cirrhosis of the liver *[see Contraindications (4)]*. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Minastrin 24 Fe if jaundice develops.

Liver Tumors

Minastrin 24 Fe is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. 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 (greater than 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

5.3 High Blood Pressure

Minastrin 24 Fe is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop Minastrin 24 Fe if blood pressure rises significantly.

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

5.4 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may also worsen existing gallbladder disease.

A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC-related cholestasis.

5.5 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Minastrin 24 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.

5.6 Headache
If a woman taking Minastrin 24 Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Minastrin 24 Fe if indicated.

Consider discontinuation of Minastrin 24 Fe in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) *[see Contraindications (4)]*.

5.7 Bleeding Irregularities and Amenorrhea
Unscheduled Bleeding and Spotting
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.

Based on patient diaries from a clinical trial evaluating the safety and efficacy of a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets, 24-35% of women experienced unscheduled bleeding per cycle. A total of 10 subjects out of 743 (1.3%) discontinued due to bleeding or spotting.

Amenorrhea and Oligomenorrhea
Women who are not pregnant and use norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate tablets may experience amenorrhea. In the clinical trial with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets and ferrous fumarate tablets, 22 to 36% of the women using norethindrone acetate 1 mg/ ethinyl estradiol 0.020 mg tablets and ferrous fumarate tablets experienced amenorrhea in at least one of 6 cycles of use. Some women may experience post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

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

5.8 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. Discontinue Minastrin 24 Fe 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)]*.

5.9 Depression
Carefully observe women with a history of depression and discontinue Minastrin 24 Fe if depression recurs to a serious degree.

5.10 Carcinoma of the Breast and Cervix
Minastrin 24 Fe is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally-sensitive *[see Contraindications (4)]*.

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.

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

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

5.14 Chloasma
Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Minastrin 24 Fe.

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

- Serious cardiovascular events and stroke *[see Boxed Warning* and *Warnings and Precautions (5.1)]*

- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

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.

The data presented in Section 6.1 are from a clinical trial conducted with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. Minastrin 24 Fe is bioequivalent to these norethindrone acetate/ethinyl estradiol tablets.

Common Adverse Reactions (Greater Than or Equal to 2% of all Treated Subjects): The most common adverse reactions reported by at least 2% of the 743 women using norethindrone acetate/ethinyl estradiol tablets were the following, in order of decreasing incidence: headache (6.3%), vaginal candidiasis (6.1%), nausea (4.6%), menstrual cramps (4.4%), breast tenderness (3.4%), bacterial vaginitis (3.1%), abnormal cervical smear (3.1%), acne (2.7%), mood swings (2.2%), and weight gain (2.0%).

Adverse Reactions Leading to Study Discontinuation: Among the 743 women using norethindrone acetate/ethinyl estradiol tablets, 46 women (6.2%) withdrew because of an adverse event. Adverse events occurring in 3 or more subjects leading to discontinuation of treatment were, in decreasing order: abnormal or irregular bleeding (1.3%), nausea (0.8%), menstrual cramps (0.5%), and increased blood pressure (0.4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Adverse reactions are grouped into System Organ Classes.

Vascular disorders: thrombosis/embolism (coronary artery, pulmonary, cerebral, deep vein).

Hepatobiliary disorders: cholelithiasis, cholecystitis, hepatic adenoma, hemangioma of liver.

Immune system disorders: hypersensitivity reaction.

Skin and subcutaneous disorders: alopecia, rash (generalized and allergic), pruritus, skin discoloration.

GI disorders: nausea, vomiting, abdominal pain.

Musculoskeletal and connective tissue disorders: myalgia.

Eye disorders: blurred vision, visual impairment, corneal thinning, change in corneal curvature (steepening).

Infections and infestations: fungal infection, vaginal infection.

Investigations: change in weight or appetite (increase or decrease), fatigue, malaise, peripheral edema, blood pressure increased.

Nervous system disorders: headache, dizziness, migraine, loss of consciousness.

Psychiatric disorders: mood swings, depression, insomnia, anxiety, suicidal ideation, panic attack, changes in libido.

Renal and urinary disorders: cystitis-like syndrome.

Reproductive system and breast disorders: breast changes (tenderness, pain, enlargement, and secretion), premenstrual syndrome, dysmenorrhea.

Cardiovascular: chest pain, palpitations, tachycardia, myocardial infarction.

7 DRUG INTERACTIONS

Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

No drug-drug interaction studies were conducted with Minastrin 24 Fe.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation.

CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of the estrogen and progestin have been noted in some cases of co-administration of HIV/HCV 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.

7.2 Effects of Combined Oral Contraceptives on Other Drugs
COCs containing 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.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

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

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.

8.3 Nursing Mothers
When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. COCs 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 Minastrin 24 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
Minastrin 24 Fe has not been studied in postmenopausal women and is not indicated in this population.

8.6 Renal Impairment
The pharmacokinetics of Minastrin 24 Fe has not been studied in subjects with renal impairment.

8.7 Hepatic Impairment
The pharmacokinetics of Minastrin 24 Fe has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded *[see Contraindications (4)* and *Warnings and Precautions (5.2)]*.

8.8 Body Mass Index
The safety and efficacy of Minastrin 24 Fe in women with a body mass index (BMI) greater than 35 kg/m^2 have 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 Minastrin 24 Fe Prescribing Information dated 07/2013.

Manufactured by:
Warner Chilcott Company, LLC
Fajardo, Puerto Rico 00738

Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866

INDICATION AND USAGE for Lo Loestrin® Fe, Minastrin® 24 Fe, and Generess® Fe
Lo Loestrin Fe, Minastrin 24 Fe, and Generess Fe are indicated for use by females of reproductive age to prevent pregnancy. Efficacy in women with a body mass index (BMI) of more than 35 kg/m² has not been evaluated. For detailed instructions on Dosage and Administration for Lo Loestrin Fe, Minastrin 24 Fe, and Generess Fe, please refer to the respective product Full Prescribing Information.

SELECTED SAFETY INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke.

Lo Loestrin Fe, Minastrin 24 Fe, or Generess Fe are 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, Minastrin 24 Fe, or Generess Fe if a thrombotic event occurs, and at least 4 weeks before and through 2 weeks after major surgery. Lo Loestrin Fe, Minastrin 24 Fe, or Generess 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, Minastrin 24 Fe, or Generess 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, Minastrin 24 Fe, or Generess Fe. Alternate contraceptive methods should be considered for women with uncontrolled dyslipidemia. Patients using Lo Loestrin Fe, Minastrin 24 Fe, or Generess Fe who have a significant change in headaches or irregular bleeding or amenorrhea should be evaluated.

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

In the clinical trial for Minastrin 24 Fe, the most common adverse reactions (incidence ≥2%) were headache, vaginal candidiasis, nausea, menstrual cramps, breast tenderness, bacterial vaginitis, abnormal cervical smear, acne, mood swings, and weight gain.

In the clinical trial for Generess Fe, the most common adverse reactions (incidence ≥2%) were nausea/vomiting, headaches/migraine, depression/mood complaints, dysmenorrhea, acne, anxiety symptoms, breast pain/tenderness, and increased weight.

Lo Loestrin Fe, Minastrin 24 Fe, or Generess Fe will not protect against HIV infection (AIDS) or other sexually transmitted diseases.

References: 1. Lo Loestrin® Fe prescribing information. Rockaway, NJ: Warner Chilcott (US), LLC; 2012. **2.** Minastrin® 24 Fe prescribing information. Rockaway, NJ: Warner Chilcott (US), LLC; 2013. **3.** Generess® Fe prescribing information. Parsippany, NJ: Actavis Pharma, Inc; January 2012.

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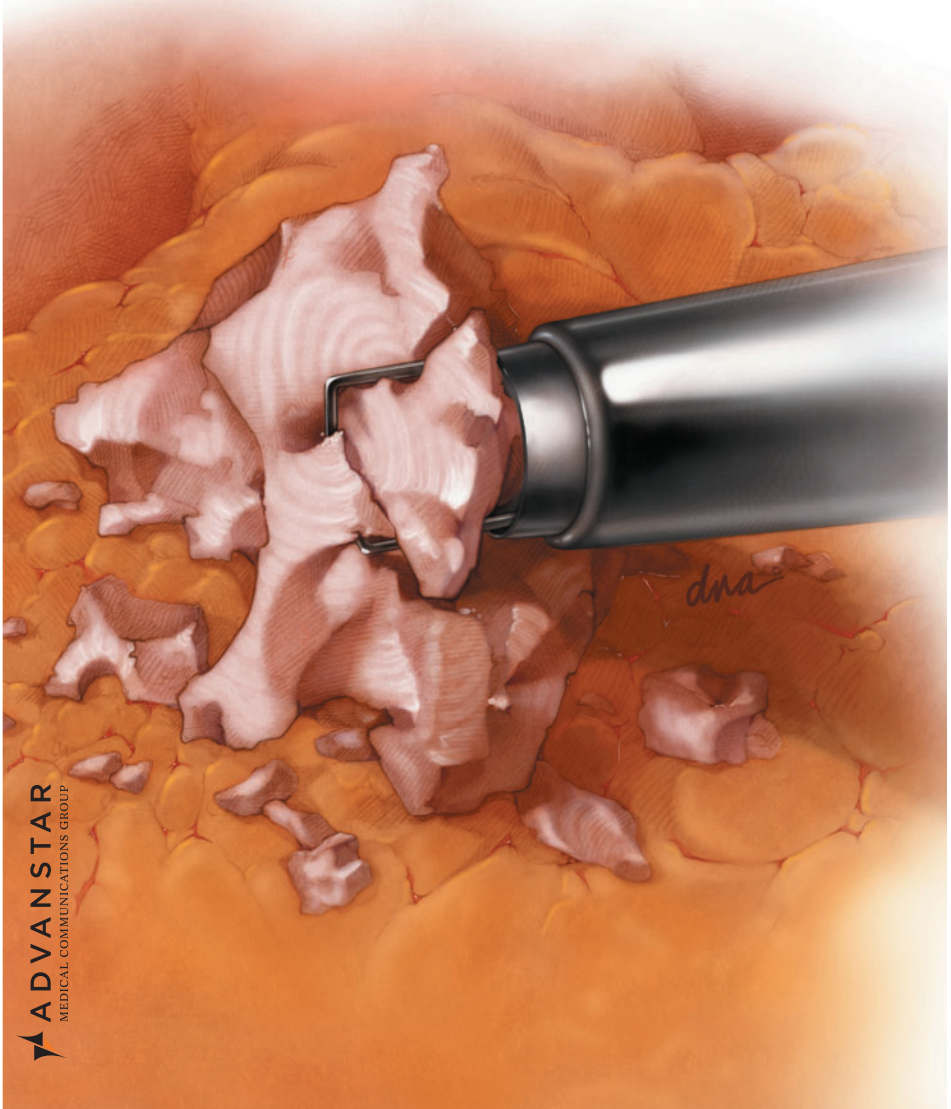
MORCELLATION DEBATE

The SCIENCE, The FACTS, The FUTURE

Sarah L. Cohen, MD, MPH



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Salpingectomy for ovarian CA prevention?

NASPAG

Teen eating disorders

TECH TOOLS

Time-lapse photography in ART

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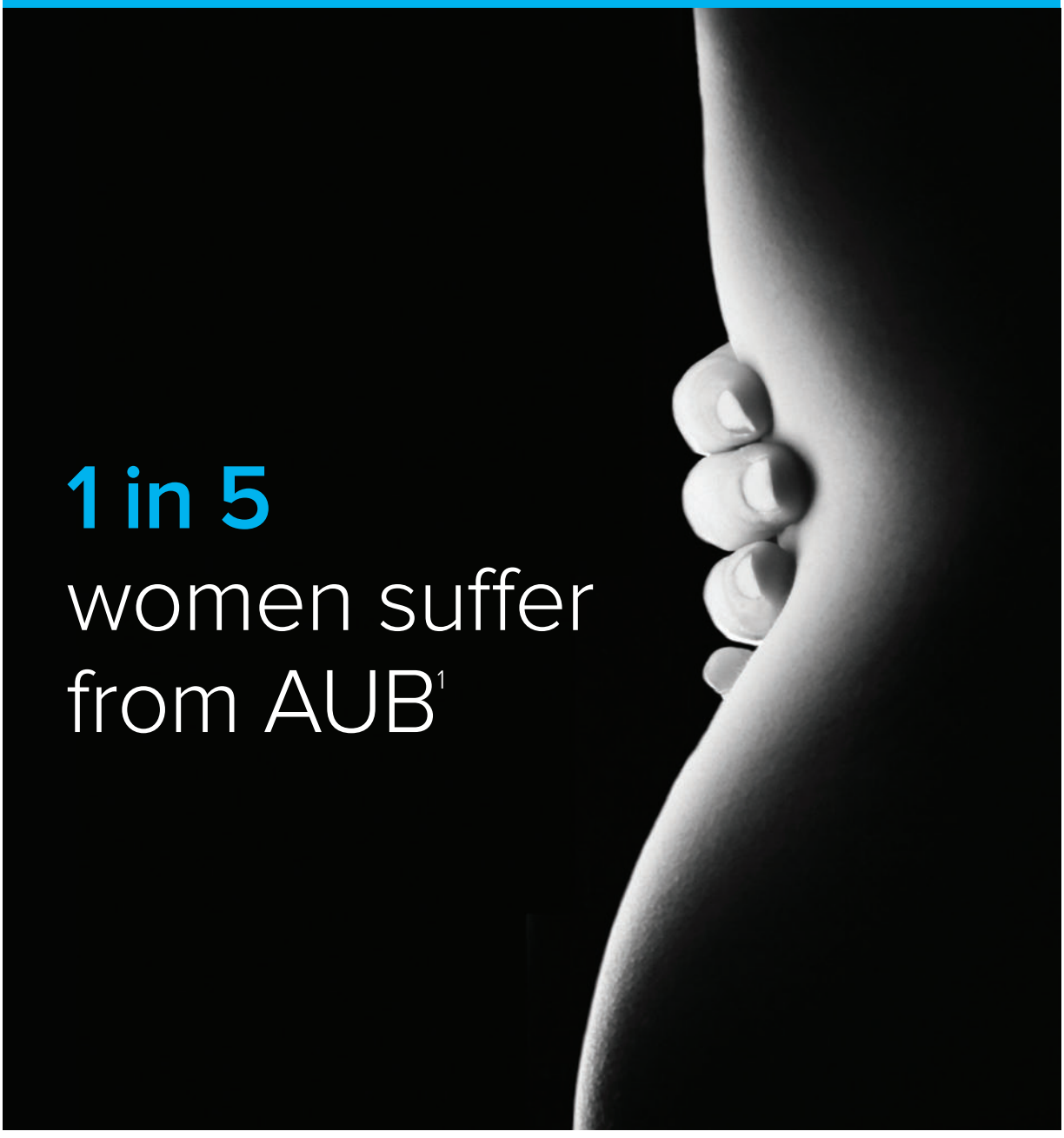
WOMEN'S HEALTH SOLUTIONS



Let her know she has options.

Far too many women suffer needlessly because they're embarrassed to talk about their heavy periods. Or they feel their childbearing plans — or the fact they are finished — leave them without options. So at her next appointment, start the conversation. Talk to her about the minimally invasive solutions by Hologic and set her free from the pain of AUB.

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Reference: 1. National Women's Health Resource Center. Survey of women who experience heavy menstrual bleeding. Data on file; 2005.

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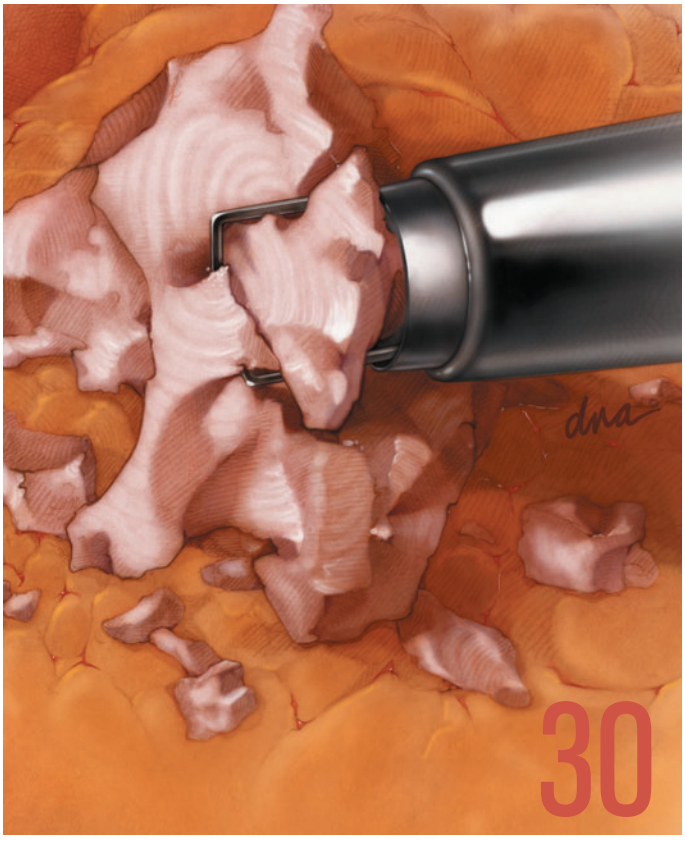

EDITOR'S NOTE Language on the cover of the promotional supplement that was distributed with the January issue should have stated: "Funding for graphics and content dissemination provided by Hologic. Dr. Einstein has advised or participated in educational speaking activities, but does not receive an honorarium from any companies, including for the writing of this supplement."

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BY **CHARLES J. LOCKWOOD, MD, MHCM**

What do ob/gyns need to know about the new healthcare exchanges?

The bottom line: More women of childbearing age will be covered but overall reimbursements will likely decline.

A new obstetric patient comes to your office recently enrolled in a Bronze tier, high-deductible, high coinsurance federally facilitated health insurance exchange plan. She immediately starts grilling you about your professional charges and your hospital's technical charges. You soon realize that she is liable for half the costs of having her baby. What is your advice?

I have already encountered recurrent pregnancy loss patients with high-deductible plans who have refused karyotypes and hysterosalpingograms because they would have to pay out of pocket and the results were unlikely to materially affect their management or prognosis. Welcome to the new world of public health insurance exchanges! Here's what you need to know about the new public exchanges and how will they will affect your practice.

> **Only half of current health plans** cover all mandated benefits and at least 60% of anticipated costs.

Exchange rules 101

The Affordable Care Act (ACA) includes 2 basic strategies for increasing health insurance coverage of the uninsured: 1) expanding Medicaid coverage to 133%–138% of the federal poverty line (FPL); and 2) providing subsidies to those with incomes between 100% and 400% of the FPL who obtain insurance through a public health insurance exchange "marketplace." The new exchange plans differ from many current plans in that they mandate 10 categories of benefits (ie, outpatient care, inpatient care, emergency services, obstetrical and newborn care, mental health, rehabilitation, lab tests, prescription drugs, preventative services, and pediatric services) and cover at least 60% of actuarially predicted health costs for that year.[1]

President Obama has endured much criticism for backtracking on his campaign promise that everyone could keep their insurance plan, since with the exception of plans that have been "grandfathered" (eg, in place without change since March 23, 2010), only half of current health plans cover all mandated benefits and at least 60% of anticipated costs.[1]

Indeed, the 4 tiers of plans offered by public exchanges—Bronze, Silver, Gold and Platinum—are constructed based on their ability to cover 60%, 70%, 80%, and 90% of actuarially projected annual healthcare costs. Enrollees are responsible for the remainder of costs. Different plans offer varying combinations

WE WANT TO HEAR FROM YOU

Send your feedback to:
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> "Because of low penalties and lax mandate enforcement, there is a **risk** that healthy young people will make the calculated decision to **opt out of the market.**"

of premiums, deductibles, copays and coinsurance to distribute these costs. Catastrophic coverage-only insurance is also available for adults under 30 years who are exempt from mandates because of low income.

One of the reasons the exchanges were opposed by the insurance industry is that very few can be denied coverage (ie, guaranteed issue) and because pricing can no longer be set through most traditional underwriting practices (ie, adjusting price based on health risks and expected costs). Thus, health plan pricing can no longer be adjusted for pre-existing medical conditions, gender, type of job, etc., although some adjustment in price is permitted for family size, geography, age, and tobacco use—a process termed "adjusted community rating."[2] Conversely, the ACA mandates a 20% to 30% discount for participation in wellness programs even though the cost-benefit data to support this policy are equivocal at best.[3]

On the other hand, the insurance industry is eager to cash in on government subsidies for exchange participants with incomes between 100% and 400% of the FPL. Premium subsidies vary with household income and are paid directly to the insurer. The Henry J. Kaiser Family Foundation has created a simple online premium subsidy calculator for determining eligible federal support.[4] For example, for a nonsmoking central Ohio family of 3 making $43,000 (215% of the FPL), who are not eligible for an employer-covered plan, the maximum percent of income they would have to pay for a premium would be 6.83%. Thus, of the $12,985 needed for a Silver plan annual premium, the government would pay the insurer $10,118 and the family would need to pay only $2,867 per year. Cost-sharing subsidies are also available for Silver plan participants with incomes less than 250% of the FPL. Using the same calculator, this family's total out-of-pocket maximum, not including the premium, would be no more than $10,400.

The key "motivation" for individuals to obtain such coverage is the ACA's mandate that imposes a tax penalty on any adult citizen not covered by an employer-sponsored health insurance plan who fails to obtain such coverage ≥3 months per year even though it is available at a cost of less than 8% of their total income. The IRS will monitor whether such coverage is in force because documentation must be included in everyone's 1040 form. Now there are 2 problems with the mandate: 1) The penalties are relatively low: $95 or 1% of household income (whichever is larger) in 2014, going up to $695 or 2.5% of household income by 2016; and 2) the IRS has minimal enforcement tools beyond withholding a portion of a filer's tax refund.

Because of low penalties and lax mandate enforcement, there is a risk that healthy young people will make the calculated decision to opt out of the insurance market. Because they were supposed to provide the premium revenue needed to cover the costs of enrolling sicker, older patients, this adverse selection could prove a financial burden for prospective insurers. The ACA has designed 3 ways to mitigate such risks. A permanent state and federal risk adjustment strategy allows exchanges to transfer revenue from plans with healthier to unhealthier populations.[5] This is supposed to minimize the impact of adverse selection and stabilize premiums. A temporary federally administered "reinsurance" program taxes health plans to create a reinsurance pool to cover up to 80% of outlier costs. This program will sunset with the anticipated entry of commercial reinsurance providers after 2016.

Risk corridors, the third strategy, are another temporary federal measure expiring in 2016 that limits losses to qualified health plans. The federal government will cover

continued on **PAGE 13**

Indication

Osphena™ (ospemifene) is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Important Safety Information

WARNING: Endometrial Cancer and Cardiovascular Disorders

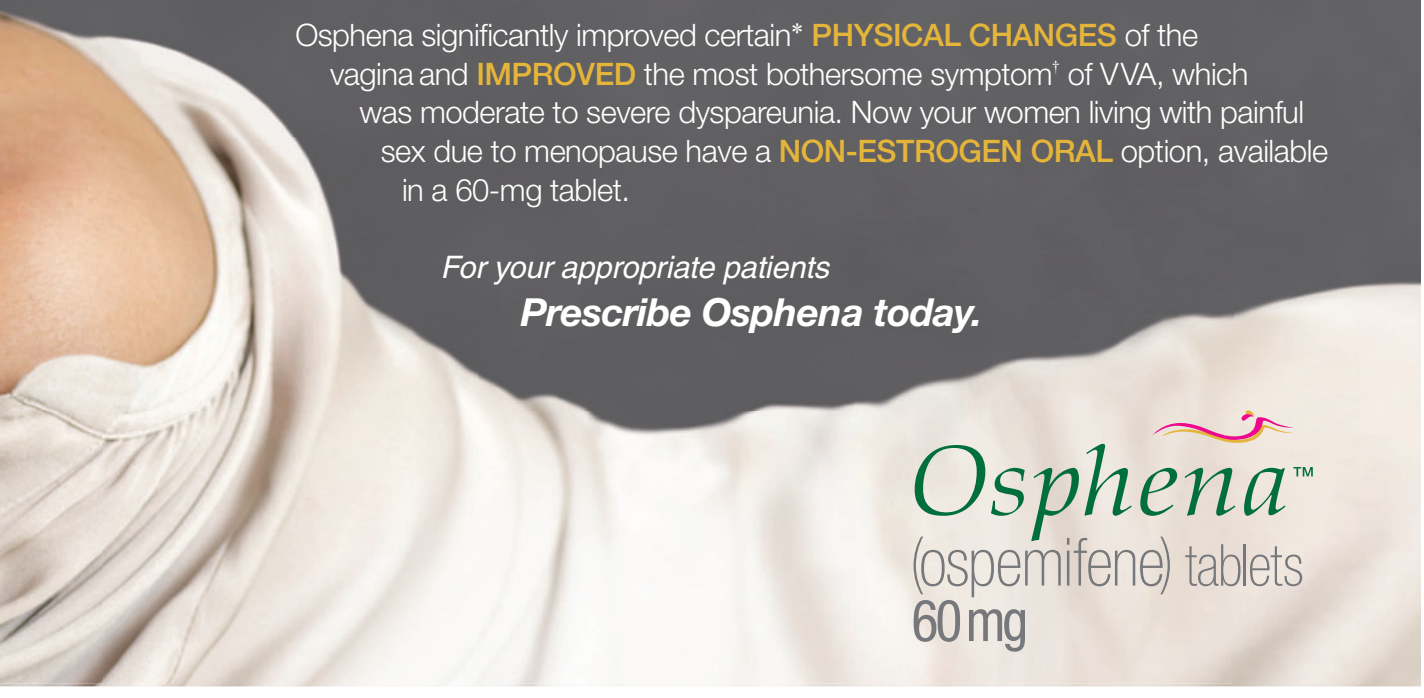
Osphena is an estrogen agonist/antagonist with tissue selective effects. In the endometrium Osphena has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen therapy. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

The Women's Health Initiative (WHI) estrogen-alone substudy reported an increased risk 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], relative to placebo. Osphena 60 mg had thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women vs. 1.04 and 0 per thousand women for placebo and a DVT incidence rate of 1.45 vs. 1.04 per thousand women for placebo. Osphena should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

*Improved certain physical changes, which were superficial cells and parabasal cells and pH of the vagina.
†Most bothersome symptom was defined as the most bothersome moderate to severe symptom at baseline.

For your women with moderate to severe dyspareunia, due to menopause

THE ONLY NON-ESTROGEN ORAL TREATMENT



Osphena significantly improved certain* **PHYSICAL CHANGES** of the vagina and **IMPROVED** the most bothersome symptom† of VVA, which was moderate to severe dyspareunia. Now your women living with painful sex due to menopause have a **NON-ESTROGEN ORAL** option, available in a 60-mg tablet.

For your appropriate patients

Prescribe Osphena today.

Osphena™
(ospemifene) tablets
60 mg

Important Safety Information

Contraindications

- Osphena should not be used in patients with undiagnosed abnormal genital bleeding, known or suspected estrogen-dependent neoplasia, active deep vein thrombosis (DVT), pulmonary embolism (PE) or active arterial thromboembolic disease or a history of these conditions
- Women who are or may become pregnant. Osphena may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus

Warnings and Precautions

Osphena has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Osphena should not be used in women with severe hepatic impairment as it has not been studied.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with Osphena 60 mg compared to placebo were: hot flush (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), muscle spasms (3.2% vs. 0.9%), hyperhidrosis (1.6% vs. 0.6%), and genital discharge (1.3% vs. 0.1%).

Do not use estrogens or estrogen agonists/antagonists, fluconazole, or rifampin concomitantly with Osphena.

Please see Brief Summary of the Full Prescribing Information, including Boxed WARNING, on the adjacent page.

osphena.com

OSPHENA™ (ospemifene) 60 mg tablets

BRIEF SUMMARY – See Package Insert for Complete Prescribing Information.

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS

Endometrial Cancer

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see *Warnings and Precautions (5.2)*].

Cardiovascular Disorders

There is a reported increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the Women's Health Initiative (WHI) [see *Warnings and Precautions (5.1)*].

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 in placebo [see *Warnings and Precautions (5.1)*]. The incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo [see *Warnings and Precautions (5.1)*]. OSPHENA should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE: OSPHENA is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

CONTRAINDICATIONS: OSPHENA is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism (PE), or a history of these conditions
- Active arterial thromboembolic disease [for example, stroke and myocardial infarction (MI)], or a history of these conditions
- OSPHENA is contraindicated in women who are or may become pregnant. OSPHENA may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

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

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per ten thousand women-years). The increase in risk was demonstrated in year 1 and persisted.

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women in placebo.

Should thromboembolic or hemorrhagic stroke occur or be suspected, OSPHENA should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo. In the OSPHENA clinical trials, a single MI occurred in a woman receiving 60 mg of ospemifene.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per ten thousand women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per ten thousand women-years). The increase in VTE risk was demonstrated during the first 2 years.

In the OSPHENA clinical trials, the incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo. Should a VTE occur or be suspected, OSPHENA should be discontinued immediately.

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

Malignant Neoplasms

Endometrial Cancer

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has agonistic effects. In the OSPHENA clinical trials (60 mg treatment group), no cases of endometrial cancer were seen with exposure up to 52 weeks. There was a single case of simple hyperplasia without atypia. Endometrial thickening equal to 5 mm or greater was seen in the OSPHENA treatment groups at a rate of 60.1 per thousand women vs 21.2 per thousand women for placebo. The incidence of any type of proliferative (weakly plus active plus disordered) endometrium was 86.1 per thousand women in OSPHENA vs 13.3 per thousand women for placebo. Uterine polyps occurred at an incidence of 5.9 per thousand women vs 1.8 per thousand women for placebo.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. The use of progestins with OSPHENA therapy was not evaluated in the clinical trials.

Clinical surveillance of all women using OSPHENA 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

OSPHENA 60 mg has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Severe Hepatic Impairment

OSPHENA should not be used in women with severe hepatic impairment [see Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders [see *Boxed Warnings, Warnings and Precautions (5.1)*]
- Malignant Neoplasms [see *Boxed Warnings, Warnings and Precautions (5.2)*]

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 practice.

The safety of OSPHENA has been assessed in nine phase 2/3 trials (N=1892) with doses ranging from 5 to 90 mg per day. The duration of treatment in these studies ranged from 6 weeks to 15 months. Most women (N=1370) had a treatment period of at least 12 weeks, 409 had at least 52 weeks (1 year) of exposure.

The incidence rates of thromboembolic and hemorrhagic stroke were 0.72 per thousand women (1 reported case of thromboembolic stroke) and 1.45 per thousand women (2 reported cases of hemorrhagic stroke), respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women, respectively in placebo. The incidence of deep vein thrombosis (DVT) was 1.45 per thousand women in OSPHENA 60 mg treatment group (2 reported cases of DVT) and 1.04 (1 case of DVT) in placebo.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with Osphena 60 mg compared to placebo were: hot flush (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), muscle spasms (3.2% vs. 0.9%), hyperhidrosis (1.6% vs. 0.6%), and genital discharge (1.3% vs. 0.1%).

DRUG INTERACTIONS

OSPHENA is primarily metabolized by CYP3A4 and CYP2C9. CYP2C19 and other pathways contribute to the metabolism of ospemifene.

Estrogens and estrogen agonist/antagonist

OSPHENA should not be used concomitantly with estrogens and estrogen agonists/antagonists. The safety of concomitant use of OSPHENA with estrogens and estrogen agonists/antagonists has not been studied.

Fluconazole

Fluconazole, a moderate CYP3A/strong CYP2C9/moderate CYP2C19 inhibitor, should not be used with OSPHENA. Fluconazole increases the systemic exposure of ospemifene by 2.7-fold. Administration of fluconazole with ospemifene may increase the risk of OSPHENA-related adverse reactions [see *Clinical Pharmacology (12.3)*].

Rifampin

Rifampin, a strong CYP3A4/moderate CYP2C9/moderate CYP2C19 inducer, decreases the systemic exposure of ospemifene by 58%. Therefore, coadministration of OSPHENA with drugs such as rifampin which induce CYP3A4, CYP2C9 and/or CYP2C19 activity would be expected to decrease the systemic exposure of ospemifene, which may decrease the clinical effect [see *Clinical Pharmacology (12.3)*].

Ketoconazole

Ketoconazole, a strong CYP3A4 inhibitor increases the systemic exposure of ospemifene by 1.4-fold. Administration of ketoconazole chronically with ospemifene may increase the risk of OSPHENA-related adverse reactions [see *Clinical Pharmacology (12.3)*].

Warfarin

Repeated administration of ospemifene had no effect on the pharmacokinetics of a single 10 mg dose of warfarin. No study was conducted with multiple doses of warfarin. The effect of ospemifene on clotting time such as the International Normalized Ratio (INR) or prothrombin time (PT) was not studied [see *Clinical Pharmacology (12.3)*].

Highly Protein-Bound Drugs

Ospemifene is more than 99% bound to serum proteins and might affect the protein binding of other drugs. Use of OSPHENA with other drug products that are highly protein bound may lead to increased exposure of either that drug or ospemifene [see *Clinical Pharmacology (12.3)*].

Multiple Enzyme Inhibition

Coadministration of OSPHENA with a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes may increase the risk of OSPHENA-related adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category X [see *Contraindications (4)*].

Nursing Mothers

It is not known whether OSPHENA is excreted in human breast milk. In a nonclinical study, ospemifene was excreted in rat milk and detected at concentrations higher than that in maternal plasma.

Pediatric Use

OSPHENA is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use

Of the 1892 OSPHENA-treated women enrolled in the nine phase 2/3 trials of OSPHENA, >19 percent were 65 years of age or older. No clinically meaningful differences in safety or effectiveness were observed between these women and younger women less than 65 years of age.

Renal Impairment

The pharmacokinetics of ospemifene in women with severe renal impairment (CrCL<30 mL/min) was similar to those in women with normal renal function [see *Clinical Pharmacology (12.3)*].

No dose adjustment of OSPHENA is required in women with renal impairment.

Hepatic Impairment

The pharmacokinetics of ospemifene has not been studied in women with severe hepatic impairment (Child-Pugh Class C); therefore, OSPHENA should not be used in women with severe hepatic impairment [see *Warnings and Precautions (5.3)*, and *Clinical Pharmacology (12.3)*].

No clinically important pharmacokinetic differences with OSPHENA were observed between women with mild to moderate hepatic impairment and healthy women [see *Clinical Pharmacology (12.3)*].

No dose adjustment of OSPHENA is required in women with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

OVERDOSAGE

There is no specific antidote for OSPHENA.

Based on OSPHENA (ospemifene) 60 mg tablets, Prescribing Information 02/2013.

SHIONOGI INC.

continued from **PAGE 9**

50% of allowable charges when an insurer's claims exceed rates set for 2014 by at least 3% and 80% when that excess hits 8% above target.

On the flip side, a health plan will pay 50% of its excess profit to the government when costs are 97% to 92% less than expected, rising to 80% when costs are <92% of that expected.

Donut holes, state vs. federal exchanges, and other problems

The Supreme Court Decision declaring the ACA constitutional but permitting states to opt out of its provision to expand Medicaid coverage has resulted in 24 states opting out as of this writing, another 23 states expanding Medicaid, and 3 using a nontraditional expansion strategy.[6] The resultant map looks much like the 2012 presidential election results. Because many of the states that chose not to expand Medicaid do not cover their citizens up to 100% of the FPL, a substantial number of patients will be ineligible for both exchanges and Medicaid—creating a so-called donut hole. A similar ideological divide exists over whether exchanges are to be run by the state or federal government.

As of this writing 17 exchanges were state-based, 7 were state-federal partnerships and 27 were federally run exchanges.[7] Obtaining assistance in choosing between plans can be a major bottleneck in implementation. State-based exchanges generally have active programs to assist citizens in choosing the best plan. States may also be "active purchasers" of plans which allows them to limit selection options and thus, costs.

Other state and federal exchanges act as "clearinghouses," setting baseline premiums.[7] The ACA made provision for "navigators" to assist enrollees in choosing plans, but more conservative states have passed legislation reducing access to such assistance as part of their strategy to scuttle the ACA.[8]

Take-home message

The good news is that exchanges should increase the number of women of childbearing age with insurance. They will now be covered for needed preventative services and contraception, which we can hope will result in enhanced preconceptual care and earlier access to prenatal care.

The bad news is that narrow provider networks may carve ob/gyns out, particularly those whose prices are high. The new patients—particularly those enrolled in Bronze and Silver plans—will also stress your revenue cycle resources and office staff. High copays, high deductibles and high coinsurance provisions will require aggressive efforts to collect payments at the time of service and after receiving partial payments from health plans. Overall reimbursements will likely decline. Finally, the high coinsurance costs may drive your patients to less expensive hospitals or birthing centers where you do not have privileges. COG

I URGE YOU TO WATCH DR. ARNOLD COHEN'S EXCELLENT VIDEO AT HTTP://CONTEMPORARYOBGYN.NET/OBGYNS-ACA-EXCHANGES THAT DESCRIBES A NUMBER OF THESE BILLING CHALLENGES.

DR LOCKWOOD, editor in chief, is Dean of the College of Medicine and Vice President for Health Sciences at The Ohio State University, Columbus, Ohio.

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Opiate abuse and pregnancy

Screen and intervene

contemporaryobgyn.net/opiate-abuse-pregnancy

Drug abuse during pregnancy has become more common in recent years. The most effective approach to screening for substance abuse during pregnancy may be through a series of nonjudgmental questions, writes author Mona Prasad, DO, MPH.

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Good advice on how to reduce #cesarean birth rate safely. Thanks #SMFM & #ACOG http://bit.ly/1jfUQZy @contempobgyn

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Contemporary OB/GYN
February 7

EXCLUSIVE: Contemporary OB/GYN Tech columnist Brian Levine, MD, and John Nosta of Forbes and Nostalab talk about their experiences as Google Glass Explorers and the potential of the technology in health care.

Contemporary OB/GYN
February 6

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Drs. Queenan & Quilligan #founders #smfm14

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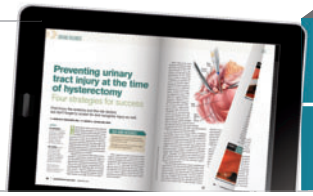

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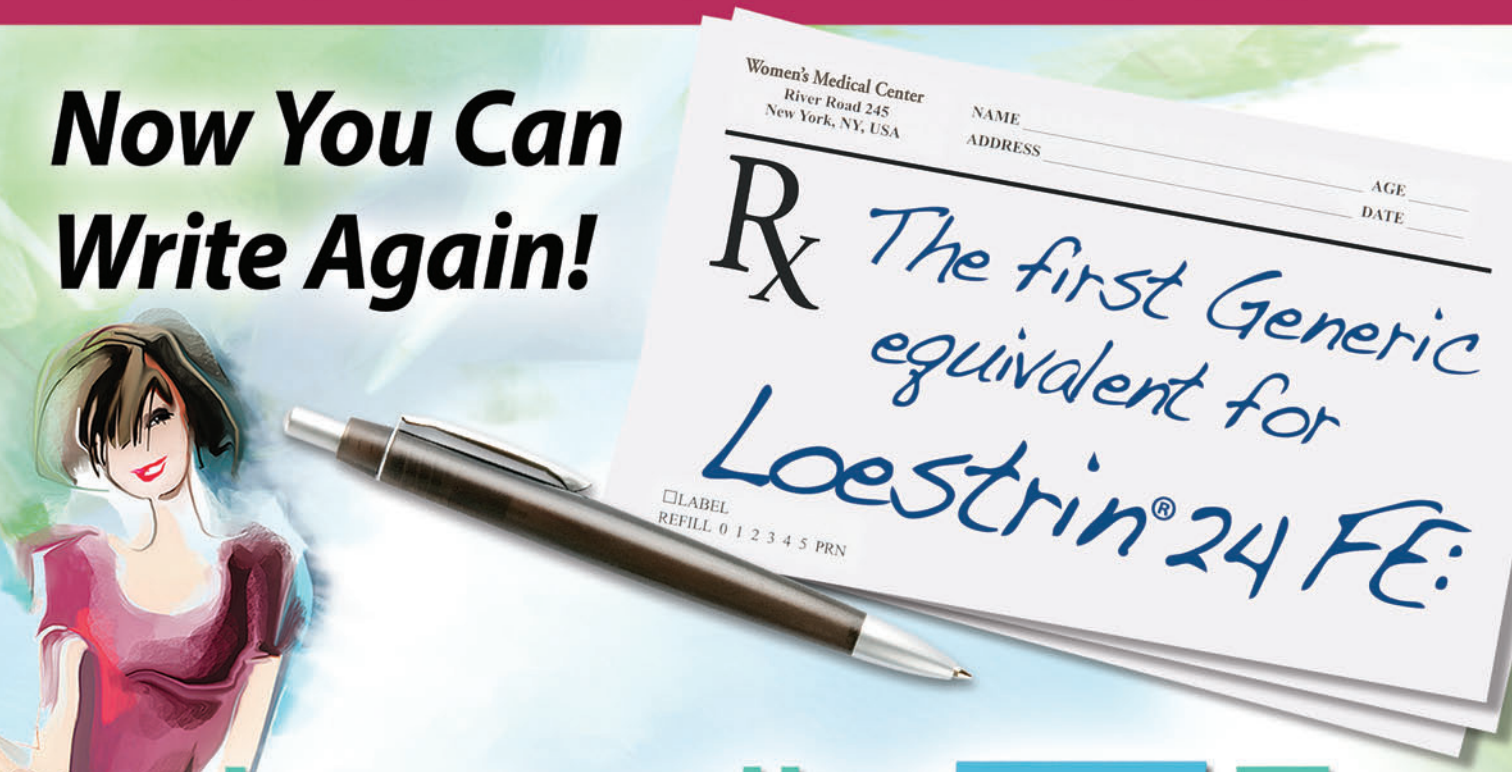
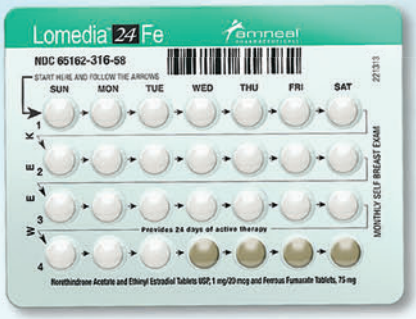


Lomedia™ 24 Fe

(Norethindrone Acetate and Ethinyl Estradiol Tablets USP, 1mg/20mcg and Ferrous Fumarate* Tablets, 75mg)



The first and only AB-rated equivalent for the discontinued Loestrin®24 Fe brand.

Let patients know the good news...

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See Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages. Full Prescribing Information, which includes the Patient Information and Boxed Warning, is available at Lomedia24Fe.com.

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Lomedia™ 24 Fe

(Norethindrone Acetate and Ethinyl Estradiol Tablets USP, 1 mg/20 mcg and Ferrous Fumarate Tablets*, 75 mg)

For oral use only
Rx Only
Brief Summary of Prescribing Information

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

INDICATIONS AND USAGE

Lomedia™ 24 Fe is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions: •thrombophlebitis or thromboembolic disorders, •a past history of deep vein thrombophlebitis or thromboembolic disorders, •cerebrovascular or coronary artery disease (current or history), •valvular heart disease with thrombogenic complications, •severe hypertension, •diabetes with vascular involvement, •headaches with focal neurological symptoms, •major surgery with prolonged immobilization, •known or suspected carcinoma of the breast or personal history of breast cancer, •carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia, •undiagnosed abnormal genital bleeding, •cholestatic jaundice of pregnancy or jaundice with prior pill use, •hepatic adenomas or carcinomas, or active liver disease, •known or suspected pregnancy, and •hypersensitivity to any component of this product.

WARNINGS

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.

If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breastfeed.

Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risk of cerebrovascular events (thrombotic and hemorrhagic strokes) although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. The amount of both hormones should be considered in the choice of an oral contraceptive. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which is judged appropriate for the individual patient.

Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In these studies, the increased risk persisted for up to or more than nine years.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The Fertility and Maternal Health Drugs Advisory Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use. An estimate of the attributable risk is 3.3 cases/100,000 for users and the risk increases after four or more years of use. 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) oral contraceptive users. However, the attributable risk of liver cancers in oral contraceptive users approaches less than one per million users.

OCULAR LESIONS

Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological 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 taken inadvertently during early pregnancy (see **CONTRAINDICATIONS** section).

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy.

GALLBLADDER DISEASE

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

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill.

ELEVATED BLOOD PRESSURE

Women with significant hypertension should not be started on hormonal contraceptives. An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral contraceptive users and with continued use. The incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **CONTRAINDICATIONS** section).

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause (see **Thromboembolic Disorders And Other Vascular Problems** in **WARNINGS**).

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. If bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem.

Absence of a withdrawal menses may also occur. In the event of amenorrhea for two cycles or more, pregnancy should be ruled out. In the clinical trial with Lomedia™ 24 Fe, 31 to 41% of the women using Lomedia™ 24 Fe did not have a withdrawal menses in at least one of 6 cycles of use.

Some women may experience post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

PRECAUTIONS

SEXUALLY TRANSMITTED DISEASES

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

PHYSICAL EXAMINATION AND FOLLOW-UP

A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives.

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

LIVER FUNCTION

Discontinue oral contraceptives if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function.

FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

CONTACT LENSES

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

DRUG INTERACTIONS

Changes in contraceptive effectiveness associated with co-administration of other products:

Anti-infective agents and anticonvulsants

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin.

Anti-HIV protease inhibitors

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with coadministration of anti-HIV protease inhibitors.

Herbal products

Herbal products containing St. John's Wort may induce some hepatic enzymes and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids, and also may result in breakthrough bleeding.

Increase in plasma levels of estradiol associated *with co-administered drugs*

Co-administration of atorvastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. 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.

Changes in plasma levels of co-administered drugs

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.

INTERACTIONS WITH LABORATORY TESTS

Oral contraceptives may affect certain endocrine and liver function tests, and blood components, such as (a) increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; and increased norepinephrine induced platelet aggregability; (b) increased thyroid-binding globulin (TBG); (c) other binding proteins may be elevated in serum; (d) sex hormone binding globulins are increased, however, free or biologically active levels remain unchanged; (e) triglycerides may be increased and levels of various other lipids and lipoproteins may be affected; (f) glucose tolerance may be decreased; and (g) serum folate levels may be depressed by oral contraceptive therapy.

PREGNANCY

Pregnancy Category X.

NURSING MOTHERS

Small amounts of oral contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

PEDIATRIC USE

Safety and efficacy of Lomedia™ 24 Fe have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 years and in users age 16 years and older. Use of this product before menarche is not indicated.

GERIATRIC USE

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

ADVERSE REACTIONS

The most common adverse events reported by 2 to 6% of the 743 women using Lomedia™ 24 Fe were the following, in order of decreasing incidence: headache, vaginal candidiasis, upper respiratory infection, nausea, menstrual cramps, breast tenderness, sinusitis, vaginitis (bacterial), abnormal cervical smear, acne, urinary tract infection, mood swings, weight gain, vomiting, and metrorrhagia.

Among the 743 women using Lomedia™ 24 Fe, 46 women (6.2%) withdrew because of an adverse event. Adverse events occurring in 3 or more subjects leading to discontinuation of treatment were, in decreasing order: abnormal bleeding (0.9%), nausea (0.8%), menstrual cramps (0.4%), increased blood pressure (0.4%), and irregular bleeding (0.4%).

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section): •thrombophlebitis, •arterial thromboembolism, •pulmonary embolism, •myocardial infarction, •cerebral hemorrhage, •cerebral thrombosis, •hypertension, •gallbladder disease, and •hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives: •mesenteric thrombosis and •retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: •nausea, •vomiting, •gastrointestinal symptoms (such as abdominal pain, cramps and bloating), •breakthrough bleeding, •spotting, •change in menstrual flow, •amenorrhea, •temporary infertility after discontinuation of treatment, •edema/fluid retention, •melasma/chloasma which may persist, •breast changes (tenderness, pain, enlargement, and secretion), •change in weight or appetite (increase or decrease), •change in cervical ectropion and secretion, •possible diminution in lactation when given immediately postpartum, •cholestatic jaundice, •migraine headache, •rash (allergic), •mood changes (including depression), •vaginitis (including candidiasis), •change in corneal curvature (steepening), •intolerance to contact lenses, •decrease in serum folate levels, •exacerbation of systemic lupus erythematosus, •exacerbation of porphyria, •exacerbation of chorea, •aggravation of varicose veins, and •anaphylactic/anaphylactoid reactions (including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms).

The following adverse reactions have been reported in users of oral contraceptives, and a causal association has been neither confirmed nor refuted: •acne, •Budd-Chiari syndrome, •cataracts, •colitis, •changes in libido, •cystitis-like syndrome, •dizziness, •dysmenorrhea, •erythema multiforme, •erythema nodosum, •headache, •hemorrhagic eruption, •hemolytic uremic syndrome, •hirsutism, •impaired renal function, •loss of scalp hair, •nervousness, •optic neuritis (which may lead to partial or complete loss of vision), •pancreatitis, and •premenstrual syndrome.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Please see package insert for full prescribing information.

More detailed information is available upon request.

For more information about Lomedia™ 24 Fe contact: Amneal Pharmaceuticals at 1-877-835-5472.

Date of Issue: October 2013.

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AMA calls for ICD-10 delay

BY DONNA MARBURY

The costs to medical practices for implementing the International Classification of Diseases-10th Revision (ICD-10) coding system have been grossly underestimated, according to a recent study by Nachimson Advisors for the American Medical Association (AMA). The association is calling for a delay in the October 1, 2014, ICD-10 go-live date in order to give practices more time to prepare for the financial and administrative requirements.

> "Large practices can expect to spend between **$2 million and $8 million to implement** the new coding system, according to the study."

Small practices can expect to spend between $56,639 and $226,105 and medium-size practices can spend between $213,364 and $824,735 to implement ICD-10. Expected costs include up to $100,000 in payment disruption for small practices, and up to $166,000 in productivity losses for medium-size practices. Large practices can expect to spend between $2 million and $8 million to implement the new coding system, according to the study. The study estimated that two-thirds of physicians will pay the upper range of cost estimates. In 2008, the AMA estimated that it would cost a small practice $83,290 to implement ICD-10.

"The markedly higher implementation costs for ICD-10 place a crushing burden on physicians, straining vital resources needed to invest in new healthcare delivery models and well-developed technology that promotes care coordination with real value to patients," AMA President Ardis Dee Hoven, MD said in a press release. "Continuing to compel physicians to adopt this new coding structure threatens to disrupt innovations by diverting resources away from areas that are expected to help lower costs and improve the quality of care."

The AMA sent a letter to the Kathleen Sebelius, secretary of the U.S. Department of Health and Human Services, outlining the hardships physicians are facing in implementing ICD-10. The letter calls for Medicare to offer "true end-to-end testing" of ICD-10 coding to ensure practices and payers will be able to communicate.

"While it will allow a physician to know whether his or her claim was received or not, it does not give any indication as to whether it will be paid, how much it will be paid, whether they have used the correct ICD-10 code, or whether Medicare believes more information is needed to adjudicate the claim," James L. Madara, MD, AMA's assistant director of federal affairs, said in the letter. "To draw a simple analogy, this is like receiving a package on your doorstep that you can only view from your window. While it is helpful to know the package has arrived, you have no idea what is inside until you are able to open it."

Other suggestions include expanding advance payment options and offering free Medicare billing software for practices facing financial hardships. The AMA also requests that the Centers for Medicare and Medicaid Services allow for a 2-year implementation period where miscoded claims are not denied, but are returned to physicians with feedback on how to correct them.

According to a February survey by the Medical Management Group Association, 79% of physicians report that they haven't begun ICD-10 implementation, or were "somewhat ready."

For more on ICD-10, see page 76.

Women, type 2 diabetes, and stroke: What's the association?

BY **SUSAN C. OLMSTEAD**

Researchers at the Pennington Biomedical Research Center in Baton Rouge, Louisiana, prospectively investigated stroke risk among 10,876 male and 19,278 female patients with type 2 diabetes. The goal of the study, which appeared in the journal *Diabetologia*, was

to better understand the relationship between glycemic control and stroke risk. The researchers note that more women than men tend to die from stroke in developed countries. In 2010 in the United States, 77,109 women and 52,367 men died from stroke, according to the study.

The study identified 2949 incident cases of stroke in these patients during a mean follow-up of 6.7 years. Among the men, although there was a trend toward increased risk of stroke as glycated hemoglobin (HbA1c) levels increased, this increased risk was not statistically significant. Among women, however, those with HbA1c of 8.0–8.9% were 19% more likely to have a stroke than were the women with normal blood sugar; those with 9.0–9.9% HbA1c were 32% more likely to have a stroke, and those above 10% HbA1c were 42% more likely to have a stroke, with each of these associations statistically significant. The adjusted hazard ratios were significantly higher in women older than 55 years.

The researchers claim that the study suggests a graded association between HbA1c and the risk of stroke among women with type 2 diabetes and that poor control of blood sugar has a stronger effect in diabetic women older than 55 years.

In a *Diabetologia* press release, researcher Dr. Gang Hu states, "Diabetes poses a substantially greater increase in the risk of stroke among women than among men, which merits further investigation. … Females with type 2 diabetes, especially postmenopausal females, are at high risk for stroke. More aggressive blood sugar treatments and better control of other risk factor levels in women with diabetes are likely to substantially reduce stroke in this subgroup."

Pregnancy in young girls presents unique risks

BY **LISA HACK**

Girls who become pregnant when they are aged younger than 15 years are more likely than slightly older women to have much older sexual partners, to not use contraception the first time they have sex, and to be Hispanic or black, suggesting that they may be particularly vulnerable to relationships with unequal power.

The findings come from a recent study using data from the 2006 to 2010 National Survey of Family Growth. The women surveyed were aged 20 to 44 years, but reported on pregnancies that occurred before they were 20 years of age.

The investigators found that 3.4% (289) of the 3384 women who reported a pregnancy before age 20 years had their first pregnancy when they were aged younger than 15 years. The remainder reported their first pregnancies to have occurred between 15 and 19 years of age.

The younger women were almost twice as likely as the older teenagers to be Hispanic, more than twice as likely to be black, and more than 3 times as likely to report that their sexual partners were least 6 years older than they were. They were also 2.5 times as likely to report that the pregnancy was unintended. They were less likely than the older women to have been raised within a religion, to be living with both biologic parents at age 14 years, and to have used contraception the first time they had sex.

The researchers conclude that this group of young women has unique social, family planning, and reproductive health needs and that pediatricians are positioned to help.

According to the March of Dimes, infants born to adolescent mothers are at higher risk than infants born to older mothers for premature birth, low birth weight, and other serious health problems and death. Compared with every other age group, infants born to mothers aged younger than 15 years have the highest risk of death during the first year of life.

A link between hormonal contraception and MS?

BY **SUSAN C. OLMSTEAD**

A study scheduled to be presented at the American Academy of Neurology's 66th annual meeting in April suggests a possible connection between use of hormonal contraception and risk of multiple sclerosis (MS).

Researchers conducted a population-based nested case-control study, "Hormonal Contraceptives and Multiple Sclerosis Susceptibility," using data from members of Kaiser

continued on **PAGE 22**

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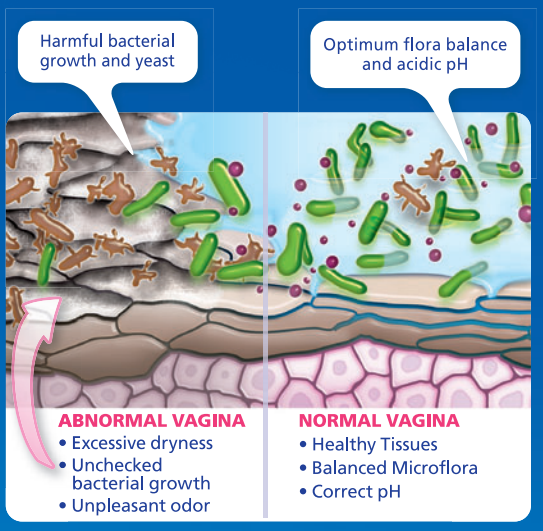

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Permanente Southern California (KPSC). They identified females aged 14-48 years who had MS or its precursor (clinically isolated syndrome [CIS]) between 2008 and 2011.

Ten controls per case were matched on age, race/ethnicity, and membership characteristics. Data were obtained from the complete electronic health record and analyzed using conditional logistic regression, adjusted for smoking and live births 3 years prior to symptom onset.

The authors identified 305 women with MS/CIS and 3050 matched-controls. Hormonal contraception was used for at least 3 months within the 3 years prior to symptom onset by 29.2% of cases and 23.5% of controls. The majority used estrogen/progestin combination pills. Risk of MS/CIS was increased slightly in women who used any hormonal contraceptive in the 3 years prior to symptoms onset, particularly those who had stopped at least 1 month prior to symptom onset (ever-users adjusted OR = 1.35, 95% CI = 1.01-1.80, P = 0.04; not current users adjusted OR = 1.50, 95%CI =1.05-2.14, P = 0.026).

In the abstract for the meeting, the researchers write that their findings suggest that use of modern hormonal contraception may be contributing, at least in part, to the rise in incidence of MS in women. Additional analysis will be presented at the meeting in a question-and-answer session on risk factors for MS.

> "Their **findings suggest** that use of modern **hormonal contraception** may be contributing, at least in part, **to the rise in incidence of MS in women.**"

cfDNA testing predicts aneuploidy in low-risk pregnancies

BY **JUDITH ORVOS**

Massively parallel sequencing of maternal cell-free DNA (cfDNA testing) has been shown better at predicting fetal aneuploidies than standard screening in a new study among a general obstetric population. Published in *The New England Journal of Medicine*, the report by the CARE Study group was funded by Illumina.

Twenty-one centers in the United States were included in the research, which was performed on 1914 women (mean age 29.6 years) with singleton pregnancies who were undergoing standard aneuploidy screening with serum biochemical assays with or without nuchal translucency measurement. cfDNA testing was performed in blinded fashion to determine the chromosome dosage for each sample.

The primary end point was a comparison of the false-positive rates for detection of fetal trisomies 21 and 18 with use of standard screening and cfDNA testing. The reference standard was birth outcomes or karyotypes.

cfDNA testing was associated with significantly lower false-positive rates than standard screening for trisomies 21 and 18 (0.3% vs 3.6%, $P < 0.001$ and 0.2% vs 0.6%, $P = 0.003$, respectively). With cfDNA testing, all cases of aneuploidy were detected (5 trisomy 21, 2 trisomy 18, 1 trisomy 13), for a negative predictive value of 100%. Positive predictive values for cfDNA testing versus standard screening were 45.5% vs 4.2% for trisomy 21 and 40.0% vs 8.3% for trisomy 18.

cfDNA testing previously has been proven to accurately detect fetal autosomal aneuploidy in high-risk pregnant women. This study, the authors said, sheds new light on false-positive rates and positive predictive values for the technology in detection of trisomies 21 and 18 in women with low-risk pregnancies. COG

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Regarding 'When opiate abuse complicates pregnancy'

TO THE EDITOR:

I wish to congratulate Dr. Prasad and *Contemporary OB/GYN* for the timely and comprehensive article about substance abuse during pregnancy ["When opiate abuse complicates pregnancy," February 2014]. I'd like to emphasize that the work of ob/gyns and MFMs to help pregnant women under these circumstances is fettered somewhat by 2 different sources.

First, we continue to battle with misinformed local and state agencies that by a) criminalizing opiate and other agent abuse during pregnancy, drive patients from care and interfere with utilization of well established and effective support/rehabilitation programs during pregnancy; and b) limiting funding for these programs and mental health professionals, increase the prospects of non-treatment and recidivism in this vulnerable transgenerational group. Sensible public health partnerships should and can be generated to resolve these roadblocks to care with our profession at the table.

Second, while the use of buprenorphine during pregnancy holds great promise for both mother and infant, the cadre of certified practitioners dispensing this medication are not required to abide by the regulatory backbone of methadone maintenance (MM) programs in many jurisdictions.

Consequently, patients are less often tested by them or referred to ancillary supportive services for social services and counseling. Communication with pregnancy care professionals is often spotty or nonexistent. Many such patients are left with the impression that they are no longer addicted and that they are no longer in an environment of risk.

The supportive success of MM programs provides a good working model that buprenorphine-dispensing professionals should draw from along with improved health professional communications to ensure optimal care of the patients we are both providing for.

Thanks for the opportunity to provide some personal insight.

John J. Botti, MD
Wilmington, North Carolina

IN REPLY:

Thank you for your letter and for bringing to light the practical issues impeding our ability to care for opiate-dependent women. I came to this arena out of my interest in infectious disease, particularly HCV mother-to-child transmission, and was quickly educated regarding the lack of resources available to this population. It is no overstatement that, were it not for the cost of treating babies with NAS, the attention to opiate-dependent mothers would approach zero.

I agree with you that partnerships to optimize the health and rehabilitation of women while pregnant are urgently needed. I have always asserted that pregnancy is a pivotal time-point for women, and if we capitalize on that motivation and extend services to the year or 18 months postpartum, we may have the ability to change the lives of both mothers and babies. Even if one only considers the babies, maternal intervention has the potential to be primary prevention for NAS and other outcomes.

With regard to buprenorphine versus MM programs, I also agree that we have to mandate that providers prescribe buprenorphine in the setting of adequate comprehensive addiction care, counseling services, and frequent drug testing. The availability of those providers is limited, as you assert, which propelled me to become certified to prescribe buprenorphine for our pregnant population in Columbus, Ohio. This has allowed me and our clinic to be the backbone for care during pregnancy and feel confident that we are not just handing out pharmacotherapy in absence of those other services.

In order to move the needle regarding care for this population, we need data. We need data to more effectively describe the problem and to prove that this intervention is worth the investment. Only with those numbers will policy change, and I work daily to try to advocate for these women.

Thank you for your interest and support. Perhaps by combining our interests, we can use our collective voice more powerfully.

Mona R. Prasad, DO, MPH

FOR PREGNANT PATIENTS WITH DIABETES

Levemir® (insulin detemir [rDNA origin] injection):

At last, the FIRST & ONLY Pregnancy Category B basal insulin analog[1]

- In a randomized controlled study, no differences in pregnancy outcomes or the health of the fetus and newborn were seen with Levemir® use[1]

Ask if Levemir® FlexPen® is available in your hospitals

FlexPen®—the #1 selling prefilled insulin pen in the world[a]
Comparable formulary coverage to insulin glargine[2]

Indications and Usage

Levemir® (insulin detemir [rDNA origin] injection) is indicated to improve glycemic control in adults and children with diabetes mellitus.

Important Limitations of Use

Levemir® is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

Important Safety Information

Levemir® is contraindicated in patients with hypersensitivity to Levemir® or any of its excipients.

Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision.

Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur.

Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening. When a GLP-1 receptor agonist is used in combination with Levemir®, the Levemir® dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia.

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Levemir®.

Careful glucose monitoring and dose adjustments of insulin, including Levemir®, may be necessary in patients with renal or hepatic impairment.

Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including Levemir®.

Adverse reactions associated with Levemir® include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, rash, pruritus, and if taken with GLP-1 receptor agonist, diarrhea.

Needles and Levemir® FlexPen® should never be shared.

Levemir® has not been studied in children with type 2 diabetes or in children with type 1 diabetes who are younger than 2 years of age.

The background risk of birth defects, pregnancy loss, or other adverse events that exists for all pregnancies is increased in pregnancies complicated by hyperglycemia.

Needles are sold separately and may require a prescription in some states.

Please see accompanying brief summary of Prescribing Information.

Levemir® FlexPen®
insulin detemir (rDNA origin) injection

novo nordisk®

[a]IMS Health Inc. IMS MIDAS (12 months ending December 2012).

References: 1. Levemir® [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2013. **2.** Fingertip Formulary®. April 2013.

Printed in the U.S.A. 0513-00016130-1 August 2013

LEVEMIR® (insulin detemir [rDNA origin] injection)

Rx ONLY

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

INDICATIONS AND USAGE: LEVEMIR® is indicated to improve glycemic control in adults and children with diabetes mellitus. Important Limitations of Use: LEVEMIR® is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

CONTRAINDICATIONS: LEVEMIR® is contraindicated in patients with hypersensitivity to LEVEMIR® or any of its excipients. Reactions have included anaphylaxis.

WARNINGS AND PRECAUTIONS: Dosage adjustment and monitoring: Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment. As with all insulin preparations, the time course of action for LEVEMIR® may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity. **Administration:** LEVEMIR® should only be administered subcutaneously. Do not administer LEVEMIR® intravenously or intramuscularly. The intended duration of activity of LEVEMIR® is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the usual subcutaneous dose could result in severe hypoglycemia. Do not use LEVEMIR® in insulin infusion pumps. Do not dilute or mix LEVEMIR® with any other insulin or solution. If LEVEMIR® is diluted or mixed, the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LEVEMIR® and the mixed insulin may be altered in an unpredictable manner. **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of insulin therapy, including LEVEMIR®. The risk of hypoglycemia increases with intensive glycemic control. When a GLP-1 receptor agonist is used in combination with LEVEMIR®, the LEVEMIR® dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia. All patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion, or glucagon administration has been observed in clinical trials with insulin, including trials with LEVEMIR®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia. The prolonged effect of subcutaneous LEVEMIR® may delay recovery from hypoglycemia. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. **Hypersensitivity and allergic reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LEVEMIR®. **Renal Impairment:** No difference was observed in the pharmacokinetics of insulin detemir between non-diabetic individuals with renal impairment and healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with renal impairment. **Hepatic Impairment:** Non-diabetic individuals with severe hepatic impairment had lower systemic exposures to insulin detemir compared to healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with hepatic impairment. **Drug interactions:** Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia. **Fluid retention and heart failure with concomitant use of PPAR-gamma agonists:** Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including LEVEMIR®, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

ADVERSE REACTIONS: The following adverse reactions are discussed elsewhere: Hypoglycemia; Hypersensitivity and allergic reactions. **Clinical trial experience:** Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. The frequencies of adverse reactions (excluding hypoglycemia) reported during LEVEMIR® clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Tables 1-4 below. See Tables 5 and 6 for the hypoglycemia findings. In the LEVEMIR® add-on to liraglutide+metformin trial, all patients received liraglutide 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with LEVEMIR® or continued, unchanged treatment with liraglutide 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with liraglutide 1.8 mg + metformin (11.7%) and greater than in patients treated with liraglutide 1.8 mg and metformin alone (6.9%). In two pooled trials, a total of 1155 adults with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=767) or NPH (n=388). The mean duration of exposure to LEVEMIR® was 153 days, and the total exposure to LEVEMIR® was 321 patient-years. The most common adverse reactions are summarized in Table 1.

Table 1: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 16 weeks and 24 weeks duration in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR®, % (n = 767)	NPH, % (n = 388)
Upper respiratory tract infection	26.1	21.4
Headache	22.6	22.7
Pharyngitis	9.5	8.0
Influenza-like illness	7.8	7.0
Abdominal Pain	6.0	2.6

A total of 320 adults with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=161) or insulin glargine (n=159). The mean duration of exposure to LEVEMIR® was 176 days, and the total exposure to LEVEMIR® was 78 patient-years. The most common adverse reactions are summarized in Table 2.

Table 2: Adverse reactions (excluding hypoglycemia) in a 26-week trial comparing insulin aspart + LEVEMIR® to insulin aspart + insulin glargine in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR®, % (n = 161)	Glargine, % (n = 159)
Upper respiratory tract infection	26.7	32.1
Headache	14.3	19.5
Back pain	8.1	6.3
Influenza-like illness	6.2	8.2
Gastroenteritis	5.6	4.4
Bronchitis	5.0	1.9

In two pooled trials, a total of 869 adults with type 2 diabetes were exposed to individualized doses of LEVEMIR® (n=432) or NPH (n=437). The mean duration of exposure to LEVEMIR® was 157 days, and the total exposure to LEVEMIR® was 186 patient-years. The most common adverse reactions are summarized in Table 3.

Table 3: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 22 weeks and 24 weeks duration in adults with type 2 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR®, % (n = 432)	NPH, % (n = 437)
Upper respiratory tract infection	12.5	11.2
Headache	6.5	5.3

A total of 347 children and adolescents (6-17 years) with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=232) or NPH (n=115). The mean duration of exposure to LEVEMIR® was 180 days, and the total exposure to LEVEMIR® was 114 patient-years. The most common adverse reactions are summarized in Table 4.

Table 4: Adverse reactions (excluding hypoglycemia) in one 26-week clinical trial of children and adolescents with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR®, % (n = 232)	NPH, % (n = 115)
Upper respiratory tract infection	35.8	42.6
Headache	31.0	32.2
Pharyngitis	17.2	20.9
Gastroenteritis	16.8	11.3
Influenza-like illness	13.8	20.9
Abdominal pain	13.4	13.0
Pyrexia	10.3	6.1
Cough	8.2	4.3
Viral infection	7.3	7.8
Nausea	6.5	7.0
Rhinitis	6.5	3.5
Vomiting	6.5	10.4

Pregnancy: A randomized, open-label, controlled clinical trial has been conducted in pregnant women with type 1 diabetes. *Hypoglycemia:* Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LEVEMIR®. Tables 5 and 6 summarize the incidence of severe and non-severe hypoglycemia in the LEVEMIR® clinical trials. For the adult trials and one of the pediatric trials (Study D), severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring assistance of another person and associated with either a plasma glucose value below 56 mg/dL (blood glucose below 50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. For the other pediatric trial (Study I), severe hypoglycemia was defined as an event with semi-consciousness, unconsciousness, coma and/or convulsions in a patient who could not assist in the treatment and who may have required glucagon or intravenous glucose. For the adult trials and pediatric Study D, non-severe hypoglycemia was defined as an asymptomatic or symptomatic plasma glucose < 56 mg/dL (or equivalently blood glucose <50 mg/dL as used in Study A and C) that was self-treated by the patient. For pediatric Study I, non-severe hypoglycemia included asymptomatic events with plasma glucose <65 mg/dL as well as symptomatic events that the patient could self-treat or treat by taking oral therapy provided by the caregiver. The rates of hypoglycemia in the LEVEMIR® clinical trials (see Section 14 for a description of the study designs) were comparable between LEVEMIR®-treated patients and non-LEVEMIR®-treated patients (see Tables 5 and 6).

Table 5: Hypoglycemia in Patients with Type 1 Diabetes

		Severe Hypoglycemia		Non-severe Hypoglycemia	
		Percent of patients with at least 1 event (n/total N)	Event/patient/year	Percent of patients (n/total N)	Event/patient/year
Study A, Type 1 Diabetes, Adults, 16 weeks In combination with insulin aspart	Twice-daily LEVEMIR®	8.7 (24/276)	0.52	88.0 (243/276)	26.4
	Twice-daily NPH	10.6 (14/132)	0.43	89.4 (118/132)	37.5
Study B, Type 1 Diabetes, Adults, 26 weeks In combination with insulin aspart	Twice-daily LEVEMIR®	5.0 (8/161)	0.13	82.0 (132/161)	20.2
	Once-daily Glargine	10.1 (16/159)	0.31	77.4 (123/159)	21.8
Study C, Type 1 Diabetes, Adults, 24 weeks In combination with regular insulin	Once-daily LEVEMIR®	7.5 (37/491)	0.35	88.4 (434/491)	31.1
	Once-daily NPH	10.2 (26/256)	0.32	87.9 (225/256)	33.4
Study D, Type 1 Diabetes, Pediatrics, 26 weeks In combination with insulin aspart	Once- or Twice-daily LEVEMIR®	15.9 (37/232)	0.91	93.1 (216/232)	31.6
	Once- or Twice-daily NPH	20.0 (23/115)	0.99	95.7 (110/115)	37.0
Study I, Type 1 Diabetes, Pediatrics, 52 weeks In combination with insulin aspart	Once- or Twice-daily LEVEMIR®	1.7 (3/177)	0.02	94.9 (168/177)	56.1
	Once- or Twice-daily NPH	7.1 (12/170)	0.09	97.6 (166/170)	70.7

Table 6: Hypoglycemia in Patients with Type 2 Diabetes

		Study E, Type 2 Diabetes, Adults, 24 weeks In combination with oral agents		Study F, Type 2 Diabetes, Adults, 22 weeks In combination with insulin aspart		Study H, Type 2 Diabetes, Adults, 26 weeks In combination with Liraglutide and Metformin	
		Twice-daily LEVEMIR®	Twice-daily NPH	Once- or Twice-daily LEVEMIR®	Once- or Twice-daily NPH	Once-daily LEVEMIR® + Liraglutide + Metformin	Liraglutide + Metformin
Severe hypoglycemia	Percent of patients with at least 1 event (n/total N)	0.4 (1/237)	2.5 (6/238)	1.5 (3/195)	4.0 (8/199)	0	0
	Event/patient/year	0.01	0.08	0.04	0.13	0	0
Non-severe hypoglycemia	Percent of patients (n/total N)	40.5 (96/237)	64.3 (153/238)	32.3 (63/195)	32.2 (64/199)	9.2 (15/163)	1.3 (2/158*)
	Event/patient/year	3.5	6.9	1.6	2.0	0.29	0.03

*One subject is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study

Insulin Initiation and Intensification of Glucose Control: Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy. *Lipodystrophy:* Long-term use of insulin, including LEVEMIR®, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy. *Weight Gain:* Weight gain can occur with insulin therapy, including LEVEMIR®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. *Peripheral Edema:* Insulin, including LEVEMIR®, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. *Allergic Reactions: Local Allergy:* As with any insulin therapy, patients taking LEVEMIR® may experience injection site reactions, including localized erythema, pain, pruritus, urticaria, edema, and inflammation. In clinical studies in adults, three patients treated with LEVEMIR® reported injection site pain (0.25%) compared to one patient treated with NPH insulin (0.12%). The reports of pain at the injection site did not result in discontinuation of therapy. Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks. *Systemic Allergy:* Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LEVEMIR®, and may be life-threatening. *Antibody Production:* All insulin products can elicit the formation of insulin antibodies. These insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LEVEMIR®, antibody development has been observed with no apparent impact on glycemic control. **Postmarketing experience:** The following adverse reactions have been identified during post approval use of LEVEMIR®. 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. Medication errors have been reported during post-approval use of LEVEMIR® in which other insulins, particularly rapid-acting or short-acting insulins, have been accidentally administered instead of LEVEMIR®. To avoid medication errors between LEVEMIR® and other insulins, patients should be instructed always to verify the insulin label before each injection.

OVERDOSAGE: An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

More detailed information is available upon request.

For information about LEVEMIR® contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
1-800-727-6500
www.novonordisk-us.com

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

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0613-00016321-1 6/2013

novo nordisk®

Levemir®
insulin detemir (rDNA origin) injection

BY ANDREW I KAPLAN, ESQ

Did lack of recovery-room care lead to patient's death?

Facts

On December 18, 2009, at 7:19 AM, a 28-year-old woman at 37 weeks' gestation presented to a hospital by ambulance with ruptured membranes and right-upper-quadrant pain. The patient/plaintiff had received her prenatal care at another hospital and had a medical history of neurofibromatosis, a genetic disorder characterized by nerve tissue tumors that can grow rapidly during pregnancy and can cause complications such as hypertension.

On initial exam, no fetal heart rate (FHR) was detected. At 7:32 AM, FHR monitoring was begun and revealed a FHR of 50 bpm. Co-defendant ob/gyn Dr. A was alerted and a STAT cesarean delivery was called at 7:44 AM. The operative record reveals that the patient was in the OR at 7:45 AM, anesthesia started at 7:47 AM, skin incision was made at 7:50 AM, and delivery was accomplished at 7:52 AM. The infant had Apgars of 1 and 2. Cord blood PCO2 was 100 with a base excess of -32.

In his operative report for the cesarean delivery, Dr. A noted that the cul-de-sac was cleared of all clots and debris. After he confirmed hemostasis, the peritoneal membrane was closed. On presentation to the delivery room, the plaintiff's blood pressure was low (82/59), with a heart rate of 127. At 8:45 AM, when the defendant resident anesthesiologist Dr. B discharged the plaintiff to the recovery room and signed off to defendant attending anesthesiologist Dr. C, the patient's blood pressure was documented at 100/50, with a heart rate of 130.

During the next 3 ½ hours, the plaintiff was monitored in the recovery room. Her blood pressure and pulse were labile, ranging from a low of 70/37 to a high of 146/103. Her heart rate was consistently tachycardic, ranging between 133 and 162. She was placed in the Trendelenburg position at 8:51 am. Approximately 3 L of IV fluid were administered. Bolusing began at 9:21 and fluid was given again at 10:44. However, the patient remained tachycardic and the exact amount of the boluses is not recorded.

At approximately 10:30 AM the patient complained of cramping in her left leg; she had a history of left leg fracture as a child and had undergone reparative surgery. She was able to move all her extremities, pedal pulses were present, and capillary refill was felt to be adequate. Venodyne boots remained in place.

The chief ob/gyn resident, Dr. D, evaluated the patient and ordered Toradol for her discomfort. An hour later the plaintiff was noted to be drowsy, lethargic, and to have minimal verbal response. Internal hemorrhage was considered, and an abdominal ultrasound confirmed what looked like a pelvic collection. The medical emergency team was called and pressors, fluids, and 2 units of packed red blood cells were administered. A femoral line was placed and the patient was intubated and taken to the OR at 12:25 PM.

Dr. A performed an exploratory laparotomy because he suspected uterine artery bleeding. A supracervical hysterectomy was performed and no bleeding from the uterine vessels was found. Dr. A called for an intraoperative vascular consult, which was answered by nonparty vascular surgeon Dr. E, who noted a large hematoma in the retroperitoneum. Upon opening the retroperitoneum, he discovered a rupture in the iliac artery, which he described as friable and attempted to repair.

Despite administration of multiple blood products, fluids, and pressors, the plaintiff coded 5 times and expired at 3:58 PM. On autopsy, the cause of death was noted as retroperitoneal hemorrhage due to spontaneous rupture of the left iliac artery as a consequence of neurofibromatosis and pregnancy.

Allegations

The plaintiff's attorneys asserted that injury to the iliac artery occurred as a result of an improperly performed cesarean delivery. They also asserted that there was a delay in appreciating and responding to the iliac artery injury, resulting in retroperitoneal hemorrhage, rupture of the common iliac artery and veins, cardiac arrest, and death.

> "The cause of the patient's rupture was her underlying disease process and not the surgery itself."

Discovery

Based on the records and the autopsy report, our obstetric expert felt that the iliac artery rupture was not caused by the cesarean delivery but rather, that it was a result of the patient's disease process. He was critical, however, of the care in the recovery room. He felt that the patient was unstable throughout her time in the recovery room because she was tachycardic throughout and her blood pressures were remarkably low. He felt she was clearly bleeding while in the recovery room and there was a failure to react to it in a timely manner.

Our obstetric anesthesia expert was critical of the care in the recovery room as well. The fact that the plaintiff's heart rate was elevated at all times meant that one had to consider that she might be bleeding. The tachycardia meant bleeding until proven otherwise. Despite the lack of documentation that bleeding was considered, the patient was placed in the Trendelenburg position for hypotension, and was given ongoing IV fluids. Although she was tachycardic, she had strong pulses and capillary refill and, as such, it appears that this was why she was thought not to be bleeding. Unfortunately, the IV boluses that were given did not serve to reduce the tachycardia and there was an obvious problem of lack of documentation by the recovery room staff.

Our vascular expert could not defend the care by our defendants and felt it was a departure from the standard of care not to obtain hemoglobin and hematocrit levels at least 1 hour after the prolonged tachycardia and hypotension in this postoperative patient. This is especially problematic in light of the fact that the recovery room staff were giving the patient fluid boluses and put her in Trendelenburg. She also had no urine output. This expert was also very critical of the nurses in the recovery room and felt that they did not do enough to bring the patient's condition to the doctors' attention. It was her opinion that earlier intervention could have changed the outcome.

The intraoperative vascular consultant further testified that the laceration he found was "ragged" and in his opinion was not a result of iatrogenic injury caused by the codefendant ob/gyn. The doctor also testified that the cause of the laceration was the patient's underlying neurofibromatosis.

Outcome

The plaintiff's demand for settlement was $3 million. Prior to depositions by the chief resident and the hospital's recovery room staff, the case settled as to the defendant hospital only in the amount of $2.2 million. The case was discontinued against codefendant ob/gyn Dr. A.

Analysis

The plaintiff's initial focus in the case was the defendant ob/gyn, in the belief that he caused the injury to the artery and failed to follow up on or appreciate the patient's downward spiral thereafter. It became apparent through the discovery process—record review and analysis, expert evaluation, and testimony of the defendant ob/gyn and the nonparty vascular surgeon—that, in fact, the cause of the patient's rupture was her underlying disease process and not the technical aspects of the surgery itself.

Once it was confirmed that the defendant ob/gyn was not assigned to follow the patient in recovery but instead had other labor and delivery responsibilities thereafter, the focus became the staff's reaction to the patient's complaints and concerning vital signs in the recovery room.

For many reasons we felt that settling the case, rather than involving the staff members responsible for the patient's care in the recovery room, was the proper course of action. COG

MR. KAPLAN is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP, specializing in medical malpractice defense and healthcare litigation. He welcomes feedback on this column via email to alkaplan@arfdlaw.com.

The morcellation debate: what you need to know

BY **SARAH L. COHEN, MD**

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She reports contracted research for Ethicon.

Tissue morcellation is by no means a new concept in laparoscopic surgery, but recent concerns regarding open power morcellation in gynecologic procedures have called the practice into question.[1] A hand-activated device for laparoscopic tissue removal was developed as early as 1973, and by 1993, the Steiner electromechanical morcellator was introduced.[2,3]

The advent of electromechanical morcellation allowed for marked improvements in ease and speed of specimen retrieval with minimally invasive approaches.[4,5] As the field of minimally invasive gynecologic surgery has evolved to encompass increasingly challenging procedures, a number of power morcellation devices have been marketed to allow removal of large pathology via small incisions and avoid the morbidity associated with laparotomy. However, this innovation is not without risks, including potential for intraoperative injury and risk of seeding of cellular tissue during the morcellation process.

Gynecologic surgeons should give consideration to the balance of benefit and harm that accompanies laparoscopic tissue morcellation, in addition to exploring surgical alternatives and methods to mitigate complications.

Risks associated with morcellation

Rates of visceral and vascular injury associated with electromechanical morcellation devices are difficult to quantify due to limited reporting. A recent systematic review of all published articles as well as the FDA device database identified 55 morcellator-related injuries during gynecologic (hysterectomy, myomectomy) and non-gynecologic (nephrectomy, splenectomy) procedures.[6] Vascular and bowel injuries were listed as the most common complications. In this review, surgeon inexperience was the most commonly listed risk factor for injury.

Aside from the risks inherent in surgical operation of morcellation devices, there is also concern about dissemination of tissue that can occur during an open power morcellation process. Fragments of tissue that are not retrieved may result in pain, infection and serious morbidity.[7,8] Intracorporeal morcellation has also been reported to result in seeding of benign[9-12] or malignant tissues.[13-16] The incidence of such complications is difficult to quantify; the AAGL practice guidelines for laparoscopic subtotal/supracervical hysterectomy state that uterine morcellation does not appear to increase the risk of subsequent diagnosis of endometriosis and only rarely results in leiomyomatosis.[17] Reported incidence of parasitic leiomyomata following laparoscopic procedures involving morcellation has been estimated at between 0.1% and 1% based on 2 retrospective studies.[11,12]

Of particular concern is the risk of morcellating an unidentified malignancy, with possible resultant upstaging of disease and worsened prognosis.[18-20] In a recent statement, the Society of Gynecologic Oncology estimated

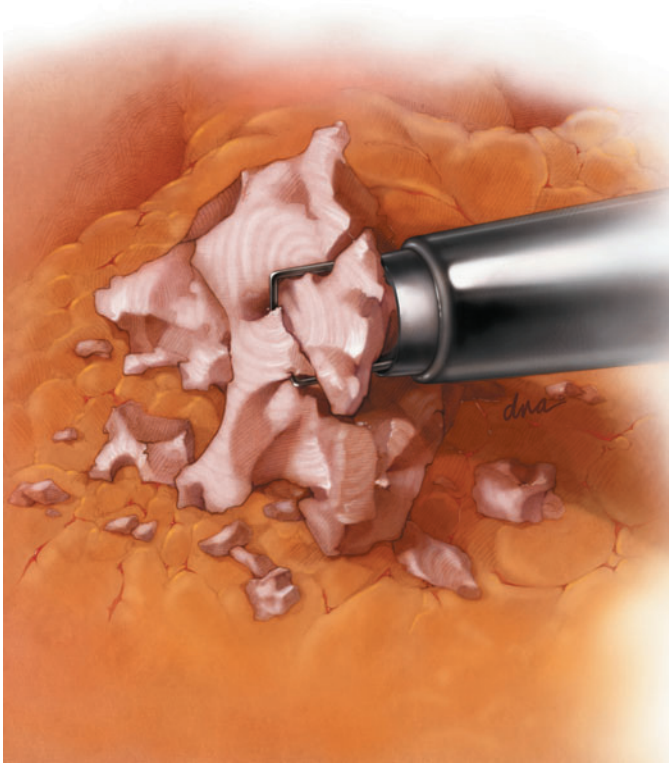
that fewer than 1 woman in 1000 who undergoes hysterectomy for a presumed leiomyomata will have an occult malignancy, and advocated for open communication with patients regarding this issue.[21] Unlike endometrial lesions, which are characterized by more reliable risk factors, symptomatology, and screening methods, uterine leiomyosarcomas are the subject of considerable concern because they are often difficult to differentiate from benign leiomyomata preoperatively. Leiomyosarcomas also are notoriously aggressive tumors associated with poor prognosis even in the absence of tissue morcellation.

Compounding the difficulties of diagnosis is the relative rarity of uterine leiomyosarcomas; incidence in the general population is estimated at 1 in 10,000 women, or approximately 1 in 1,000 women undergoing surgery for presumed fibroids.[20,22-24] Suggested clinical factors that may heighten concern for malignancy include advancing patient age and presence of new or increasing uterine mass in a postmenopausal patient. The average age at presentation is 60 years; however, leiomyosarcomas have been reported in patients as young as their mid-20s.[25] The rate of uterine growth has not been demonstrated to be a reliable predictor for malignancy.[24] Screening techniques for uterine sarcomas are limited, but magnetic resonance imaging (MRI), particularly diffusion-weighted, and serum samples of lactate dehydrogenase (LDH) have been suggested as potential screening methods.[26,27] One small prospective study demonstrated high sensitivity and specificity with the combination of dynamic MRI and measurement of total LDH and LDH isoenzyme type 3, but the results have not been reproduced on a larger scale.[27]

Surgical alternatives to open power morcellation

Laparotomy for hysterectomy or myomectomy is a definitive option for avoiding tissue morcellation, but it comes at the expense of increased morbidity and recovery time compared to minimally invasive approaches.[28,29] When the uterine size is such that the specimen can be delivered vaginally, performing a vaginal hysterectomy or total laparoscopic hysterectomy, rather than supracervical hysterectomy, is also an option.

Minilaparotomy is another alternative to open power morcellation for specimen retrieval.[30,31] Depending on the size of the mass, the specimen can either be removed intact via the minilaparotomy incision (typically < 4 cm in length), or it can be



placed into a bag and manually morcellated to avoid spillage at the level of the abdominal wall or within the peritoneal cavity. Minilaparotomy allows for perioperative outcomes similar to that for a laparoscopic approach.[32-34] Specimen retrieval and/or contained manual morcellation also can be performed via colpotomy, even if total hysterectomy has not taken place.[35-37] A small randomized trial comparing transumblical and transvaginal specimen removal found decreased postoperative pain with the transvaginal method, but similar patient satisfaction, cosmesis and sexual function.[38]

Contained power morcellation is another promising option whereby tissue dissemination can be avoided. In these cases, electromechanical morcellation is performed in an enclosed environment within the abdomen, such as an endobag or artificial pneumoperitoneum.[39]

Implications for practice

The well-known benefits of minimally invasive gynecologic surgery must be measured along with the small but real risks associated with tissue morcellation. Taking into account patient-specific factors, appropriate preoperative screening for malignant conditions should be undertaken and open power

ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATIONS, INC.

Some institutions and groups defining stances on morcellation

The story of a physician in Boston who is undergoing treatment for uterine cancer that may have been spread by morcellation has been picked up by the popular press. News outlets including *The Wall Street Journal*, ABC News, *USA Today*, and *The New York Times* have published stories about cancer patient Amy Reed, MD, PhD, and her husband, Hooman Noorchashm, MD, PhD, who in response to his wife's illness has begun a campaign urging a moratorium on uterine morcellation.

His change.org petition had garnered more than 5000 signatures as of late February.

In response to these stories and the resulting increase in public concern over the possibility of this procedure spreading and upstaging undetected cancer, some societies and institutions are developing formal policies on morcellation.

In December 2013, the Society of Gynecologic Oncology (SGO) issued a statement that said in part, "[morcellation] is generally contraindicated in the presence of documented or highly suspected malignancy, and may be inadvisable in premalignant conditions or risk-reducing surgery."

It went on to recommend that "patients … who might require intracorporeal morcellation should be appropriately evaluated for the possibility of coexisting uterine or cervical malignancy" while acknowledging that currently no reliable method exists to differentiate benign from malignant leiomyomas.

According to *The Wall Street Journal*, Temple University Hospital in Philadelphia recently set limits on morcellation. Doctors there are being told to perform hysterectomies as conservatively as possible, and open procedures are required for uterine sizes larger than 18 weeks. Three Boston-area hospitals and the Cleveland Clinic are also reviewing or creating policies regarding morcellation and doctors are being told to spell out the potential risks to patients, *The Wall Street Journal* reports.

The American College of Obstetricians and Gynecologists (ACOG) has not issued new guidelines for its members concerning morcellation, but says, "ACOG recently conducted a preliminary review of the literature on morcellation, and the findings are consistent with … the clinical guidance contained in existing ACOG Practice Bulletins and Committee Opinions. As ACOG updates its guidelines, we will further consider any newly available information and incorporate it at that time."

Jon I. Einarsson, MD, PhD, MPH, Deputy Editor of *Contemporary OB/GYN* and the director of the division of minimally invasive gynecologic surgery at Brigham and Women's Hospital, Boston, anticipates changes ahead in how morcellation is performed. "Electromechanical morcellation has enabled gynecologists to offer patients a minimally invasive approach for specimen extraction for over 2 decades," he noted. "However, morcellation in its current form has drawbacks that have been highlighted by recent events. I believe that in the next few years, open electromechanical morcellation will be a thing of the past.

"Novel methods of enclosed specimen extraction are already being developed and will probably come to market within the next 2 to 3 years. I predict that this disruptive technology will dramatically change our methods for specimen extraction moving forward."

By Susan C. Olmstead

morcellation avoided in cases of confirmed or likely malignancy.

Surgeons who choose to use a power morcellator should be experienced with the device operation and make an effort to retrieve all specimen fragments from the peritoneal cavity following morcellation. Strong consideration should also be given to alternative specimen retrieval options that are associated with decreased risk of retained specimen fragments or cellular seeding. In particular, a focus on innovations in preoperative screening for uterine sarcomas as well as advanced morcellating technology is critical to improve patient outcomes. COG

CONTINUED ON **PAGE 39**

BRISDELLE™ (paroxetine) capsules Rx only

Brief Summary; Consult package insert for full Prescribing Information

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), have been shown to increase the risk of suicidal thoughts and behavior in pediatric and young adult patients when used to treat major depressive disorder and other psychiatric disorders. Because BRISDELLE is an SSRI, monitor patients closely for worsening and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.

INDICATIONS AND USAGE

BRISDELLE is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

Limitation of Use:

BRISDELLE is not indicated for the treatment of any psychiatric condition. BRISDELLE contains a lower dose of paroxetine than that used for psychiatric conditions. The safety and efficacy of this lower dose of paroxetine in BRISDELLE have not been established for any psychiatric condition. Patients who require paroxetine for treatment of a psychiatric condition should discontinue BRISDELLE and initiate a paroxetine-containing medication that is indicated for such use.

CONTRAINDICATIONS

Monoamine Oxidase Inhibitors

Concomitant use of an MAOI with BRISDELLE or within 14 days of stopping treatment with BRISDELLE is contraindicated because of an increased risk of serotonin syndrome. The use of BRISDELLE within 14 days of stopping an MAOI is also contraindicated *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Drug Interactions (7.3)]*.

Starting BRISDELLE in a patient who is being treated with linezolid or intravenous methylene blue, both of which inhibit monoamine oxidase, is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Drug Interactions (7.3)]*.

Thioridazine

Concomitant use of BRISDELLE with thioridazine is contraindicated, because thioridazine prolongs the QT interval, and paroxetine can increase thioridazine levels *[see Drug Interactions (7.1)]*.

Pimozide

Concomitant use of BRISDELLE with pimozide is contraindicated because pimozide prolongs the QT interval, and paroxetine increases pimozide levels *[see Drug Interactions (7.1)]*.

Hypersensitivity to any Ingredient in BRISDELLE

BRISDELLE is contraindicated in patients with a history of hypersensitivity to paroxetine or any of the other ingredients in BRISDELLE.

Pregnancy

Menopausal VMS does not occur during pregnancy and BRISDELLE may cause fetal harm *[see Use in Specific Populations (8.1)]*.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors

BRISDELLE is not approved for any psychiatric condition.

Antidepressants, including those that contain an SSRI, increase the risk of suicidal thinking and behavior (suicidality) in pediatric and young adult patients when used to treat major depressive disorder (MDD) and other psychiatric disorders. There is limited information regarding suicidality in women who use BRISDELLE for treatment of VMS. The BRISDELLE trials excluded women with a presence or history of previous psychiatric disorders.

Consider discontinuing BRISDELLE in patients with worsening depression or those who experience emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

All patients being treated with BRISDELLE should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of treatment.

Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in patients being treated with antidepressants for MDD as well as for other psychiatric and nonpsychiatric indications. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Families and caregivers of patients being treated with BRISDELLE should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SSRIs, including paroxetine, alone but particularly with concomitant use of serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat depression and others such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Monitor patients for the emergence of serotonin syndrome.

The concomitant use of BRISDELLE with MAOIs is contraindicated. Do not start BRISDELLE in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking BRISDELLE. BRISDELLE should be discontinued before initiating treatment with the MAOI *[see Contraindications (4.1) and Dosage and Administration (2.2)]*.

If concomitant use of BRISDELLE with other serotonergic drugs (e.g., triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) is clinically warranted, consider the increased risk of serotonin syndrome and carefully observe the patient, particularly during treatment initiation *[see Contraindications (4.1) Drug Interactions (7.3)]*.

Discontinue BRISDELLE and any concomitant serotonergic agents immediately if the above events occur and initiate supportive symptomatic treatment.

Potential Impact on Tamoxifen Efficacy

It is uncertain whether the co-administration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 *[see Drug Interactions (7.1)]*. However, other studies have failed to demonstrate such a risk. When tamoxifen is used for the treatment or prevention of breast cancer, weigh the likely benefit of BRISDELLE for treating VMS vs. the risk of possible decreased tamoxifen effectiveness, and consider avoiding the concomitant use of BRISDELLE for VMS treatment.

Abnormal Bleeding

SSRIs, including BRISDELLE, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Caution patients about the risk of bleeding associated with the concomitant use of BRISDELLE and NSAIDs, aspirin, or other drugs that affect coagulation *[see Drug Interactions (7.1)]*.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs, including BRISDELLE. Elderly patients may be at greater risk. In many cases, the hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported in patients using SSRIs. Also, patients taking diuretics or who are volume-depleted can be at greater risk. Consider discontinuation of BRISDELLE in patients with symptomatic hyponatremia and institute appropriate medical intervention.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Bone Fracture

Epidemiological studies on bone fracture risk following exposure to SSRIs have reported an association between SSRI treatment and fractures. It is unknown to what extent fracture risk is directly attributable to SSRI treatment. If a BRISDELLE-treated patient presents with unexplained bone pain, point tenderness, swelling, or bruising, consider the possibility of a fragility fracture.

Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania

BRISDELLE is only indicated for the treatment of moderate to severe VMS and is not approved for use in treating either depression or bipolar depression. However, prior to initiating treatment with BRISDELLE, all patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It is generally believed (though not established in controlled trials) that use of an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder.

Seizures

In premarketing testing of paroxetine, seizures occurred in 0.1% of paroxetine-treated patients. Use BRISDELLE cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Evaluate and consider discontinuing use in any patient who develops seizures.

Akathisia

The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment. Discontinue treatment with BRISDELLE if akathisia occurs.

Acute Angle Closure Glaucoma

Mydriasis has been reported in the premarketing studies with paroxetine. Cases of acute angle closure glaucoma associated with paroxetine therapy have been reported in the literature. Because mydriasis can cause acute angle closure in patients with narrow angle glaucoma, when BRISDELLE is prescribed for patients with narrow angle glaucoma, caution them to report visual symptoms.

Potential for Cognitive and Motor Impairment

BRISDELLE has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that the drug treatment does not affect them adversely.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Suicidality *[see Warnings and Precautions (5.1)]*
- Serotonin syndrome *[see Warnings and Precautions (5.2)]*
- Abnormal bleeding *[see Warnings and Precautions (5.4)]*
- Hyponatremia *[see Warnings and Precautions (5.5)]*
- Bone Fracture *[see Warnings and Precautions (5.6)]*
- Mania/Hypomania *[see Warnings and Precautions (5.7)]*
- Seizure *[see Warnings and Precautions (5.8)]*
- Akathisia *[see Warnings and Precautions (5.9)]*

Clinical Trials Experience

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

The data described below reflect exposure to BRISDELLE in the one 8-week Phase 2 randomized, placebo-controlled trial and the two Phase 3 randomized, placebo-controlled, 12-week and 24-week trials for the treatment of moderate to severe VMS *[see Clinical Studies (14)]*. In these trials, a total of 635 women were exposed to BRISDELLE 7.5 mg administered orally once daily and 641 women received placebo. The majority of BRISDELLE-treated patients were Caucasian (68%) and African American (30%), with a mean age of 55 years (range 40 to 73 years). Women with a history of suicidal ideation or suicidal behavior were excluded from these studies.

Adverse Reactions Leading to Study Discontinuation: A total of 4.7% of women taking BRISDELLE discontinued from the clinical trials due to an adverse reaction, compared to 3.7% of women on placebo; the most frequent adverse reactions leading to discontinuation among paroxetine-treated women were: abdominal pain (0.3%), attention disturbances (0.3%), headache (0.3%), and suicidal ideation (0.3%).

Common Adverse Reactions: Overall, based on investigators' determinations about what events were likely to be drug-related, about 20% of women treated with BRISDELLE reported at least 1 adverse reaction in the three controlled studies. The most common adverse reactions (≥ 2% and more common among BRISDELLE-treated women) reported in these studies were headache, fatigue/malaise/lethargy, and nausea/vomiting. Of these commonly reported adverse reactions, nausea occurred primarily within the first 4 weeks of treatment and fatigue occurred primarily within the first week of treatment, and decreased in frequency with continued therapy.

The adverse reactions that occurred in at least 2% of patients in the BRISDELLE group and at a higher incidence than placebo are shown in Table 1 for the pooled Phase 2 and Phase 3 trials.

Table 1 Frequency of Adverse Reactions in the Phase 2 and Phase 3 Trials (≥ 2% and at a higher incidence than placebo)

	Frequency n (%)	
	BRISDELLE (n = 635)	Placebo (n = 641)
Nervous system disorders		
Headache	40 (6.3)	31 (4.8)
General disorders and administration site conditions		
Fatigue, malaise, lethargy	31 (4.9)	18 (2.8)
Gastrointestinal disorders		
Nausea, vomiting	27 (4.3)	15 (2.3)

Certain symptoms were seen more frequently in women at the time of discontinuation of BRISDELLE compared to women discontinuing placebo, and have also been reported upon discontinuation of other formulations of paroxetine, particularly when abrupt. These include increased dreaming/nightmares, muscle cramps/spasms/twitching, headache, nervousness/anxiety, fatigue/tiredness, restless feeling in legs, and trouble sleeping/insomnia. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms with other formulations of paroxetine.

Serious Adverse Reactions: In the pooled Phase 2 and Phase 3 trials, three BRISDELLE-treated patients reported a serious adverse reaction of suicidal ideation and one BRISDELLE-treated patient reported a serious adverse reaction of suicide attempt. There were no serious adverse reactions of suicidal ideation or suicide attempt reported among the placebo-treated patients.

Postmarketing Experience

The following adverse reactions have been identified from clinical studies of paroxetine and during post-approval use of other formulations of paroxetine. Because some of 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.

Blood and Lymphatic System Disorders: Idiopathic thrombocytopenic purpura, Events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, agranulocytosis).

Cardiac Disorders: Atrial fibrillation, Pulmonary edema, Ventricular fibrillation, Ventricular tachycardia (including torsades de pointes).

Gastrointestinal Disorders: Pancreatitis, Pancreatitis hemorrhagic, Vomiting.

General Disorders and Administration Site Conditions: Death, Drug withdrawal syndrome, Malaise.

Hepatobiliary Disorders: Drug-induced liver injury, Hepatic failure, Jaundice.

Immune System Disorders: Anaphylactoid reaction, Angioedema, Toxic epidermal necrolysis.

Investigations: Elevated liver tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction).

Metabolism and Nutrition Disorders: Diabetes mellitus inadequate control, Type 2 diabetes mellitus.

Nervous System Disorders: Neuroleptic malignant syndrome, Paresthesia, Somnolence, Tremor.

Psychiatric Disorders: Aggression, Agitation, Anxiety, Confusional state, Depression, Disorientation, Homicidal ideation, Insomnia, Restlessness.

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary hypertension.

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis, Stevens-Johnson syndrome.

DRUG INTERACTIONS

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

Potential for BRISDELLE to Affect Other Drugs

Paroxetine is a strong CYP2D6 inhibitor. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 *[see Clinical Pharmacology (12.3)]*. Table 2 contains examples of drugs with a metabolism that may be affected by co-administration with BRISDELLE.

Table 2 Effects of Paroxetine on Other Drugs

Concomitant Drug Name	Effect of Paroxetine on Other Drugs	Clinical Recommendations
Thioridazine	Increased plasma concentrations of thioridazine Potential QTc prolongation	Concomitant use of thioridazine and BRISDELLE is contraindicated.
Pimozide	Increased plasma concentrations of pimozide. Potential QTc prolongation	Concomitant use of pimozide and BRISDELLE is contraindicated.
Tamoxifen	Reduced plasma concentrations of active tamoxifen metabolite	Consider avoiding concomitant use of tamoxifen and BRISDELLE.
Tricyclic Antidepressant (TCA) (e.g., Desipramine)	Increased plasma concentrations and elimination half-life	Plasma TCA concentrations may need to be monitored and the dose of TCA may need to be reduced if a TCA is co-administered with BRISDELLE. Monitor tolerability.
Risperidone	Increased plasma concentrations of risperidone	A lower dosage of risperidone may be necessary (see the Full Prescribing Information for risperidone). Monitor tolerability.
Atomoxetine	Increased exposure of atomoxetine	A lower dosage of atomoxetine may be necessary (see Full Prescribing Information for atomoxetine). Monitor tolerability.
Drugs Highly Bound to Plasma Protein (e.g., Warfarin)	Increased free plasma concentrations	The dosage of warfarin may need to be reduced. Monitor tolerability and the International Normalized Ratio.
Digoxin	Decreased plasma concentrations of digoxin	Dosage of digoxin may need to be increased. Monitor digoxin concentrations and clinical effect.
Theophylline	Increased plasma concentrations of theophylline	Dosage of theophylline may need to be decreased. Monitor theophylline concentrations and tolerability.

Use caution if co-administering BRISDELLE with other drugs that are metabolized by CYP2D6, including nortriptyline, amitriptyline, imipramine, desipramine, fluoxetine, phenothiazines, risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide).

Potential for Other Drugs to Affect BRISDELLE

The metabolism and pharmacokinetics of paroxetine may be affected by the induction and inhibition of drug metabolizing enzymes such as CYP2D6. Table 3 contains a list of drugs that may affect the pharmacokinetics of BRISDELLE when administered concomitantly *[see Clinical Pharmacology (12.3)]*.

Table 3 Effects of Other Drugs on Paroxetine

Concomitant Drug Name	Effect of Concomitant Drug on Paroxetine	Clinical Recommendations
Phenobarbital	Decreased paroxetine exposure	No dose adjustment for BRISDELLE. Monitor clinical effect of BRISDELLE.
Phenytoin	Decreased paroxetine exposure	
Fosamprenavir/ Ritonavir	Decreased plasma concentration of paroxetine	
Cimetidine	Increased plasma concentration of paroxetine	

Use caution if co-administering BRISDELLE with other drugs that inhibit CYP2D6 (e.g., quinidine).

Other Potentially Significant Drug Interactions

Monoamine Oxidase Inhibitors (MAOIs)

Serious adverse reactions such as serotonin syndrome have been reported in patients receiving a concomitant SSRI and MAOI, in patients started on an SSRI who recently received an MAOI and in patients started on an MAOI who recently received an SSRI. Therefore, concomitant use of MAOIs with BRISDELLE or use of BRISDELLE and an MAOI within 14 days of each other is contraindicated *[see Dosage and Administration (2.2), Contraindications (4.1) and Warnings and Precautions (5.2)]*.

Serotonergic Drugs

If concomitant use of BRISDELLE with other serotonergic drugs (e.g., triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) is clinically warranted, consider the increased risk of serotonin syndrome and carefully observe the patient, particularly during treatment initiation *[see Warnings and Precautions (5.2)]*.

An interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking paroxetine. Consequently, concomitant use of BRISDELLE with tryptophan is not recommended.

If concomitant use of BRISDELLE with a serotonergic drug is warranted, carefully observe the patient, particularly during treatment initiation. There have been postmarketing reports of serotonin syndrome with the use of an SSRI and a triptan.

BRISDELLE contains paroxetine, which is also the active ingredient in other drugs. The concomitant use of BRISDELLE with other paroxetine products is not recommended *[see Indications and Usage (1)]*.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs are co-administered with NSAIDs, aspirin, and warfarin or other drugs that affect coagulation. There may be a pharmacodynamic interaction between paroxetine and warfarin that causes an increased bleeding diathesis despite unaltered prothrombin time. Carefully monitor patients receiving warfarin therapy when BRISDELLE is initiated or discontinued *[see Warnings and Precautions (5.4)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X

Risk Summary

BRISDELLE is contraindicated in pregnant women because menopausal VMS does not occur during pregnancy and paroxetine can cause fetal harm. Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy may have an increased risk of cardiovascular malformations. Cardiac malformations are a common congenital abnormality. These data would suggest that the risk of a cardiac abnormality following paroxetine exposure in the first trimester may increase the risk from 1% to 2%. Exposure to SSRIs in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN). No teratogenicity was seen in reproductive development studies conducted in rats and rabbits. However, an increase in rat pup deaths was seen during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation, at a dose approximately equal to the maximum recommended human dose (MRHD) for VMS (7.5 mg) on an mg/m^2 basis. 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. *[see Use in Specific Populations (8.1)]*

Nursing Mothers

Paroxetine is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from BRISDELLE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established; BRISDELLE is not indicated in the pediatric population.

Geriatric Use

Clinical studies of BRISDELLE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients may have elevated paroxetine plasma concentrations compared to younger patients. However, no BRISDELLE dose adjustment is considered necessary in elderly patients [*see Clinical Pharmacology (12.3)]*.

SSRIs have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.5)]*.

Renal Impairment

No BRISDELLE dose adjustment is considered necessary in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

Hepatic Impairment

No BRISDELLE dose adjustment is considered necessary in patients with liver impairment *[see Clinical Pharmacology (12.3)]*.

OVERDOSAGE

Human Experience with Overdosage

There is limited clinical experience with BRISDELLE overdosage in humans, as there were no overdoses reported in the clinical studies.

Spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported; some of these cases were fatal and some of the fatalities appeared to involve paroxetine alone. Of nonfatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (267 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse reactions associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsades de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any SSRI. Consult with a certified poison control center for up-to-date guidance and advice on treatment of overdosage.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. In managing overdosage, consider the possibility of multiple drug involvement.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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What ob/gyns need to know about health policy in 2014

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The field of obstetrics and gynecology has swiftly evolved to keep pace with new forms of healthcare delivery. While in the past, ob/gyns practiced independently, today many have salaries and most practice in group settings. We employ physician extenders more than ever and share vaginal deliveries with midwife colleagues. Alternatives to major surgery such as hysterectomy have expanded, and as surgical volumes have declined the complexity of the technology we use has increased.

Many of our patients are actively engaged in decisions and want evidence justifying our recommendations. Furthermore, our decisions and the outcomes of our care are being measured and reported to health plans, state governments, and the public.

Electronic medical records (EMRs) have in some ways made ob/gyn practice easier, but in many settings, the systems have only served to complicate workflows. With the implementation of the Affordable Care Act (ACA) our field has a new set of challenges. To overcome them we must be more innovative in our practice patterns, integrate evidence in all that we do, and be more imaginative about our care teams and locations.

Affordable Care Act

The ACA was passed in 2010 but has been rolled out in phases. It is the most dramatic shift in access to insurance coverage since Medicare and Medicaid were enacted in 1965. Millions of Americans have already gained insurance coverage and millions more will be entering the insurance market this year. Several key provisions have already affected our profession. Most notably, starting in September 2010, young adults up to age 26 were able to join their parents' insurance plans—resulting in 3 million young adults of reproductive age gaining coverage.[1]

When fully implemented, ACA is expected to increase by more than 30 million the number of Americans with health insurance.[2] The

main drivers of this broader expansion are increases in Medicaid eligibility and tax credits for private health plan coverage through health insurance exchanges that will take effect this year.

What are the benefits of these changes to ob/gyns and their patients?

What benefits might we see in our practices from the millions of Americans being covered by insurance? Ultimately, health insurance increases access to care, which can lead not only to higher use but also to reduced morbidity and mortality.[3] A recent study by Sommers et al found that young adults who gained coverage by staying on their parents' plans had fewer delays or gaps in care.[4] Another study looked at the impact of gaining insurance through an insurance lottery in Oregon.[5] It found that Oregonians who gained Medicaid coverage had 40% more emergency department visits than those who did not.

This means that Americans use more healthcare and have unprecedented access to our offices and facilities. We are going to need to decide how we juggle all these new patients—what core services we will continue to perform, and who we will need to transition to care by our physician extenders because of limited capacity. We will also need to become savvier about using EMRs to enhance patient outcomes and provide data required by contracts with payers.

We will need to understand the advantages and disadvantages of new health plans and determine whether to join new plans offered through the public and private exchanges—because accepting them will mean more patients and potentially lower reimbursement. That may mean extending office hours and adding staff.

What will be the impact of individual mandates?

The major ACA-related change in 2014 is insurance expansion. This year, however, also marks the start of tax penalties to be levied against those who go without insurance for 3 or more consecutive months. The penalty for not having insurance in 2014 will be calculated in 1 of 2 ways and Americans will pay whichever is higher:

- **1% of yearly household income.** The maximum penalty is the national average yearly premium for the plan that is the most inexpensive (Bronze plan) offered through the exchange in the state in which the individual lives
- **$95 per person for the year ($47.50 per child under 18).** The maximum penalty per family using this method is $285.

Every year this fee will increase. In 2015 it will be 2% of annual income or $325 per person. In 2016 it will be 2.5% of income or $695 per person. The penalties will then be adjusted for inflation. For those who are uninsured for part of the year, 1/12 of the total annual penalty applies to each month of noninsurance for those who go without insurance for 3 consecutive months or more.[6]

What is the status of employer mandates?

Ninety-five percent of US businesses have fewer than 50 employees. Under the ACA, only businesses with 50 or more employees are mandated to provide insurance. Initially, penalties were going to be levied in 2014 against business with 50 or more employees who failed to provide employees with insurance. This timeline has been pushed back, and most recently mid-sized businesses that employ 50 to 99 full-time workers were provided a 2-year extension. These employers will not be fined for failing to provide coverage until 2016.

Larger businesses (employing 100 or more full-time workers) will be subject to the mandate beginning January 2015. However, for 2015 they need to provide coverage to only 70% of their workers, ramping up to 95% by 2016.

Effect of ACA on health plan coverage and costs

Also in 2014, new protections for patients will be put in place that impact insurance coverage. Insurance companies will be prohibited from denying coverage or refusing to renew a policy to an individual with a pre-existing condition. The law stipulates that in the individual and small group markets, companies cannot charge higher rates due to gender. Plans also will be unable to impose annual limits on the amount of coverage for services that an individual with that plan will receive.

Finally, for individuals enrolled in a clinical trial, insurance companies will be unable to drop or limit coverage because of participation in the trial. These changes will be unlikely to impact ob/gyn practice to a great degree, but they will likely allow women greater access to insurance coverage and thus increase demand for ob/gyns.

Several provisions of the ACA that went into effect on January 1, 2014 will impact insurance affordability. Although individuals are penalized if they

> "Rather than simply paying for each service, payers are more interested in **paying for value and outcomes.**"

do not purchase coverage, tax credits were put in place for people with incomes between 100% and 400% of the poverty line (in 2010, 400% of the poverty line was approximately $43,000 for an individual or $88,000 for a family of four) to facilitate purchase of insurance through the exchanges. The law also helps families control healthcare costs by establishing reduced cost sharing (deductibles) for key services important to women's health, such as preventive visits, breast pumps, contraception, and screening for sexually transmitted illnesses.

For small businesses who would like to offer health insurance, the ACA implements the second phase of the small business tax credit for qualified businesses. This credit is up to 50% of the employer's contribution to provide health insurance for employees.

For Americans who earn less than 133% of the poverty level (approximately $14,000 for an individual and $29,000 for a family of four) and who live in states that have chosen to expand Medicaid, coverage will also be available. States that choose to expand will receive 100% federal funding for the first 3 years and 90% federal funding thereafter. Prior to the ACA, federal funding for Medicaid was dependent on a state's income levels and ranged from paying around 50% of costs for Medicaid up to a maximum of about 80% in the poorest state—Mississippi.

The ACA's public health exchanges offer plans that are grouped into 1 of 4 tiers based on cost and coverage–Bronze, Silver, Gold, and Platinum. Although there are essential benefits that must be covered by all plans, the tiers vary both by additional services covered as well as cost sharing required of the individual.

The marketplaces are supposed to be fully operational in 2014 but significant glitches in enrollment and other core systems during the 2013 enrollment period suggest that multiple delays will be encountered—particularly in states that rely solely on the federal government for creation of their exchanges.

Value-based payments

The ACA-related changes previously described are those likely to have the greatest near-term impact on ob/gyn practice overall. For those of us whose practices are small businesses, ACA also affects our ability to provide insurance for our workers. Beginning in 2015, new payment provisions that apply to all ob/gyn practices will link payments to quality of care. Physicians who are able to demonstrate better outcomes will receive higher payments than their colleagues who cannot demonstrate improved outcomes.

Although these provisions will initially only affect Medicare, the shift is likely the policy wave of the future for all healthcare payments. Rather than simply paying for each service (fee-for-service), payers are more interested in paying for value and outcomes. Practices are likely to reorganize more creatively around physicians operating at the top of their training and to take advantage of payments available under ACA for nontraditional physician extenders such as care coordinators and for services like nutrition and tobacco cessation counseling.

Outcomes-based payments

By 2015, we should also see new payment methodologies based on outcomes, such as shared-savings models, patient-centered medical homes, and bundled payments, increasingly replacing fee-for-service models. One of the first areas in which

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private insurance companies are focusing is lowering the number of low-risk cesarean deliveries to nulliparas and non-medically indicated elective deliveries.

Wyoming Medicaid has stopped paying for all elective deliveries with no medical indication. South Carolina Blue Cross and Medicaid and Texas Medicaid do not pay for elective deliveries before 39 weeks. Thus far, private industry has focused more on payment incentives for primary care providers than on ob/gyns. One example is Cigna's collaborative accountable care program, which uses primary care providers and nurse care coordinators. These initiatives are in 17 states and involve more than 4000 physicians.[7]

Because the field of quality measurement in ob/gyn is newer, we will have more challenges in using EMR data to demonstrate better outcomes. However, efforts like ACOG's reVITALize, which last year defined a new measurement strategy for both obstetrics and gynecology, will help lead the way.[8]

In 2014, traditional fee-for-service programs will coincide with new payment methodologies. Given that this is a transition period on payment, physicians may have various revenue streams linked to a variety of payment methodologies. Initially, payments will likely increase as a result of quality measurement programs, but over time, those who do not know their own data may fall behind the curve. Sophisticated IT systems, data-reporting, and shared networks will be a fundamental requirement of practices in 2014 and beyond.

Mass HIway

In January, the State of Massachusetts launched the Massachusetts Health Information Highway (Mass HIway), a health information exchange that can be used by both Massachusetts Medicaid and private insurers to implement bundled payment and enables clinicians to directly submit information on immunizations, cancer care, and other public health monitoring data from their EMRs.[9]

Massachusetts is ahead of many states in sharing data with other providers, the public, and payers, but greater transparency on outcomes is a policy trend that is not going away.

Increased interactivity

In 2014 we will see more of a push to move care out of the physician's office and hospital setting and make 24/7/365 care more available to patients in ways other than emergency department visits. This means that we should see creative ways emerge to pay us for our time on phone and email consults and we should also see a trend of more online, interactive health resources (think about how you do your online banking).

Summary

Although the passage and politics surrounding implementation of the ACA have been tumultuous, it seems certain for now that the law will stand at least until 2016 if not permanently and our practices will have to change, in some ways for the better.[10] One thing is certain: There will not be a time of more dynamic increase in the number of Americans gaining health care in our careers. CDG

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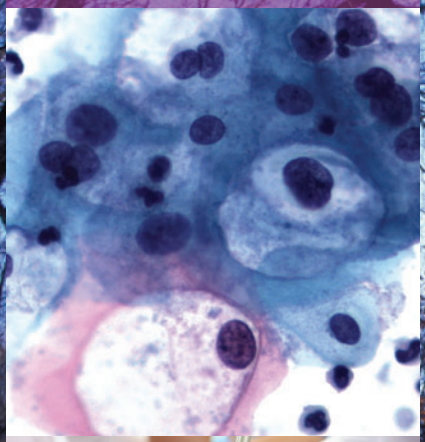

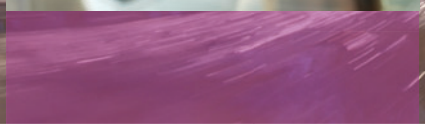

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References: 1. Liverani CA, et al. Am J Transl Res 2012; 4(4): 452-457 **2.** References available at www.gen-probe.com **3.** Aptima® HPV Assay package insert #503789 Rev A 2013,Table 13

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Prophylactic salpingectomy
The future of ovarian cancer prevention?

BY **A. RAUDA TELLAWI, MD,** AND **VADIM V. MOROZOV, MD**

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Dr. Morozov reports receiving royalties from Solour Surgical, holding patents for surgical devices for pelvic organ prolapse and total laparoscopic hysterectomy, receiving a grant from TEDCO/MII, holding ownership interest in Titan Medical, and serving as a consultant/proctor for Intuitive Surgical.

Ovarian cancer is notorious for its late stage at diagnosis and its poor prognosis. Many theories have circulated about the origin and development of ovarian cancer in both BRCA-positive and BRCA-negative women. Earlier theories emphasized that ovarian cancer originates in the ovary, with multiple cycles of ovulation, as well as possibly pelvic inflammation, triggering mutations that ultimately lead to loss of tumor suppressor control.

Newer research, however, shows that ovarian cancer may originate in the fallopian tube, and more specifically, the fimbriated end of the fallopian tube. This leads practitioners to ask the questions: Should I offer my patients prophylactic salpingectomies for primary ovarian cancer prevention? Should both tubes be removed in their entirety during elective surgeries, such as tubal ligations and hysterectomies?

Although there are no prospective randomized clinical trials that address this issue, we will examine the concept here.

The scope of the problem

Nearly 22,000 women are diagnosed with ovarian cancer each year in the United States alone and 190,000 globally; it contributes to nearly 16,000 deaths in the United States and 114,000 deaths worldwide each year.[1] Although there are modifiable risk factors for ovarian cancer, such as use of oral contraceptives, family history is one factor that cannot be modified. At least 10% of ovarian cancers originate in BRCA-positive women, who have a 27%–56% lifetime risk of developing ovarian cancer. BRCA-positive women who choose to have prophylactic surgery have an approximately 96% rate of cancer-free survival, whereas those who opt for close surveillance have a 69% cancer-free rate.[2]

The success rate for prophylactic surgery in the BRCA population is based on one principle: removing tissue that has the potential to become malignant before it can do so. Where ovarian cancer originates is a question that must, therefore, first be answered so that prophylactic surgeries can be done to remove as little tissue as possible while maximizing the benefit for the patient.

Theories on ovarian cancer development

There are 2 widely circulated theories on the origins and progression of ovarian cancer. Endometroid and clear-cell carcinomas are thought to originate from multiple genetic events, such as mismatch repair mutations, that activate the KRAS/BRAF pathway, beta-

catenein activation, and PTEN mutations, which then progress to cancer. Mutations in the KRAS/BRAF pathway tend to lead to a slower progression in ovarian cancer development.

Some researchers theorize that retrograde flow from the uterus creates endometriotic cysts on the ovaries that predispose to the changes in the cell cycle pathways.[3] Others theorize that ovarian cancer originates from endometriosis, via damage from exposure to Mullerian factors during menstruation, or even from inclusion cysts on the ovary that invaginate and, in that process, accrue DNA damage. Still other researchers theorize that pelvic inflammation may cause similar oxidative stress and pathway alterations.[4]

The histology of other epithelial ovarian cancers may follow a more malignant pathway involving p53 tumor suppressor mutations. Such mutations lead to the development of serous carcinoma, which metastasizes rapidly by direct peritoneal spread.

The theories beyond what triggers these changes to tumor suppressor genes are many. In 1971, Fathalla developed the "incessant ovulation theory," which held that constant damage, via oxidative stress, and repair of the ovarian epithelium after each cycle of ovulation led to an increased chance of tumor development.[5]

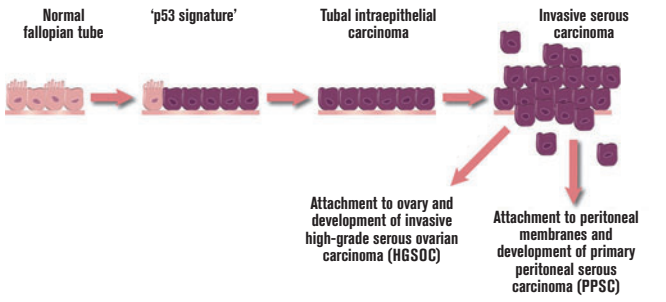
Cramer and Welch in 1983 hypothesized that regular gonadotropin stimulation and elevated estrogen levels stimulate proliferation of the ovarian epithelium; with stimulation comes the risk of DNA damage and progression to cancer.[6]

Advances in understanding ovarian cancer

In recent years, researchers at the Massachusetts General Hospital (Boston) and other institutions have found strong p53-positive sites at the fimbriated ends of the fallopian tubes of both BRCA-positive and BRCA-negative women.[1] In their 2007 paper, Crum et al used a protocol for sectioning and extensively examining the fimbriated end (SEE-FIM) to search for p53-signatures, sites where there were multiple copies of the p53 tumor suppressor genes.[2] They also looked for signs of early tubal intraepithelial carcinomas (TICs) and p53 signatures in women with a history of BRCA mutation who had undergone prophylactic surgery, and women who had surgery for other benign or malignant conditions (eg, fibroids or endometrial cancer).

They found that 80% of women with BRCA mutations and 89% of women without that genetic history had p53 signatures in the fimbriated end of the fallopian tube, and 100% of the TICs they found were associated with the p53 signature.

FIGURE 1 Morphologic development of high-grade serous carcinoma from the fallopian tube



Source: Drapkin R, Karst AM. The new face of ovarian cancer modeling: Better prospects for detection and treatment. *F1000 Med Reports*. 2011;3:22. Used with permission.

Inflammation from consistent ovulation, as well as retrograde flow during menstruation, could be the trigger that sets off the cascade of p53 expression, mutation, and metaplasia (Figure 1).[4,7] Although ovarian cancer may originate from these p53 signature sites in the fimbria, ovarian cancers are not referred to as primary tubal cancers because the tubal component is not the dominant component, nor is it the first to be identified in most cases of ovarian cancer (Figure 2).[7,8]

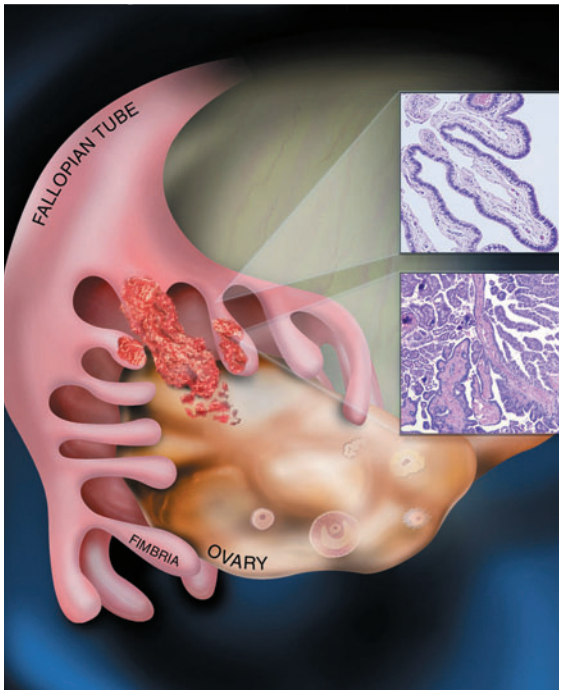
This new theory of ovarian carcinogenesis presents new questions for gynecologic surgeons. Can a simple salpingectomy be offered to BRCA-positive patients in the future? Would a prophylactic salpingectomy at the time of hysterectomy or tubal ligation be the best way to help BRCA-negative women avoid the potential risk of developing ovarian cancer? Should all such women be offered a bilateral salpingo-oophorectomy (BSO)?

The BRCA-positive population

Studies performed in the late 1990s showed that early serous carcinomas of the fallopian tube were present in 2%–10% of BRCA-positive patients undergoing prophylactic BSO.[2] Kindelberger et al studied 55 tubes and ovaries from BRCA-positive women and noted that 41 (75%) had tubal (n = 5), peritoneal (n = 6), or ovarian (n = 30) carcinomas and that foci of TIC were identified in 5 of 5, 4 of 6, and 20 of 30 of these cases, respectively.[9] Ninety-three percent of TICs involved the fimbriae.

Many BRCA-positive women are offered prophy-

FIGURE 2 Origination of high-grade serous ovarian cancers in fimbriated end of fallopian tube



Source: Drapkin R, Karst AM. The new face of ovarian cancer modeling: Better prospects for detection and treatment. *F1000 Med Reports*. 2011;3:22. Used with permission.

lactic bilateral mastectomies and BSOs after their diagnosis is confirmed. These women often wait until after their childbearing years to perform the BSO, in hopes that they will have children and also maximize their time before entering surgical menopause. Yet a significant proportion of these women already have TICs present in their tubes at the time of their prophylactic surgeries, and others have already have progression to ovarian cancer.

At the 24th Annual Ella T. Grasso Ovarian Cancer Symposium, the suggestion of bilateral salpingectomy with ovarian retention (BSOR), and eventual oophorectomy for risk reduction at or near the average age of menopause, were discussed.[10,11]

Leblanc et al coined the term "radical fimbriectomy" for BSOR and performed this procedure on a group of 14 BRCA-positive patients.[3] Both tubes and the fimbrio-ovarian junction were laparoscopically removed, as well as one-quarter of the ovary itself, while preserving the ovary's blood supply in the infundibulopelvic ligament. The team then waited 15 minutes to confirm that blood supply to the ovary remained patent despite the partial oophorectomy.

In their pathology results, they found that 2 of 14 women had p53 signatures in the fimbriated end of the fallopian tube, and 1 of those 2 also had a similar mutation in the small portion of the ovary that was adjacent to that fimbriated end.[3] The patients who had this procedure done would require close monitoring in the future, given their BRCA history.

Although this study was small, the work of this team is novel, and presents a good basis upon which to build future studies.

The BRCA-negative population

A change in approach for ovarian cancer prophylaxis for the BRCA-negative population is one that should be both feasible and easy to implement but requires rigorous testing. In this population, tubal involvement is found in at least 15% of ovarian cancers during pathology assessment.[2]

Studies have shown that patients who have received a simple bilateral tubal ligation (BTL) or hysterectomy, using the current widely used techniques, have had decreased rates of development of ovarian cancer.[12-14]

Some may question whether a total hysterectomy and BSO must be performed to ensure that all segments of the fallopian tube have been removed. In 2010, Cass et al found that a full BSO does not leave behind residual tube, nor does the cornual portion of the tube develop cancer, but some practitioners and patients may continue to worry despite these data.[15]

By using the procedure outlined by Leblanc's team, it should be easy and possible to offer women requesting a bilateral tubal ligation a BSOR, and to incorporate a salpingectomy at the time of hysterectomy for benign disease.

Future directions

The question of the best mode for ovarian cancer screening and prevention is a fundamental one that researchers across the world have been working to answer. Research has clearly shown that the fimbriated end of the fallopian tube contains p53 signatures, or precursor lesions that lead to the development of ovarian cancers in both BRCA-positive and BRCA-negative populations.

This leads to a window of opportunity for gynecologists: offering patients a salpingectomy during benign gynecologic surgeries as one of the few options available for ovarian cancer prophylaxis for

CONTINUED ON **PAGE 66**

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

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Cardiovascular Disorders and Probable Dementia

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

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

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The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

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Cardiovascular Disorders- An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately. Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately. *Stroke* - In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years). In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) .The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. *Coronary Heart Disease*- In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2]. 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)[1]. In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years)[1]. An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5. In postmenopausal women with documented heart disease (n=2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall. *Venous Thromboembolism*- In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately. In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[4]. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. **Malignant Neoplasms**- *Endometrial Cancer*- An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. *Breast Cancer*- The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[2]. The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups[6]. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial date on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration. The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. *Ovarian Cancer* - The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 [95 percent CI, 0.77-3.24]. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen plus progestin and 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. **Probable Dementia-** In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8]. In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 womenyears[8]. When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8]. **Gallbladder Disease-** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported. **Hypercalcemia -**Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level. **Visual Abnormalities-** Retinal vascular thrombosis has been reported in 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, estrogens should be permanently discontinued. **Addition of a Progestin When a Woman Has Not Had a Hysterectomy-** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. **Elevated Blood Pressure-** In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. **Hypertriglyceridemia-** In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs. **Hepatic Impairment and/or Past History of Cholestatic Jaundice-** Estrogens may be poorly metabolized in patients with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. **Hypothyroidism-** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range. **Fluid Retention-** Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed. **Hypocalcemia-** Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur. **Exacerbation of Endometriosis-** A few cases of malignant transformation of residual endometrial implants have been reported in women treated post hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered. **Hereditary Angioedema** Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. **Exacerbation of Other Conditions** Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions. **Photosensitivity/Photoallergy** The effects of direct sun exposure to Divigel application sites have not been evaluated in clinical trials. **Application of Sunscreen and Topical Solutions** Studies conducted using other approved topical estrogen gel products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels. The effect of sunscreens and other topical lotions on the systemic exposure of Divigel has not been evaluated in clinical trials. **Flammability of Alcohol-Based Gels - Alcohol based gels are flammable.** Avoid fire, flame, or smoking until the gel has dried. Occlusion of the area where the topical drug product is applied with clothing or other barriers is not recommended until the gel is completely dried. **Potential for Estradiol Transfer and Effects of Washing** There is a potential for drug transfer from one individual to the other following physical contact of Divigel application sites. In a study to evaluate transferability to males from their female contacts, there was some elevation of estradiol levels over baseline in the male subjects; however, the degree of transferability in this study was inconclusive. Patients are advised to avoid skin contact with other subjects until the gel is completely dried. The site of application should be covered (clothed) after drying. Washing the application site with soap and water 1 hour after application resulted in a 30 to 38 percent decrease in the mean total 24-hour exposure to estradiol. Therefore, patients should refrain from washing the application site for at least one hour after application. **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 increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels, 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-l-antitrypsin, ceruloplasmin). Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning]*.
- Malignant Neoplasms *[see Boxed Warning]*.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted for Divigel. **Metabolic Interactions -** *In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort *(Hypericum perforatum)* preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and result in side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy Divigel should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy. **Nursing Mothers-** Divigel should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when Divigel is administered to a nursing woman. **Pediatric Use-** Divigel is not indicated in children. Clinical studies have not been conducted in the pediatric population. **Geriatric Use-** There have not been sufficient numbers of geriatric women involved in studies utilizing Divigel to determine whether those over 65 years of age differ from younger subjects in their response to Divigel. *The Women's Health Initiative Studies* In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age. In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age.

The Women's Health Initiative Memory Study In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo. Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8]. **Renal Impairment-** The effect of renal impairment on the pharmacokinetics of Divigel has not been studied. **Hepatic Impairment-** The effect of hepatic impairment on the pharmacokinetics of Divigel has not been studied.

OVERDOSAGE

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

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Eating disorders in adolescents and young adult women:

Implications for reproductive health

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Eating disorders (EDs) are serious, often debilitating chronic illnesses that typically start in adolescence. About 90% of ED patients are female. In addition to anorexia nervosa (AN) and bulimia nervosa (BN), the most recent *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) has included binge eating disorder.[1] Past DSM editions included the category "eating disorder not otherwise specified" (EDNOS), and many young people fell into this group. Modifications of the other ED criteria and the addition of the category "other specified feeding or eating disorder" led to the elimination of EDNOS. Avoidant/restrictive food intake disorder (ARFID) is one more new category; it is especially relevant for children and adolescents. Table 1 outlines the DSM-5 ED criteria.[1]

The prevalence of EDs has increased in recent decades, likely due in part to better recognition as well as the marked medical and societal focus on obesity and dieting. Current prevalence estimates among adolescents and young adults in the United States are 0.5% to 1.0 % with AN, 1% to 2% with BN, and about 5% with other EDs.[2] Of special concern is that ED diagnoses are increasingly being made in preadolescents (<12 years), putting this young population at heightened risk for delayed physical and psychosocial development.[3] These prevalence figures are clearly underestimates. The 2011 Youth Risk Behavior Surveillance, a biannual national survey of high school students by the Centers for Disease Control and Prevention, found 61% of females were trying to lose weight, and in the past 30 days 12% of females had not eaten for 24 hours or more, 5% took diet pills/supplements, and 4% induced vomiting or took laxatives to lose or not gain weight.[4] Thus, many young women are engaging in unhealthy eating and dieting behaviors, even if they do not meet DSM criteria for an ED.

EDs can affect every organ system; patients may present with any combination of gynecologic, cardiac, gastrointestinal, neurologic, orthopedic, or psychiatric signs and symptoms (Table 2). Young women with EDs are seldom forthcoming about their ED thoughts

TABLE 1 DSM-5 diagnostic criteria for eating disorders

Anorexia nervosa

- Energy intake is less than is required, leading to significantly low body weight for age, sex, developmental stage, and physical health. Significantly low weight is defined as a weight less than minimally normal or, for children and adolescents, less than that minimally expected based on prior growth.
- Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight
- Disturbance in the way in which body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of current low body weight

  Restricting type: Weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

  Binge-eating/purgingt ype: The individual has engaged in recurrent episodes of binge eating or purging behavior (self-induced vomiting or misuse of laxatives, diuretics, or enemas).

Bulimia nervosa

- Recurrent episodes of binge eating—eating an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances and feeling a lack of control over eating during episode.
- Recurrent inappropriate compensatory behaviors to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.
- Binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months.
- Self-evaluation is unduly influenced by body shape and weight.

Other specified feeding or eating disorder (formerly "eating disorder not otherwise specified")

Conditions in which the feeding and eating behaviors cause significant distress or impairment in functioning but do not meet full criteria for another ED. Examples are:

Atypical anorexia nervosa: All criteria for anorexia nervosa are met, except that despite significant weight loss, the individual's weight is within or above the normal range.

Subthreshold bulimia nervosa (of low frequency and/or limited duration): All criteria for bulimia nervosa are met, except that binge eating and inappropriate compensatory behaviors occur, on average, less than specified in BN criteria.

Purgingd isorder: Recurrent purging behavior to influence weight or shape (eg, self-induced vomiting; misuse of laxatives, diuretics, or other medications) in the absence of binge eating.

Avoidant/restrictive food intake disorder

- An eating or feeding disturbance (eg, apparent lack of interest in eating or food; avoidance based on sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate caloric needs; associated with one (or more) of the following: significant weight loss or poor growth, significant nutritional deficiency, dependence on enteral feeding or nutritional supplements, marked interference with psychosocial functioning.
- The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.
- The eating disturbance does not occur exclusively during the course of AN or BN, and there is no evidence of a disturbed body image.
- The eating disturbance is not attributable to a concurrent medical condition; the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

Abbreviations: ED, eating disorder, AN, anorexia nervosa; BN, bulimia nervosa
Source: *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed (DSM 5).[1]

and behaviors, often leading to unnecessary testing and delayed diagnosis. Because of parental concerns, children and adolescents may be more likely to see a healthcare provider earlier in their course than are older patients.

EDs are multifactorial in origin, with a strong genetic component.[3,5] They are not volitional, although dieting often precedes the ED. Patients with AN at low weight show elevated ghrelin, a hunger-stimulating hormone secreted mainly by the stomach and

pancreas, and a low level of leptin, a hormone secreted by adipocytes. These abnormalities are likely a physiologic adaptation to a starved state, rather than causal. A constellation of personality and psychologic traits such as perfectionism and low self-esteem are often but not always seen in those with EDs. Comorbid psychiatric conditions, especially anxiety and depression, are common.[6] Again, are these factors causative or more a result of the disordered eating and weight changes? Our thinness-obsessed culture influences everyone; young women seem to be especially vulnerable to unrealistic and unattainable "body ideals," and yet few develop an ED.

Menstrual irregularities

Primary care providers and gynecologists see many adolescent and young women with primary or secondary amenorrhea or irregular periods. Although the differential diagnosis of menstrual irregularities is vast in this age group, EDs need to be near the top of the list. Because the patient with an ED will rarely disclose her eating or weight-control behaviors, it is incumbent on the practitioner to be aware of red flags that suggest an ED as the cause of her menstrual problem (Table 3).

Amenorrhea

For the first time, DSM 5 did not include amenorrhea as one of the criteria for the diagnosis of AN. Reasons for the change included that previous criteria precluded premenarchal girls or those on hormonal contraception from receiving the diagnosis of AN. Amenorrhea occurs in more than 90% of those with AN and as many as 50% of those with BN and other specified eating disorders.[7,8]

Numerous mechanisms are believed to be involved in causing amenorrhea. Gonadotropin-releasing hormone (GnRH) pulsatility is lost (reverting to a prepubertal pattern), with resultant decrease in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion, ovarian suppression, and estradiol levels. Hypoleptinemia seems to also play a role in hypothalamic-pituitary-ovarian axis suppression.[8] Puberty and menarche may be delayed in those girls whose ED began prior to the expected time of puberty. Secondary amenorrhea can occur even before there is significant weight loss. Although weight/body mass index (BMI) are critical factors in menstrual irregularities, amenorrhea can occur even in those at normal weight or overweight, regardless of the specific ED diagnosis.[9]

Clinicians, patients, and parents often want to know when menses will return. Return of menses is viewed as a marker of biologic health and is typically used as a treatment goal (rather than a specific weight). Being within a normal weight range is clearly necessary, but not sufficient. Research has identified the following predictors for return of menses: within 6 months of achieving 90% of expected body weight (EBW); weight at which menses stopped plus 5 lb; serum estradiol level of greater than 30 pg/mL; and BMI at 15% to 20% for age.[10,11]

Persistent amenorrhea can also be seen in those who are exercising intensely, purging frequently (vomiting, laxative abuse), or showing marked fluctuations in their weight. An obese young woman who loses 40 lb to weigh 180 lb can develop the same menstrual irregularities as one who started out normal weight and became underweight. It is likely that ongoing dieting and psychosocial stressors also contribute to menstrual irregularities, although the mechanisms are unknown.[8]

A subset of women with EDs meets criteria for the female athlete triad: disordered eating, amenorrhea, and low bone mineral density (BMD). Girls at highest risk for this constellation of signs and symptoms are those doing long-distance running, gymnastics, figure skating, or ballet. For some, the weight loss starts in an attempt to improve performance or at the urging (direct or indirect) of a coach or teacher, but then the behaviors become compulsive or excessive. The resultant hypoestrogenemic state, along with intense physical activity, puts these young women at increased risk for stress fractures—thus outweighing any benefit that weight-bearing exercise has for bone health.[12]

Irregular menses

At least half of women with BN have irregular menses, even though they are not underweight, and half had a history of amenorrhea.[13] Researchers have found that factors independently associated with irregular menses include higher frequency of vomiting, lower total thyroxine (T4), and lower fat intake. At 12-month follow-up, 43% still had irregular periods. These women had a greater discrepancy between their maximum and minimum weights, longer duration of ED symptoms, and were more depressed.[13]

In a nonclinical sample of high school students, investigators found that 15% of the young women had periods less than once a month (their definition of "irregular").[14] Those who reported vomiting

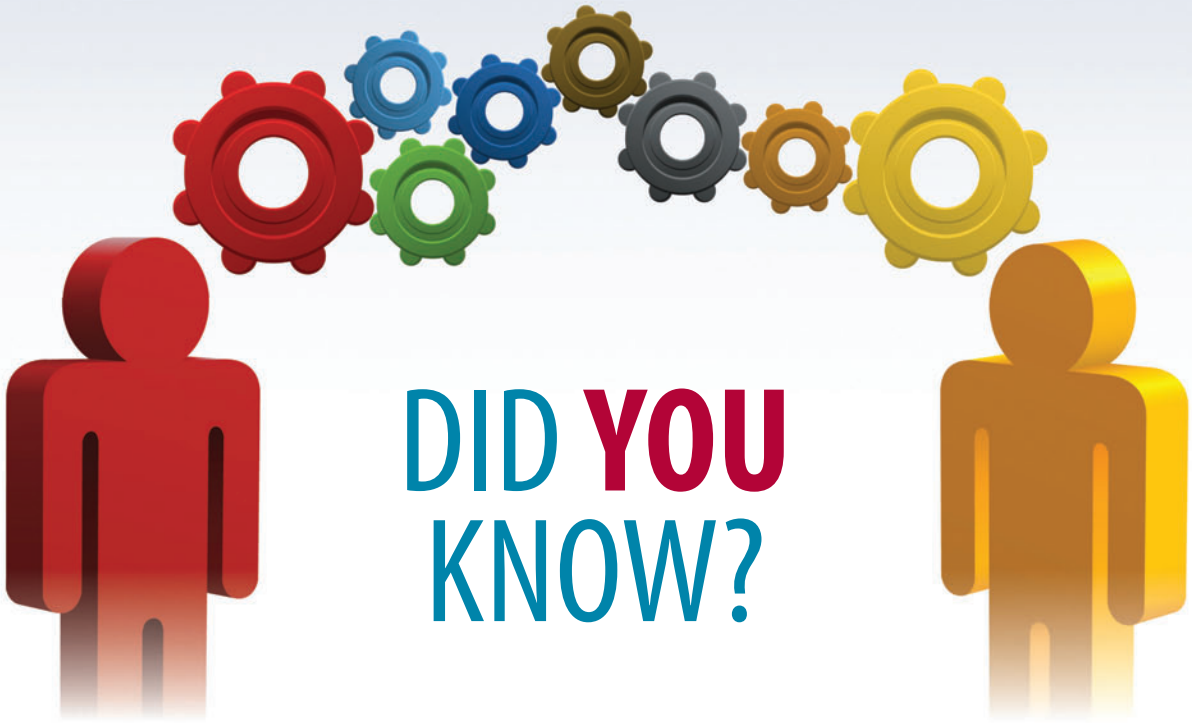
TABLE 2 Common medical and psychosocial complications of EDs

Organ system	Anorexia nervosa	Bulimia nervosa
Cardiovascular	Bradycardia Hypotension Orthostatic changes Abnormal ECG	Abnormal ECG (if abnormal electrolytes)
Gastrointestinal	Constipation Early satiety Decreased intestinal motility Bloating	Esophagitis (V) Dental problems (V) Parotid, salivary gland enlargement (V) Constipation (L)
Endocrine	Amenorrhea Irregular menses Atrophic breasts Pubertal delay Growth retardation Low T3	Irregular menses Amenorrhea
Neurologic	Syncope Headaches Difficulty concentrating	Syncope Headaches Difficulty concentrating
Skin	Dry skin Lanugo Dull, thinning hair Cold, blue extremities Peripheral edema	Callouses on extensor surface of hands (V) Peripheral edema (L)
Skeletal	Low bone density Stress fracture	
Psychosocial	Depression Flat affect Anxiety Irritability Low self-esteem Obsessive thinking; compulsive behaviors Social isolation	Depression Anxiety Irritability Low self-esteem
Hematologic	Leukopenia (rarely anemia, thrombocytopenia) Low ESR	
Electrolytes	Low sodium (if water loading) High BUN Dehydration	Hypokalemia (V) Hypochloremia (V) Metabolic alkalosis (V) Metabolic acidosis (L) High BUN (L) Dehydration (L,V)

Abbreviations: BUN, blood urea nitrogen; ECG, electrocardiogram; EDs, eating disorders; ESR, erythrocyte sedimentation rate; L, laxatives; T3, triiodothyronine; V, vomiting

1 to 3 times a month to control their weight were 1.5 times more likely to have irregular periods than those who did not vomit. Girls who vomited more than once weekly were more than 3 times as likely to have irregular menses. The menstrual irregularity was explained by the frequency of purging, not by the girls' weight.

Girls diagnosed with the newest DSM category, ARFID, can be underweight and have delayed puberty or secondary amenorrhea. Often they do not seem to have an eating disorder; they may state that they are too thin and want to gain weight but have a



DID **YOU** KNOW?

70% of women **without** bacterial vaginosis (BV) tested positive for *Gardnerella vaginalis* according to a clinical study.[1]

No single organism causes BV.

The NuSwab Bacterial Vaginosis (BV) test:

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1. Fredricks DN, Fiedler TL, Thomas KK, Oakley BB, Marrazzo JM. Targeted PCR for detection of vaginal bacteria associated with bacterial vaginosis. *J Clin Microbiol.* 2007 Oct;45(10):3270-3276.
2. Cartwright CP, Lembke BD, Ramachandran K, et al. Development and validation of a semiquantitative multitarget PCR assay for diagnosis of bacterial vaginosis. *J Clin Microbiol.* 2012;50(7):2321.

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TABLE 3 Red flags suggesting an ED

- Excessive weight loss
- Resistance to gaining weight
- Marked weight fluctuations
- Preoccupation with food, calories, portions, weight, body size and/or shape
- Excessive or obsessive exercising
- Menstrual irregularities, including amenorrhea
- Constipation
- Always feeling cold
- Mood swings; irritability
- Social isolation—especially from situations involving food
- Evidence of vomiting (odor; postprandial trips to bathroom)
- Finding laxatives, diet pills in patient's belongings
- Food "disappearing" from kitchen; hiding food, wrappers, etc.

Abbreviations: ED, eating disorder

variety of reasons that prevent this—such as being excessively picky eaters; history of choking/gagging with fear of that happening again; and a fear of vomiting or abdominal pain if they eat more. Lack of recognition or awareness of this entity can lead to missed diagnosis and delays in care.

Other sequelae of eating disorders

Effect on bone

Peak bone mass is influenced by race, genetics, physical activity, calcium and Vitamin D intake, and gonadal steroids, among others. The hypoestrogenemia commonly seen in those with AN has an adverse effect on bone mineralization. Because adolescence is when approximately one-half of final bone mass is acquired, ED-associated amenorrhea is especially deleterious for bone health.[15] Low BMD can occur after as little as 6 months of amenorrhea and is seen in at least half of AN patients. These young women are at increased risk for pathologic fractures. There is growing concern that, even with a return to healthy weight and resumption of menses, normal peak bone mass may never be achieved, thus placing these women at long-term risk for fractures.

In contrast to postmenopausal women, the low BMD seen in adolescents and young women with EDs is a result of both increased bone resorption and decreased bone formation. Multiple factors are believed to be involved in ED-associated bone loss: hypoestrogenemia, relative hypercortisolemia, hypoleptinemia, decreased insulin-like growth factor 1 (IGF-1), vitamin and micronutrient deficiencies, and decreased muscle mass.[15,16]

BMD is typically assessed by dual-energy x-ray absorptiometry (DXA). DXA scans in children and adolescents must be interpreted using appropriate reference data. T scores should not be used, as this compares the patient's BMD to that of young adults (at peak bone mass). Rather, Z scores, based on age- and gender-matched controls, should be calculated to correctly interpret the DXA. Appropriate terminology for abnormal BMD in children and adolescents is "low BMD for age," rather than "osteopenia" or "osteoporosis." Although there is ample evidence that low BMD in an adolescent is a significant risk for stress fracture, the BMD fracture threshold for adolescents and young adults has not been established.

Numerous strategies to improve bone density in ED patients have been tried, and this remains an active area of research. Most of these trials involved hormone replacement, either combination oral contraceptive pills (OCPs) or conjugated estrogens. OCPs have not been shown to significantly prevent or reverse low BMD in this population.[15] Furthermore, it is not uncommon for these young women on hormonal therapy to interpret regular withdrawal bleeding as proof that they are fine and do not need to gain weight or stop their weight-control behaviors.

In a placebo-controlled trial, investigators demonstrated that physiologic estradiol replacement (given transdermally) improved spine and hip BMD in adolescent AN patients.[16] The authors suggest that this treatment was effective because physiologic doses of estrogen do not suppress IGF-1, whereas the relatively high estrogen dose found in OCPs does suppress IGF-1. Of note, no difference was observed between treated and untreated girls in weight gain or lean or fat mass. Thus, physiologic doses of transdermal estrogen may help prevent ED-associated low BMD, especially in those girls who fail to gain weight and re-establish menses in spite of nutritional and psychologic therapy.

Trials of bisphosphonates have shown mixed results; these are not recommended to treat low BMD in young ED patients. Long-term safety data in young people are lacking; of special concern are these drugs' long half-life, potential to be released from bone years later, and ability to cross the placenta.

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The only certain effective "treatment" for ED-associated low BMD is nutritional rehabilitation, weight gain to a healthy range, and resumption of spontaneous menses.[17,18]

Effect on fertility

Although future fertility may not be an immediate issue for adolescents, it may be a concern for them later. While amenorrheic, a woman is highly unlikely to get pregnant, but there have been reports of women with AN conceiving. Patients seen in an infertility clinic were screened and then interviewed to detect EDs.[19] Nearly 17% met criteria for AN, BN, or EDNOS. Almost 60% of those with a history of amenorrhea or oligomenorrhea had an ED, but none had disclosed their ED behaviors to their ob/gyn. Women who recover from EDs do not seem to have an increased risk of infertility.[20]

When to suspect an ED

Because it is common for young women to hide or minimize being overly concerned with weight, dieting, eating behaviors, and exercise habits, healthcare providers should be mindful of common red flags (Table 3). It is also common for ED patients to deny they have a problem when asked about their eating behaviors and dieting. Practitioners will be more successful when questions are asked honestly and nonjudgmentally. Several well-validated ED screening questionnaires exist, but these are not practical for use in an office setting.

On the other hand, the SCOFF questionnaire is brief and easy to use, although it has not been validated in adolescents (Table 4).[21]

Adolescents with menstrual irregularities should be asked routinely about their weight history (maximum and minimum in the past year); eating habits, including typical daily intake; if they purge (vomit, take diet pills or laxatives); and their exercise habits.

Physical exam findings that may suggest an ED include: weight and BMI less than 15% for age; bradycardia; low blood pressure; and orthostatic changes in heart rate or blood pressure. Patients with AN may have very dry skin, dry and thinning hair, lanugo, breast atrophy, and cold and blue hands and feet. Swollen parotid or submandibular glands and dental problems (eg, eroded dental enamel, caries) may be seen in those who are purging. Other than low weight in patients with AN, however, most patients with EDs will have a normal exam.

TABLE 4 SCOFF questionnaire

1. Do you make yourself **S**ick because you feel uncomfortably full?
2. Do you worry you have lost **C**ontrol over how much you eat?
3. Have you recently lost **O**ver 1 stone (14 lb) in a 3-month period?
4. Do you believe yourself to be **F**at when others say you are too thin?
5. Would you say that **F**ood dominates your life?

Yes=1 point; score of >2 suggests AN or BN

Abbreviations: AN, anorexia nervosa; BN, bulimia nervosa
Source: Morgan JF, Reid F, Lacey JH.[21]

Making the diagnosis of an ED

No laboratory study either diagnoses or rules out an eating disorder. Some abnormalities are common and due to malnutrition (such as low white blood cell count; low total triiodothyronine (T3) with normal thyroid-stimulating hormone; and low FSH, LH, and estradiol). Laboratory testing is helpful when ruling out other diagnoses (eg, pregnancy, polycystic ovary syndrome) or when looking for acute complications of the ED (eg, electrolyte abnormalities due to purging). A thorough and sensitive history and careful physical exam (including getting an accurate weight) are the most important diagnostic tools.

Management

Detailed discussion of treating ED patients is beyond the scope of this article. Most patients can be treated as outpatients; optimal treatment is provided by a team that includes a medical provider, dietician, and mental health professional. General treatment goals are to help the patient restore and maintain a healthy weight and nutritional status, identify and cope with any psychosocial issues that contributed to the ED, and establish healthful eating. Studies have demonstrated improved outcomes with early intervention and family involvement in treatment.

Numerous psychotropic medications have been tried and studied in this patient population.[22] Selective serotonin reuptake inhibitors (SSRIs) have not been shown to help with weight gain in patients with AN, although these agents may help with comorbid anxiety or depression. More recently, atypical anti-

CONTINUED ON **PAGE 62**

NOW AVAILABLE

THE FIRST AND ONLY

therapy to pair conjugated estrogens with the estrogen agonist/antagonist bazedoxifene, also known as a selective estrogen receptor modulator (SERM).

- Bazedoxifene is used, instead of progestin, to help protect the uterine lining against hyperplasia that may result from estrogen-alone treatment

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. 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.

IMPORTANT SAFETY INFORMATION

Women taking DUAVEE should not be taking 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 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.

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.

INDICATIONS

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.

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. 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.

To view an educational webcast, visit duaveehcp.com/signup2

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

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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/m²
A 17% reduction in bazedoxifene exposure was predicted in women with BMI > 27 kg/m² (N=144) compared to those with BMI ≤ 27 kg/m² (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.

CONTINUED FROM **PAGE 58**

psychotics, especially olanzapine, have been tried, with mixed results. In contrast, SSRIs have been shown to decrease the frequency of binging and purging in patients with BN. Fluoxetine is the only FDA-approved medication for the treatment of BN.

Hospitalization is indicated for patients with severe medical or psychiatric signs or symptoms. Several professional organizations have established guidelines for hospitalization.[3,23,24]

Prognosis

Most adolescents and young adults eventually recover from their EDs, although the course is often bumpy and may last years.[25] Some patients will have a resolution of one type of ED (such as AN) and then, sometimes abruptly, develop the characteristics of a different type (such as BN). AN has the highest mortality rate of any psychiatric diagnosis, with patients usually dying from suicide or complications of the ED (eg, arrhythmia).[26]

Summary

Eating disorders develop in vulnerable individuals from an interplay of genetics and a host of personality and sociocultural factors. They are associated with high rates of morbidity and mortality and have especially deleterious medical and developmental effects on children and adolescents. Menstrual disturbances are very common and may be associated with nonreproductive sequelae such as bone loss. Effective treatment requires nutritional rehabilitation to achieve a healthy weight and psychologic help with underlying emotional issues. Optimal treatment is provided by an interdisciplinary team and includes the family. COG

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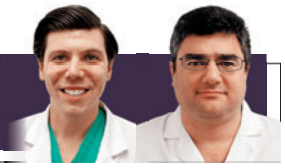


Time-lapse photography and ART

The technology may allow for easier selection of normal embryos and perhaps lead to eSET becoming the standard of care

In 2011, 163,039 assisted reproductive technology (ART) cycles were performed in the United States, resulting in 47,818 live births and 61,610 live-born infants, according to the Centers for Disease Control and Prevention (CDC) 2011 Assisted Reproductive Technology Fertility Clinic Success Rates Report.[1] Nearly 70% of the ART cycles thus did not result in a live birth, underscoring how difficult it is to select the right embryo.

With demand for ART increasing, clinics will continue to feel financial pressure to improve the efficacy and efficiency of ART cycles. In a recent article by Chambers et al, the authors point out that "there are striking international differences in utilization of ART and embryo transfer (ET) practices, even among developed countries where the prevalence and causes of infertility are similar. The reasons for such disparities are multifactorial, and include the diversity of regulatory and funding environments, demographic differences, and the influence of sociocultural norms."[2]

Despite more than 30 years of research and an array of scientific innovations, we have yet to find the proverbial "Holy Grail" of IVF success: A way to definitively identify developmentally normal embryos. If clinicians/embryologists were able to pick the absolute "best" embryos, then elective single embryo transfer (eSET) would be the standard of care, decreasing the number of multifetal pregnancies and resultant complications. In fact, according to the CDC data cited above, multifetal pregnancies are a common occurrence.

An old technology is 'new' again

Now new hope for identifying normal embryos is coming from an old technology: time-lapse photography. Around since the early 20th century, time-lapse photography was first used by scientists who took continuous sequential photographs of plants and played back the images at a fast speed so that hours or days of change could be appreciated in a matter of seconds. We have all seen time-lapse images of flowers blooming, clouds moving, or even people going about their daily lives. What is miraculous about these short clips is that when they are played at normal speeds, time appears to be elapsing more quickly, allowing subtle changes to be identified and studied.

Time-lapse photography applied to embryo development is commonly called morphokinetics because it combines the morphological criteria that are typically used for embryo grading/evaluation with the kinetics of development for each embryo at certain predefined checkpoints.

Morphokinetics eliminates the need for an embryologist to take an embryo out of an incubator at set intervals and evaluate its development under a microscope. Instead, the embryo remains in a chamber, where images are continuously recorded and evaluated remotely.

What piques our interest about time-lapse photography is the completely noninvasive nature of the technology. Time-lapse photography requires only a modified incubator system, an embryo, a camera, and a computer to process the images. Coupled with the many advances in ART labs in the past decade—such as improvements in embryo culture that allow embryos to grow longer and more robust, innovations in embryo biopsy techniques allowing clinicians to get better samples of genetic material, and the myriad other new technologies for enhanced genetic evaluation of an embryo—time-lapse

photography could be a game-changer.

Two companies currently manufacture time-lapse technology for embryo evaluation: Auxogyn and Unisense FertiliTech. Auxogyn's product is the noninvasive Early Embryo Viability Assessment (Eeva) System. Unisense FertiliTech's product is the EmbryoScope. Both technologies allow for simultaneous imaging of multiple embryos and remote access to data/images.

Improving success rates through continuous incubation

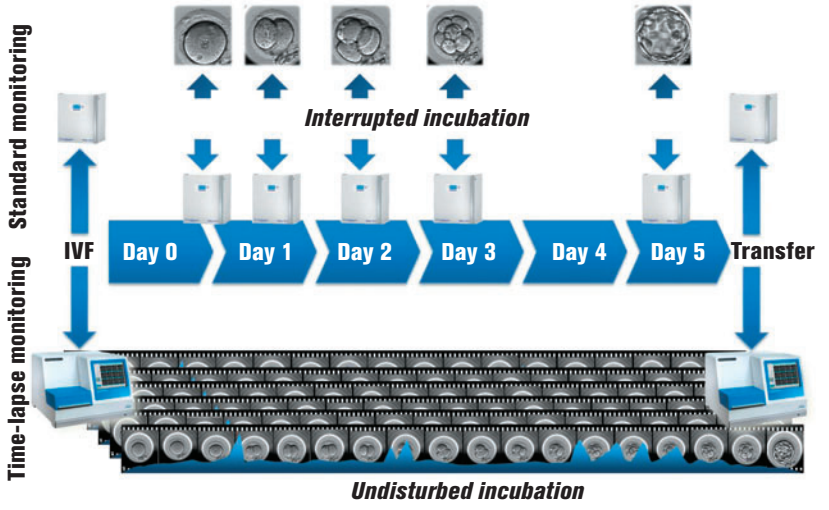
What makes this technology a game-changer is that it allows embryos to develop in an undisturbed environment while giving the embryologist better ability to assess them. In conventional IVF labs, embryos are evaluated daily, but removing them from the incubator interrupts incubation (Figure). With continuous time-lapse monitoring systems, embryos are continuously incubated, often until the day of transfer. This limits temperature variations and the potential effects of environmental exposures, movement, and trauma.

Although these factors may not all be crucial for proper embryo development, maintaining a continuous temperature does seem to mimic the normal physiology of the human reproductive tract.

This may explain why time-lapse photography appears to be improving ART success rates so dramatically. A 2012 retrospective analysis indicated that culture and selection of embryos with time-lapse monitoring significantly improved the relative probability of clinical pregnancy (+20.1% per oocyte retrieval, +15.7% per embryo transfer).[3]

Data derived from the developmental imaging have become invaluable for other reasons. Chromosomally normal and abnormal embryos have been noted to have different kinetic behavior.[4] Data on "normal" embryo behavior, however, are still being amassed, so these studies should be read with caution. Before we can call something abnormal, we need to make sure we know what is normal.

FIGURE Standard versus time-lapse embryo monitoring



Source: FertiliTech Inc. Used with permission.

A new culture of embryology

The last aspect of time-lapse technology that really excites us is the potential for performing embryologic assessment remotely. Images could be processed, scored, and evaluated by computers, to assist in ultimately selecting the best embryo for replacement. Patients in regions where resources are scarce, such as the developing world, could have access to world-class embryologic assessment.

A senior or supervising embryologist could oversee images from clinics around the world and offer guidance, teaching, and insight remotely. In fact, the products offered by both of the companies mentioned above have tablet-compliant features.

It is incredible to think that a photographic method that is more than 110 years old is now the state of the ART today. COG

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> In the absence of good screening tests, this procedure is **the only form of prophylaxis** for a cancer that is difficult to detect and often lethal when found.

CONTINUED FROM **PAGE 48**

the general population. It likewise provides BRCA-positive patients with the possibility of having bilateral salpingectomies with ovarian retention until they approach menopause.

Questions remain

Research has not yet determined an exact percentage of BRCA carriers in whom TICs lead to cancer. We do not know the pathways by which tubal ligations reduce the risk of cancer. It is not known at what age it would be best to perform salpingectomy, nor how long may be best to wait before performing subsequent oophorectomy in order to maximize risk reduction.

On a related note: Would ovarian retention, along with the retention of the estrogen and progesterone the ovary produces, also increase the risk of earlier breast cancers in these women, if they have not yet had prophylactic mastectomies?

In our opinion, introduction of bilateral salpingectomies at the time of tubal ligation or hysterectomy for benign gynecologic patients is a reasonable option. In the absence of good screening tests, this procedure is the only form of prophylaxis for a cancer that is difficult to detect and often lethal when found.

Physicians should at least present patients with this option during presterilization and prehysterectomy counseling. Prospective studies will need to be conducted to see if this procedure actually does decrease the risk of ovarian cancer development over time. COG

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F. A. MOORE III, MD, AND TAMMY M. DUPUY, MD

Postmenopausal genital tract tuberculosis

A report of two cases in the southern United States

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Female genital tuberculosis (FGT) is rare in the United States. Of the 9951 reported cases of tuberculosis in 2012, fewer than 1% affected the genital tract and the majority occurred in foreign-born people.[1] Postmenopausal women account for fewer than 10% of cases of genital tuberculosis, and it is estimated that tuberculosis of the cervix accounts for 0.1%–0.65% of tuberculosis cases worldwide.[2-4] Our review of the US medical literature revealed only 1 case report of tuberculosis of the cervix diagnosed in the United States and reported in the medical literature in the past 37 years.[5]

Genital tract tuberculosis can involve the internal pelvic organs as well as the external genital organs. Usually the fallopian tubes are involved, followed sequentially by the uterus, ovaries, cervix, vagina, and vulva.

Pelvic tuberculosis is an entity with a variety of presentations and is often mistaken for ovarian carcinoma.[6] The most common findings are pelvic mass (90%), elevated CA-125 (90%), ascites (60%), sterility (45%–55%), pelvic pain (45%–50%), poor general health (26%), and menstrual disturbances (10%–20%).[2,7]

Cervical tuberculosis frequently mimics cervical carcinoma. Presentation may include postcoital bleeding, vaginal discharge, pelvic pain, mucopurulent cervicitis, ulcerations, and exophytic lesions.

Here we describe 2 cases of FGT in postmenopausal women. The first case involves the pelvic organs and mimics ovarian carcinoma. The second involves the cervix and presents as suspected cervical carcinoma.

Case 1

A postmenopausal 52-year-old Vietnamese woman who emigrated from Vietnam to Louisiana in 1996 presented to the emergency department (ED) with complaints of abdominal pain, nausea, and bright red blood in her stools. Her last menstrual period had been approximately 5 years before. She was afebrile and in no distress. Abdominal examination revealed a soft, non-tender, non-distended abdomen with bowel sounds present. Stool was heme-negative. She was prescribed dicyclomine for abdominal pain and promethazine for nausea and sent home.

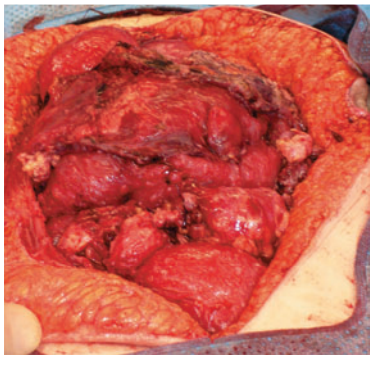
She presented to the ED 2 months later with complaints of worsening abdominal pain and nausea unrelieved by medication. She reported daily bowel movements and denied bloody stools. Her abdomen was slightly distended with normal bowel sounds. Computed tomography scan of the abdomen and pelvis revealed ascites, omental thickening with nodularity in the mesentery, possible involvement of the capsule of the liver, thickening of the wall of the small bowel, and mildly distended small bowel loops. There was a 3-cm cystic lesion in the right lower abdomen, an enlarged lymph node in the right lower quadrant, and a 3.7-cm solid lesion in the left adnexa. She

was referred to a gynecology clinic because of suspicion for ovarian cancer.

When evaluated in the gynecology clinic 4 days later, the woman described a "heavy feeling" in her lower abdomen. She denied fever, chills, night sweats, or weight loss. On examination, a small vesicular exophytic lesion of the cervix was noted, and an approximately 4- x 5-cm left adnexal mass was palpated. A Pap smear was negative. No cervical biopsies were performed. Transvaginal ultrasound showed a normal uterus, cervix, vagina, and bladder. The right ovary measured 3 x 2.8 x 2.1 cm. In the left adnexa was a 7.3 x 6.5 x 3.5-cm complex cystic mass with a "fishnet" appearance. Our gynecologic oncology consultant recommended an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and staging. CA-125 was 235 U/mL. Preoperative chest x-ray revealed normal heart and lungs.

Exploratory laparotomy revealed extensive intra-abdominal adhesions with apparent miliary process (Figure 1). Approximately 3 liters of ascites were evacuated and lysis of adhesions was performed. The pelvic mass was unresectable. An omentectomy was performed and the tissue sent to pathology for frozen section, which revealed a granulomatous process. Multiple biopsies of the lesions were taken throughout the abdominal cavity for fungal and mycobacterial studies.

FIGURE 1 **Upon exploratory laparotomy, a diffuse miliary process and significant adhesive disease were encountered throughout the abdomen and pelvis.**



Postoperatively the patient was placed in respiratory isolation and a tuberculin skin test (PPD) was reported positive at 20 mm. Three sputum samples were collected daily; the first 2 were positive for acid-fast bacilli (AFB). While the patient was in the hospital, antimicrobial therapy consisting of rifampin, isoniazid (INH), pyrazinamide, and ethambutol (RIPE) was initiated. Abdominal cultures were positive for *Mycobacterium tuberculosis* per DNA probe and sputum cultures were positive for *Mycobacterium avium complex*, also per DNA probe. Drug susceptibility testing indicated INH-resistant *M. tuberculosis*. The patients' drug regimen consisted of 2 months of RIPE therapy, then INH and rifampin, then moxifloxacin, rifampin, and ethambutol for 9 months. At 1 year, the patient was doing well with no symptoms of abdominal pain. Her ascites had resolved and her pelvic exam was normal.

Case 2

A 47-year-old postmenopausal Filipino woman who had been living in the United States for approximately 18 months presented to the ED with a 1-year history of vaginal spotting, vaginal discharge, lower abdominal pain, dyspareunia, postcoital bleeding, and absence of menses for 2 years prior to the vaginal bleeding. Initial evaluation included a gynecologic exam, cervical cultures, and an appointment at a gynecology clinic.

Pelvic examination at the time of the initial gynecology visit revealed a friable, hemorrhagic, nodular cervix, with a purulent exudate (Figure 2). The adnexa were mildly tender and indurated bilaterally. Results of cervical cultures done at the ED visit were positive for *Chlamydia trachomatis*. Impression was severe mucopurulent cervicitis secondary to chlamydia, and therapy with azithromycin was initiated. On follow-up visit, there was no improvement in either reported symptomatology or the appearance of the cervix. Multiple cervical biopsies were obtained to rule out squamous cell carcinoma of the cervix. (A previous Pap smear was unsatisfactory.)

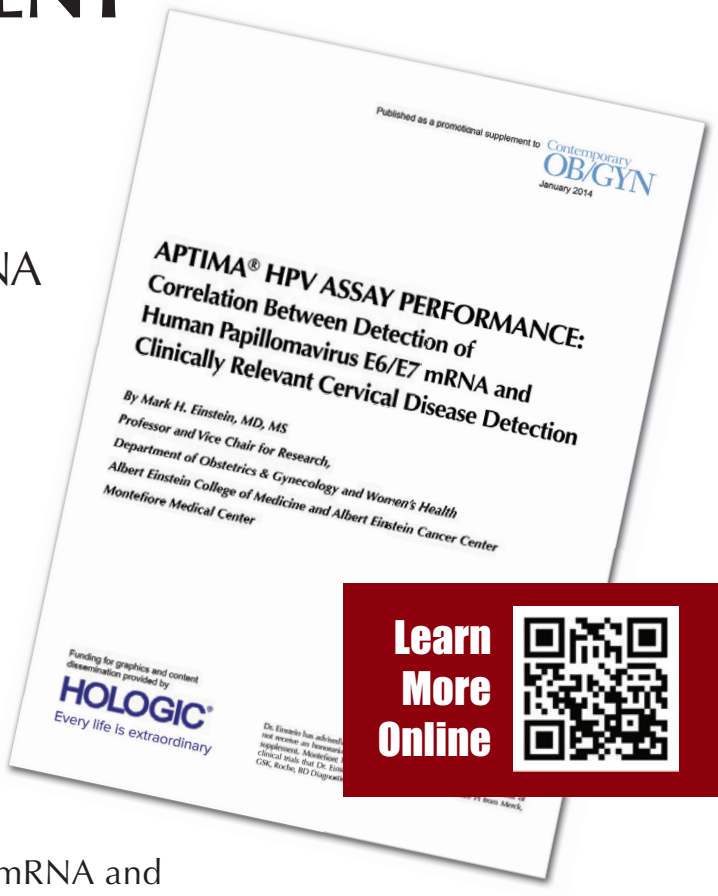
Biopsy results reported chronic granulomatous cervicitis with acute ulceration. AFB and periodic acid-Schiff stains were negative. Because the biopsy was suggestive of tuberculosis, the patient returned for further biopsies to obtain smears and cultures for AFB and fungi, and to perform a PPD and chest radiograph. Further history was obtained. She denied cough, anorexia, night sweats, or weight loss, but did reveal that her sister had died years earlier in the Philippines while being treated for tuberculosis.

The PPD was positive at >10 mm, and the chest radiograph revealed patchy, abnormal opacities in the lung apices bilaterally with a 0.7-cm calcified coin lesion just above the left hemi-diaphragm. *M. tuberculosis* was isolated from the cervical biopsy per DNA probe and susceptibility testing indicated susceptibility to RIPE and streptomycin. Fungal studies were negative.

The patient was referred to the East Baton Rouge Par-

SPECIAL SUPPLEMENT

Aptima® HPV Assay Performance: Correlation Between Detection of Human Papillomavirus E6/E7 mRNA and Clinically Relevant Cervical Disease Detection



It is estimated that approximately 80% of sexually active women will become infected with one or more HPV types in their lifetime. In cells that are infected, HPV DNA either can remain in episomal form or can integrate into the cell genome, which *often* (but not always) results in the expression of HPV E6 and E7 mRNA and proteins. Detection of the presence of E6/E7 mRNA indicates that the infection has become more biologically and likely clinically "active," and is therefore potentially oncogenic.

The Aptima HPV assay detects E6/E7 mRNA from the 14 most oncogenic HPV variants.

This special supplement to the January 2014 issue of ***Contemporary OB/GYN*** discusses the biology and disease progression of HPV infection and explains the technologically unique mechanism of the clinically validated, FDA-approved Aptima HPV assay. The Aptima HPV assay detects E6/E7 mRNA from the 14 most oncogenic HPV variants. The Aptima HPV assay has shown equivalent sensitivity and improved specificity compared to the most frequently used DNA HPV test in studies involving over 50,000 women worldwide. The assay meets both international and U.S. guidelines for cervical cancer screening.

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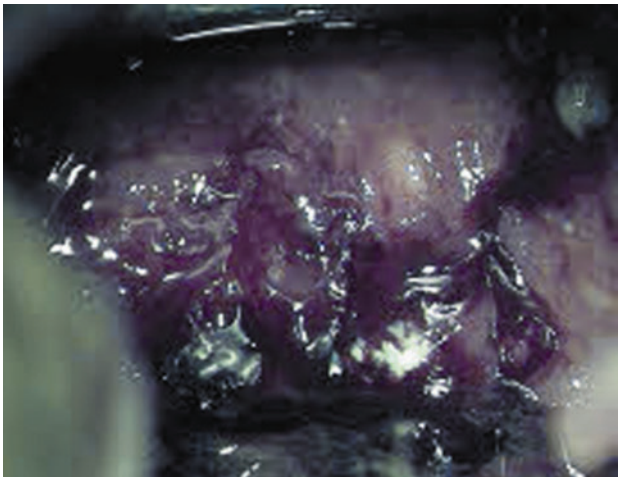
FIGURE 2 **Upon speculum examination, a friable, hemorrhagic, nodular cervix with purulent exudates and a loss of all anatomic landmarks was noted.**



ish tuberculosis clinic for treatment and begun on RIPE therapy. Three months after initiation of therapy, she returned to our clinic for follow-up. She was asymptomatic and speculum examination revealed a healed atrophic cervix consistent with her postmenopausal status and resolution of her disease.

Comment

The female genital tract can be infected with acid-fast or tuberculous bacilli by hematogenous spread, lymphatic spread, direct extension, and through sexual contact.[2] Hematogenous spread begins in the lungs, with the primary lung infection usually undetectable by the time diagnosis of the genital tract occurs. Lymphatic spread occurs from the alimentary tract when milk contaminated with bovine tubercle bacillus is consumed. Direct extension occurs from intraperitoneal surfaces and begins by invading the mucosa of the fallopian tubes.[2] Tubercle bacilli may also be sexually transmitted by a partner with tuberculous epididymitis or infected sputum.[3]

Infertility is one of the most common presenting signs of FGT. In a postmenopausal woman, signs and symptoms can be similar to those found in gynecologic malignancies. Involvement of the fallopian tubes occurs in 90%–100% of cases of genital tract tuberculosis. The uterus is affected in 50%–60% of cases, followed by the ovaries (20%–30%), cervix (5%–15%), and vagina/vulva (1%).[2] If the cervix is involved, 70%–75% of cases have involvement of the endocervix, whereas only 25% of cases involve the exocervix.

Sporadic case reports of cervical tuberculosis from endemic areas of the world exist in both foreign and US literature.[1] However, we have been unable to find reports of cervical tuberculosis diagnosed in the United States and reported in the US literature in more than 3 decades.

FGT is not easily diagnosed because tissue is required to identify granulomatous disease and to perform cultures. The Mantoux test, or PPD, has a sensitivity of only 55% in women with FGT; therefore it is not a reliable indicator of disease.[8] Treatment of FGT is medical, usually RIPE therapy.

When a postmenopausal patient presents with signs and symptoms of a gynecologic malignancy, one must consider FGT, especially in women who have immigrated to the United States. Sixty-three percent of TB cases in the United States involve foreign-born individuals. The top 4 countries of origin are Mexico (20.9%), the Philippines (12.3%), India (8.5%), and Vietnam (7.2%).[1] A thorough history should be obtained in cases of suspected FGT, including a personal history of disease, close contact with infected persons, travel, and former residence in endemic regions. It is important to consider FGT as a cause of gynecologic disease because the primary treatment for FGT is medical, not surgical.

Acknowledgements

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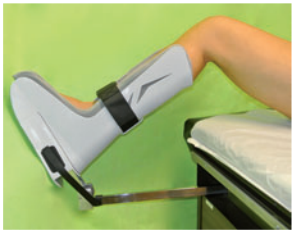

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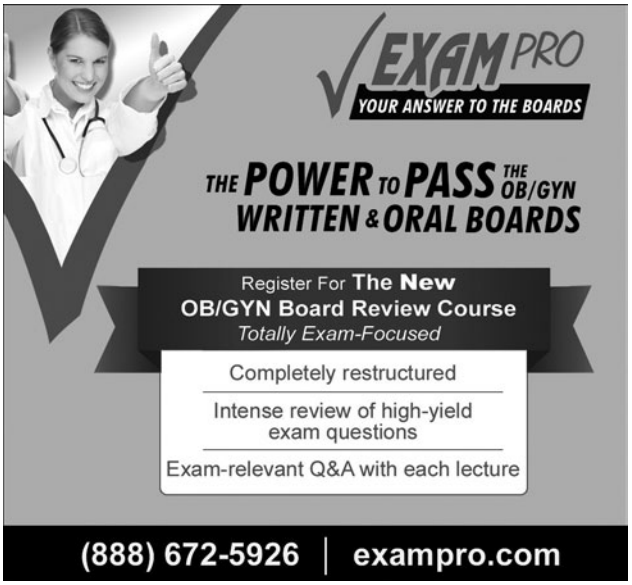

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CALENDAR

APRIL

6-9: The North American Society of Psychosocial Obstetrics and Gynecology Annual Meeting
Columbus, Ohio
www.naspog.org/index.php/2014-annual-meeting

12: Oregon Section of American Congress of Obstetricians and Gynecologists 22nd Annual Meeting "State of the Art: Clinical Pearls for OB/GYNs"
Portland, Oregon
mpcohen@teleport.com

23-26: National Osteoporosis Foundation Interdisciplinary Symposium on Osteoporosis
New Orleans, Louisiana
www.nof-iso.org

24-26: North American Society for Pediatric and Adolescent Gynecology Annual Clinical and Research Meeting
Philadelphia, Pennsylvania
http://naspag.org/index.php/pagecourses

26-30: The American College of Obstetricians and Gynecologists Annual Clinical Meeting
Chicago, Illinois
http://www.acog.org/About_ACOG/ACOG_Departments/Annual_Clinical_Meeting

JULY

7-11: American Medical Association Annual Meeting
Chicago, Illinois
http://www.ama-assn.org/ama/pub/about-ama/our-people/house-delegates/meeting-dates.page

21-26: American Urogynecologic Society and International Urogynecological Association Scientific Meeting
Washington, DC
https://augs-iuga2014.org

SEPTEMBER

5-7: ACOG Districts VI, VIII & IX Annual Meeting, "Scholars and Sommeliers: Learning from California's Leaders"
Napa, California
http://www.acog.org/Education_and_Events/Annual_District_Meetings

10-13: Soceity of Laparoendoscopic Surgeons Minimally Invasive Surgery Week/Annual Meeting and Endo Expo
Las Vegas, Nevada
http://www.sls.org/i4a/pages/index.cfm?pageid=1

11-13: American Gynecological and Obstetrical Society Annual Meeting
Chicago, Illinois
http://agosonline.org/meetings.html

OCTOBER

15-18: North American Menopause Society Annual Meeting
National Harbor, Maryland
http://www.menopause.org/annual-meetings/future-meetings#

18-22: American Society for Reproductive Medicine
Honolulu, Hawaii
http://www.asrm.org/annualmeeting.aspx

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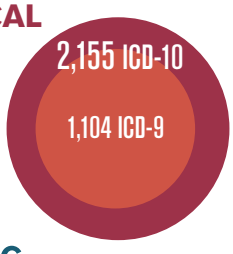
SECTION EDITOR

ICD-10 AND THE OB/GYN

On October 1, 2014, the United States makes the switch from ICD-9 to ICD-10 codes. In anticipation, from March 3 to March 7, the Centers for Medicare & Medicaid Services (CMS) is holding a national testing week for current direct submitters (providers and clearinghouses). With ICD-10 comes coding specificity at the sixth and seventh character level, which is not optional and will require extensive preparations by physicians and their office staff. For obstetrics alone, for example, the 10th revision includes nearly twice as many codes as the 9th revision.

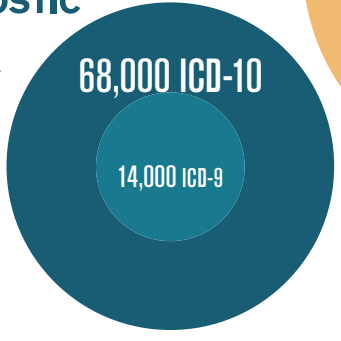
OBSTETRICAL CODES

Source: ICD-10 coding: ICD-10-CM vs. ICD-10-PCS. http://www.icd10codesearch.com/coding.php.



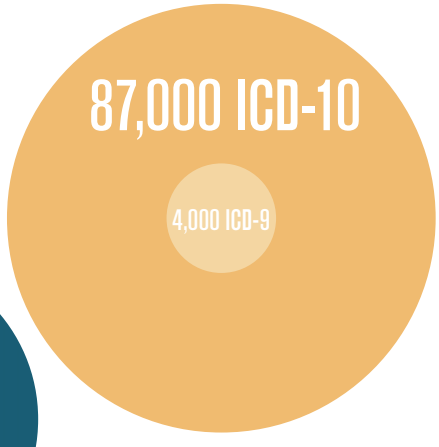
DIAGNOSTIC CODES

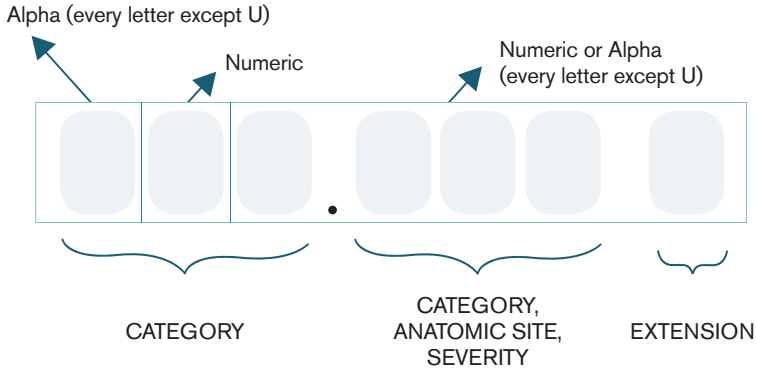
Source: AAPC. ICD-10: The history, the impact, and the keys to success. http://aapcmarketing.s3.amazonaws.com/documents/AAPC_ICD-10_white_paper.pdf



PROCEDURE CODES

Source: Carmichael A. Exploring ICD-10-CM's Chapter 15: Pregnancy, childbirth & the puerperium. http://www.icd10monitor.com.





2014 CPT MANUAL

329
changes

175
new codes

107
code descriptor revisions

47
code deletions

Source: Stanz R. Preparing physicians for ICD-10: Split claims, CMS testing, and more solutions. Medical Economics. http://medicaleconomics.modernmedicine.com/medical-economics/news/preparing-physicians-icd-10-split-claims-cms-testing-and-more-solutions